Skin Diseases in Females

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Editors

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Contents

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Part I
Clinical Dermatology

Chapter 1
Physiology of Skin: Gender-Based Differences

Pallavi Ailawadi

1.1 Introduction

The skin, also known as the integument, is the largest organ in the body, covering its entire outer surface and serves as a first-order physical and immunological barrier against the environment.

The functions of skin include thermoregulation and protection against ultraviolet (UV) light, microorganisms, toxins, and mechanical trauma. It also functions in immunologic surveillance, sensory perception (pain, temperature, touch, and deep pressure), control of insensible fluid loss, endocrine activity (vitamin D production), and homeostasis.

The skin is also a highly dynamic and adaptive organ, with different composition and specialized functions at different body sites. It is intricately connected to the functioning of the body, and it acts as a mirror to the internal characteristics. Also, genetic and hormonal factors affect the structure and function of the skin, and these gender-based differences between women and men are reflected in the skin. Further, exogenous and environmental factors affect the skin. It is imperative for dermatologists to have a working knowledge about all these for a better understanding of pathogenesis of diseases and finding more effective therapies in different gender-linked disorders as well as to provide appropriate cosmetic treatments.

In this chapter, we discuss the various gender-linked anatomical, physiological, and biochemical differences between skin in men and women and focus on skin changes in females at puberty.

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1.2 Hormonal Influence on Skin

Through the initial years of life, the physiological properties of skin seem equal in both genders, whereas with the beginning of puberty the differences become apparent. One of the fundamental differences in the skin of men and women is in the metabolism as well as response to sex hormones. Testosterone, estrogen, and progesterone are present at birth, levels increase during puberty and determine the secondary sexual characteristics of the individual. Beyond sexual functions, they also exert many physiological and pathological effects on skin. Majorly, the circulating androgens are produced by testis, ovaries, and adrenal glands, but skin is also an important peripheral steroidogenic organ and has the capability to produce androgens both de novo from cholesterol and using adrenal precursors, like dehydroepiandrosterone (DHEA), through own enzymatic activities. In the sebocytes, sweat glands, and dermal papilla cells, testosterone is converted to dihydrotestosterone (DHT) by 5-alpha reductase enzyme. The tissue effects of androgens are mediated through binding to the androgen receptor (AR), which is an X-chromosome-encoded, ligand-activated, intracellular receptor and is present in epidermal and follicular keratinocytes, melanocytes, sweat gland cells, sebocytes, dermal papilla cells, dermal fibroblasts, and endothelial cells. Both testosterone and DHT can bind to AR, but DHT has tenfold higher affinity to AR compared to testosterone These enzymes, as well as the AR, have a differential expression and distribution throughout the skin in both sexes and this regulates the effects of androgens on the skin, including hair growth, sebum production, wound healing, and cutaneous barrier function. Any changes/polymorphisms in the levels of enzymes/AR which confer enhanced responsiveness have important implications in the development of hyperandrogenism and skin diseases including seborrhoea, acne, androgenetic alopecia, and hirsutism.

Additional, in women, aromatase enzyme converts testosterone to estradiol in the skin and apart from the abovementioned androgenic actions, these also play a role in skin aging, pigmentation, and skin cancer. Interestingly, progesterone has not been found to play a role in the pathogenesis of skin disorders [1].

The skin also responds differently to nonsexual hormones in both sexes. Men have higher levels of urinary cortisol than women, which might be due to higher stress levels in men. Increased levels of cortisol may account for delayed skin healing, and this coupled with higher sun exposure in men and the resulting UV induced immune-suppression makes men more prone to skin cancers [2].

1.3 Facial and Body Hair

Facial and body hair have important cultural, psychological, and behavioral effects in both men and women. The distribution of hair over body is different in both genders, determined mainly by the effect of androgens and also the racial and genetic

factors. The androgenic effect on hair growth varies according to body site. At puberty, vellus hair on the face is transformed to terminal hair on the face, scalp, beard, axilla, and pubic area, and opposite effect happens on the scalp while no effect is seen on the eyelashes. However, in females, higher serum levels of testosterone in masculinizing syndromes can cause facial hirsutism and female pattern hair loss and cause significant psychologic distress. The hair in women is denser and the percentage of telogen hair is lower as compared to men [3].

1.4 Skin Thickness and Elasticity

The dermis contains ground substance and elastic fibers, which contribute to the thickness of skin. At all ages, men have thicker skin and difference varies with anatomical site, being up to 20% on the forearm [4]. The skin thickness changes over the lifetime of the individual; while one study reports reduction in skin thickness in both sexes starting at the age of 45, other authors report linear decrease in skin thickness with age in men starting at the age of 20 years [5], whereas in women, it seems to remain constant until the age of 50 years, and then starts decreasing [4]. It has also been reported that the weight of hydroxyl-proline/mm [2] in skin decreases linearly with age at the same rate in both sexes by about 1% per year throughout adult life [4]. As this is indicative of collagen loss, it may also be the reason for skin thinning with age.

Skin elasticity, measured by a twistometer, does not differ between the sexes, but it increased only in women after hydration. As hydration softens the stratum corneum, the difference in dermal thickness expresses itself as a difference in extensibility and thinner dermis in women allows a rapid extensibility of the skin. With age, elasticity decreases sharply after the age of 35 in both sexes [5].

Estrogen and other androgens play a role in wound healing and concurrently, women at all ages have faster rates of re-epithelization and wound healing as compared to men. There is no gender-based difference for epidermal properties like daily shedding of the outer sheet of stratum corneum, transepidermal water loss, and barrier function [6].

1.5 Sebum

Androgenic stimulation leads to an increase in size and secretory activity of sebaceous glands. Across various studies among Caucasian [6] as well as Korean men [7], it has been reported that men have higher sebum production and larger pore size, with average values for sebum secretion being significantly higher in men than in women in the age group of 20 to over 69 years, but not for range 15 to 19 years. Interestingly, in women, there is a significant decrease in sebum output in the 50 to 70 age range, probably a result of decreased ovarian activity, whereas the secretion

in men remains unaltered, making the difference in sebaceous gland activity more apparent [7]. Excess sebum is associated with undesirable aesthetic phenomena like pore enlargement and pathological phenomena such as acne.

1.6 Sweat

Sweat can be produced by eccrine glands, which are present as well as active since birth, and also apocrine sweat glands, which become functional around puberty. The hormonal control might be involved only in the maturation of apocrine glands but not in maintaining their function, as it has been seen that gonadectomy of adults does not affect the latter. Sweat is odorless and subsequent bacterial action is necessary for odor production. Men and women have different microflora, and sweat in men has been found to be more odorous. Upon physical exercise, males sweat at a larger rate, about 30–40% more than females (800 ml/h versus 450 ml/h), and correction for body surface does not suppress the difference [8]. With increasing age, there is marked reduction in sweating activity and the body temperature threshold for the onset of sweating increased by nearly one half degree Celsius in both men and women older than 70 years, more pronounced in aged females [9].

1.7 Surface pH

The gender and sex hormones have generally not been found to exert (or have only minor) effects on skin surface pH. However, sweat, sebum, and microflora may influence the acidity of the skin and perhaps, due to the abovementioned gender-linked differences, the surface pH may vary in men and women. In the study by Luebberding et al., skin pH was highest in the cheeks in both sexes and female forehead and male hand had the lowest pH and except for a few areas, the pH value of female subjects was always >5, higher than that of the men [10]. This may be attributed to the increased levels of acidifying substances like free fatty acids, generated by sebaceous gland lipases, and lactic acid derived from the eccrine gland, both being raised in men due to higher sebum and sweat rates than women. With regard to age, an increasing trend in pH value was only seen in men [10]. Further, the pH of skin in women may also be influenced by the use of cosmetics.

1.8 Skin Tone

Skin color is modulated by melanin, hemoglobin, and other pigments like carotene. Although no gender-based difference has been reported for melanocyte distribution, women have been found to have a lighter skin color as compared to men, who have darker and less reflective complexion as compared to women in their individual

ethnic groups [11]. This could be due to various reasons including a more vascularized upper dermis, melanin, and presence of facial hair as well as higher sun exposure in men. Further, men have a higher skin melanin index, increased facultative pigmentation is noted after sun exposure, and they retain it for longer time and women's skin lightens faster than men's skin [12]. Hormones could be playing a role because these changes arise during puberty and also increase with age and in general, both sexes darken as age increases. In addition, skin in women is more homogenous in color than in men; reflectance spectrophotometry has shown that regional variations in color are smaller in women than in men [12].

1.9 Muscle Mass and Body Fat

Men have more lean body mass and less fat, which contributes to the external appearance of the face and the body. The rate of muscle protein synthesis is identical in young women and men, and reduces by 30% in elderly women [13]. Larger muscle mass and higher rates of protein synthesis in men have long been attributed to higher levels of testosterone.

Apart from the muscle mass, difference in body fat also contributes to the visual differences between men and women. Women have larger amounts of subcutaneous fat and store more fat in the gluteal-femoral region, whereas men store more fat in the visceral depot and various studies have documented larger body mass index, waist circumference, hip circumference, and waist-to-hip ratio in boys as compared to girls [14].

Further, age-related muscle atrophy and modifications of fat affect facial characteristics of both sexes. In elderly women, perioral wrinkles and sagging chin are common, whereas aging men show deep expression wrinkles. The perceived age of men and women is also variable, as shown in studies where men have been found to appear 0.37 years older than their age and women 0.54 years younger [15].

Additionally, another hormone called as leptin regulates energy intake and energy expenditure, control of appetite and metabolism, and the potential accumulation of fat in the body. Gender-based differences in serum levels of leptin have been noted, being higher in fasting women than in men. Also, leptin correlates positively with bioavailable estrogen in postmenopausal women, and negatively with total or bioavailable testosterone in men [16]. Fat oxidation at rest and catecholamine-mediated free fatty acid release from the leg and from subcutaneous tissue in the upper body are larger in men than in women [17].

1.10 Cutaneous Vasculature

Hormonal factors affect the blood flow in the skin and gender-based differences were found during the reproductive years. The influence of female sex hormones has also been seen in vasospastic diseases, such as Raynaud's phenomenon; it is

more common in women, more prevalent in reproductive years, and improves during pregnancy.

The effect of sex hormones on the blood vessel wall, or indirect systemic action is further elicited by the cyclic variation during the menstrual cycle. Basal flow is lowest in the luteal phase, highest in the preovulatory phase. Estrogens influence the sympathetic nervous system, inducing an upregulation of vasoconstrictive alpha adrenoceptors, leading to a reduction of basal cutaneous blood flow in women as compared to men. Further, these differences exist only in young women and not in postmenopausal women over 50 years [18].

Thermal variations in vasculature also show a gender-based difference. Local heating induces vasodilatation at a lower skin temperature in women but no difference was noted between men and women in the maximum skin blood flow following heating of the skin. On the other hand, there was a prolonged vasoconstriction response to cooling in young women as compared to men [19]. The cutaneous blood flow response to topical and intradermal administration of histamine was comparable in men and women, which indicates that there are no functional gender-linked differences in skin microvascular response to histamine [20].

The oxygen pressure at the skin surface is mainly determined by changes in skin blood flow and significantly higher levels of transcutaneous oxygen pressure were noted in women, which might be due to thinner epidermis in women [21].

1.11 Skin Sensorial Properties

It has been seen that men and women have different response to tactile and sensory stimuli. Men have less sensitivity to pain and temperature extremes whereas women are less sensitive to cold in winters [22, 23]. Women were more sensitive to small temperature changes and to pain caused by either heat or cold [23]. Further, lower threshold of pricking pain sensation in the forearms of women was noted but pressure threshold was lower in women than in men on the palm and on the sole, but not on the forearm [24]. These differences can possibly be explained by the differences in skin thickness, blood flow, and in the neural structure/function in both sexes.

1.12 Response to Exogenous Triggers

The incidence of irritant dermatitis is higher in women than in men, which may be attributed to occupational factors causing more exposure, whereas experimental irritant dermatitis does not differ between men and women [25].

1.13 Immune System and Skin Cancer

The immunology of skin is different in both sexes, making men more susceptible to bacterial and viral infections and women more prone to autoimmune and inflammatory diseases. Also, men are more prone to skin cancer, with squamous cell carcinomas and melanoma being twice more common in older men [2, 26]. The prevalence of melanoma is 1.72% in men and only 1.22% in women, and twofold high rates of death from melanoma have been seen in men compared to women [2]. The differences in cancer incidence and prevalence in men can be possibly explained by the UV- and stress-induced immune-suppression in human skin and are higher in men due to occupational and social responsibilities. Psychological stress has also been shown to impair the immune response associated with contact hypersensitivity and delayed-type hypersensitivity, and the high level of urinary cortisol found in men might be an indicator of higher psychological stress in men [27]. These two factors might account for the greater occurrence of skin cancer in men.

1.14 Cosmetic and Dermatological Implications of Gender-Based Differences in Skin

The study of differences in skin of both sexes helps in improving understanding of not just dermatological disease and their treatment but also in development of cosmetic treatments for antiaging, skin repair, and overall health. Since hormones play an important role in the physiology of skin, various cosmetic and dermatological treatments work by modulating their binding to skin androgen receptors, especially important in treatment of hair and sebaceous gland disorders. Through this approach, reduction of sebum production in the glands could be used in treating excess oil, acne, and to control pore size, which is known to be larger in men. Similarly, antiandrogen treatments are used in treatment of androgenic alopecia in men and hirsutism in women. But these disorders are generally due to a complex interplay of multiple factors and do not always respond expectedly to hormonal treatments, thus demanding more understanding and research into their pathogenesis. When it comes to facial and body hair removal, methods for the same are different in both sexes and indeed, learning about the skin types and responses in men and women might lead to better pre- and post-shave/wax treatments and development of appropriate approaches to ease the associated discomforts with hair removal, such as redness, dryness, ingrown hairs, and hyper-reactivity.

Since excess sweating is associated with a social stigma, a deeper understanding of male perspiration, its role in cooling the body, may result in better gender-specific cosmetic preparations. The different level of sebum/sweat on the surface of the skin as well as differences in tactile and sensory perception in both sexes might influence the way men perceive the sensations associated with the topical application of products. A sound knowledge of these differences allows development of appropriate

formulations for men and women, which take into account the rates of absorption and of penetration, as well as the residual after-feel.

The skin tone is also different in both sexes and depends on factors like melanin and hemoglobin. Development of gender-specific treatments for skin lightening, pigmentary disorders as well as for skin redness, broken capillaries, and rosacea will benefit from future learning about microcirculatory properties and control of melanin synthesis in men and women. Since the immunology and lifestyle/job factors make men more prone to skin cancer, it is imperative to study about broad-spectrum UVA and UVB protection in men and development of sun protection measures. Further, the process of aging and the factors associated with it are different in both sexes, and a better understanding of this can lead to development of gender-specific measures, thus leading to better compliance and results.

1.15 Skin Changes in Females at Puberty

Puberty is the period of life that leads to adulthood through various physical, physiological, and psychologic changes. The onset of puberty is announced by the appearance of secondary sexual characteristics, gonadal maturation, and through this process, children metamorphose into reproductively mature adolescents. A sound knowledge of the process of puberty is especially salient for understanding and treating the adolescent skin for various associated dermatoses as well as to cater to the immense physical and psychosocial demands of this subset of patients.

1.16 Hormonal Control of Puberty

The hypothalamic-pituitary-gonadal axis is fully active during the fetal and neonatal period, enters a resting phase through childhood, and is reactivated at the time of puberty to induce sexual maturation and subsequent fertility. The onset of puberty is initiated by pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus and subsequent release of the gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone), and the sex steroids (estradiol and/or testosterone), which bring about the changes of puberty, both external (secondary sexual characteristics) and internal (gonadal maturation) along with increase in height, weight, and accompanying psychological and behavioral changes. Estradiol is the main hormone in females influencing the breast and genitals, and promotes uterine maturation and fat deposition in typical female contour. The development of axillary and pubic hair, a process termed pubarche, is brought about by adrenal androgen production (dehydroepiandrosterone sulfate, DHEA), a physiological event termed as adrenarche. This is dependent on pituitary ACTH production and is independent of the hypothalamic-pituitary-gonadal axis [28].

1.17 Önset of Puberty in Girls

Although there is some physiological variation, the sequence of events during puberty usually happens over 3–4 years. The age at puberty onset varies greatly across different ethnic populations, and between the individual and both sexes. The onset of puberty begins at a younger age in girls than boys. The development of breast buds at thelarche is one of the earliest signs of puberty in girls and ranged from age 9.96 ± 1.82 years in white North American girls, 8.87 ± 1.93 years in African American girls, and 10.8 years in Indian girls. Pubic hair growth begins at around age 9. These features evolve through adolescence and are rated into 5 stages according to Tanner's criteria, designated as Tanner stages B1 through B5 for breast development and PH1 through PH6 for pubic hair growth. The average age at menarche is 13 years, ranging from 12 to 13.4 years in Indian girls and it is regarded as the final marker of puberty. In girls with late initiation of puberty, there can be a decrease in the interval between thelarche and menarche [29, 30].

Genetic factors account for most of the inter-individual variations in pubertal timing; association of timing is strongest between mothers and daughters. Early onset of puberty has been documented in girls who are obese and overweight and girls are more likely to have idiopathic central precocious puberty. Environmental factors are clearly important as well; puberty gets delayed at higher altitudes and in undernourished children [30].

1.18 Skin Changes in Puberty

It is said that the skin is the largest nonreproductive target acted upon by estrogens and androgens. Sebaceous glands are androgen dependent and respond dramatically to testosterone, during puberty leading to increased sebum production, which can result in noticeably oilier skin. The impact that estrogen has on sebocytes is still unclear but it has been demonstrated that estrogen suppresses levels of sebum production and gland activation, particularly at high doses [31].

The apocrine glands are present at birth in the axillae, genital organs, anus, and nipples. These are androgen-dependent glands and their size and activity increase during puberty. The role of apocrine glands in humans is unclear. The secretions of apocrine glands are degraded by bacteria on the surface of the skin, resulting in an unpleasant body odor. Probably they play a role of pheromones and sexual attractants. During puberty, there are multiple factors associated with excessive sweating or hyperhidrosis. It does have an emotional basis, but can also be related with hormonal disturbances, characteristic of this period, and can also accompany improper diet consisting of warm and hot meals and drinks.

Estrogen plays a prominent role in overall skin health. Estrogen is associated with increased collagen production leading to skin thickness, increased extracellular hyaluronic acid which results in an increased hydration eventually leading to

tissue water retention and turgescence. It also contributes to faster wound healing and improved barrier function. Progesterone effects on the skin are less firmly established [32].

1.18.1 Skin Pigmentation

Polygenically determined constitutive pigmentation reveals differences between the two genders, beginning at the onset of puberty. The role of sex hormones in the process of melanogenesis is well known and expectedly, adrenarche and gonadarche lead to higher skin and hair pigmentation in children during prepubertal and early pubertal age. Despite this, the skin becomes lighter during puberty, this effect being more in girls than in boys and reasons for this are not well known and cannot be explained by the influence of testosterone and estrogens, as these have the opposite effect on pigmentation. In fact, it has been suggested that increased constitutive skin pigmentation is one of the earliest morphological signs of puberty [33]. In a study on the differences in both sexes in the pigmentation on the medial side of the arm during the stages of puberty, it was found that at the early stage, girls tend to be darker than boys, similar pigmentation at the middle stage, while girls have a significantly lighter skin color at the late stage [33].

1.18.2 Hair Distribution

Before puberty, terminal hair is limited to the scalp, eyelashes, and eyebrows. Following puberty, due to increase in androgen levels, vellus hair transform to terminal hair at various sites on the face and body, starting in the pubic regions. The first pubic hair is sparse, long, lightly pigmented, and almost straight. Gradually, it becomes darker, coarser, curled, and extends in area to form an inverse triangle. Axillary hair first appears approximately 2 years after the start of pubic hair growth. The development of terminal hair continues in regular sequence on other areas including the legs, thighs, forearms, abdomen, buttocks, back, arms, and shoulders. Interestingly, androgens do not affect all hairs equally as during this phase, scalp hair begins to reduce whereas the eyebrows remain essentially unchanged.

1.18.3 Skin Microbiome

The microbiome refers to natural flora, microorganisms that are normally resident on skin and these also undergo a change during puberty. In one study, it was observed that a variety of bacteria, including *Streptococcus* and Gram-negatives like *Moraxella*, *Haemophilus*, and *Neisseria*, dominated the microbiomes of Tanner

stage 1 children. During puberty, there is a shift in the microbiome leading to a reduction in the abovementioned species and dominated by lipophilic bacteria, including *Propionibacterium*, *Corynebacterium*, and *Turicella*, that are associated with sebaceous skin region of Tanner stage 5 individuals [34].

This could be explained by increased epidermal lipids resulting from androgen-stimulated increased sebaceous gland activity during puberty. The higher sebum concentration favors growth of lipophilic bacteria and the metabolism of skin lipids by these bacteria reduces skin pH, which inhibits staphylococcal and streptococcal species. Additionally, other pubertal skin changes like increased apocrine gland activity and increased density and thickness of body hair also contribute to the shifts in microbiome. Also, immature immune system in children may permit the colonization and growth of a wider range of bacteria whereas with growing age, immunology of skin matures and reduces the flora.

1.19 Dermatological Problems Associated with Puberty

Puberty is an important time in the life of an individual, not just because of the physical, social, and emotional changes but also because of certain disorders related to the hormonal and immunological alterations that happen over this time. The common dermatological problems of adolescence are majorly related to fluctuations in hormone levels, mainly androgens, and increase in their levels can herald the start of genetically programmed familial androgen-dependent disorders. Androgen-dependent hair disorders—hirsutism in women and androgenetic alopecia in both sexes—cause significant psychological distress. Increased size of sebaceous glands and overproduction of sebum lead to oily skin, clogged pores, enlarged pore size and acne as well as seborrheic dermatitis. In fact, acne vulgaris is the most commonly diagnosed dermatosis in patients in the age group of 11 and 30 years. It is believed to affect about 80% of persons in this age group or even 100% of young people, taking into account lesions of low severity. The hormonal and emotional upheavals of puberty can also lead to excessive sweating, known as hyperhidrosis. It can also be caused due to improper diet consisting of warm and hot meals and drinks. The change in the microbial flora of the axillary area could affect the eccrine and apocrine secretions in this area, leading to malodorous sweat, a problem called as bromhidrosis. Other disorders related to apocrine glands including Hidradenitis suppurativa and Fox-Fordyce disease also appear around this age group. Further, certain nevi have androgen receptors and may respond to changes during puberty, including increase in size and pigmentation in congenital melanocytic nevi and prominent terminal hairs may form within them. Nevus sebaceous becomes more prominent with thicker and nodular surface. A nevus like the Becker nevus may appear for the first time during this age. Although a lot is known about these dermatoses, there are still a lot of gaps and gaining a deeper understanding of the pathogenesis of these disorders will lead to development of much more effective treatment strategies.

References

1. Zouboulis CC, Chen WC, Thornton MJ, Qin K, Rosenfield R. Sexual hormones in human skin. Horm Metab Res. 2007;39(2):85–95.
2. Lasithiotakis K, Leiter U, Meier F, Eigentler T, Metzler G, Moehrle M, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. Cancer. 2008;112:1795–804.
3. Giacomoni PU, Mammone T, Teri M. Gender-linked differences in human skin. J Dermatol Sci. 2009;55(3):144–9.
4. Shuster S, Black M, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. Br J Dermatol. 1975;93:639–43.
5. Leveque JL, Corcuff P, de Rigal J, Agache P. In vivo studies of the evolution of physical properties of the human skin with age. Int J Dermatol. 1984;23:322–9.
6. Jacobi U, Gautier J, Sterry W, Ladermann J. Gender-related differences in the physiology of the stratum Corneum. Dermatology. 2005;211:312–7.
7. Roh M, Han M, Kim D, Chung K. Sebum output as a factor contributing to the size of facial pores. Br J Dermatol. 2006;155:890–4.
8. Green JM, Bishop PA, Muir IH, Lomax RG. Gender difference in sweat lactate. Eur J Appl Physiol. 2000;82:230–5.
9. Foster KG, Ellis FP, Doré C, Exton-Smith AN, Weiner JS. Sweat responses in the aged. Age Ageing. 1976;5:91–101.
10. Luebberding S, Krueger N, Kerscher M. Skin physiology in men and women: in vivo evaluation of 300 people including TEWL, SC hydration, sebum content and skin surface pH. Int J Cosmet Sci. 2013;35:477–83.
11. Roh K, Kim D, Ha S, Ro Y, Kim J, Lee H. Pigmentation in Koreans: study of the differences from Caucasians in age, gender and seasonal variations. Br J Dermatol. 2001;144:94–9.
12. Frost P. Human skin color: a possible relationship between its sexual dimorphism and its social perception. Perspect Biol Med. 1988;32:38–58.
13. Smith G, Atherton P, Villareal D, Frimel T, Rankin D, Rennie M, et al. Differences in muscle protein synthesis and anabolic signaling in the postabsorptive state and in the response to food in 65–80 year old men and women. PLoS One. 2008;3:1–9.
14. Lee S, Kuk JL, Hannon TS, Arslanian SA. Race and gender differences in the relationships between anthropometric and abdominal fat in youth. Obesity. 2008;16:1066–71.
15. Bulpitt C, Markowe H, Shipley M. Why do some people look older than they should? Postgrad Med J. 2001;77:578–81.
16. Thomas T, Burguera B, Melton LJ III, Atkinson EJ, O'Fallon WM, Riggs BL, et al. Relationship of serum leptin levels with body composition, and sex steroid and insulin level in men and women. Metabolism. 2000;49:1278–84.
17. Toth MJ, Gardner AW, Arciero PJ, Calles-Escandon J, Poehlman ET. Gender differences in fat oxidation and sympathetic nervous system activity at rest and during submaximal exercise in older individuals. Clin Sci. 1998;95:59–66.
18. Bartelink ML, Wollersheim A, Theeuwes A, et al. Changes in skin blood flow during the menstrual cycle: the influence of the menstrual cycle on the peripheral circulation in healthy female volunteers. Clin Sci. 1990;78:527–32.
19. Walmsley D, Goodfield MJD. Evidence for an abnormal peripherally mediated vascular response to temperature in Raynaud's phenomenon. Br J Rheumatol. 1990;29:181–4.
20. Tur E, Aviram G, Zeltser D, et al. Histamine effect on human cutaneous blood flow: regional variations. Acta Derm Venereol. 1994;74:113–6.
21. Orenstein A, Mazkereth R, Tsur H. Mapping of the human body skin with transcutaneous oxygen pressure method. Ann Plast Surg. 1988;20:419–25.
22. Meh D, Denislic M. Quantitative assessment of thermal and pain sensitivity. J Neurol Sci. 1994;127:164–9.

23. Sato H, Yamasaki K, Yasukouchi A, Watanuki S, Iwanaga K. Sex differences in human thermoregulatory response to cold. J Hum Ergol. 1988;17:57–65.
24. Weinstein S, Sersen E. Tactual sensitivity as a function of handedness and laterality. J Comp Physiol PsychoI. 1961;54:665–9.
25. Bjornberg A. Skin reactions to primary irritants. Acta Derm Venereol (Stockh). 1975;55:191–4.
26. Dal H, Boldemann C, Lindelo¨ f B. Trends during a half century in relative squamous cell carcinoma distribution by body site in the Swedish population: support for accumulated sun exposure as the main risk factor. J Dermatol. 2008;35:55–362.
27. Streilein J, Taylor J, Vincek V. Relationship between ultraviolet radiation induced immunesuppression and carcinogenesis. J Invest Dermatol. 1994;103:S107–11.
28. Abreu AP, Kaiser UB. Pubertal development and regulation. Lancet Diabetes Endocrinol. 2016;4(3):254–64.
29. Wu T, Mendola P, Buck G. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the third National Health and nutrition examination survey, 1988-1994. Pediatrics. 2002;110(4):752–7.
30. Agarwal KN. The Growth- infancy to adolescence. 3rd ed. India: CBS Publishers; 2015. p. 1–30. and 87–93
31. Geller L, Rosen J, Frankel A, Goldenberg G. Perimenstrual flare of adult acne. J Clin Aesthet Dermatol. 2014;7(8):30–4.
32. Shah MG, Maibach HI. Estrogen and skin. An overview. Am J Clin Dermatol. 2001;2(3):143–50.
33. Sitek A, Żądzińska E, Rosset I, Antoszewski B. Is increased constitutive skin and hair pigmentation an early sign of puberty? Homo. 2013;64(3):205–14.
34. Oh J, Conlan S, Polley EC, Segre JA, Kong HH. Shifts in human skin and nares microbiota of healthy children and adults. Genome Med. 2012;4(10):77.

Chapter 2
Pregnancy-Specific Dermatoses

Suruchi Vohra and Mark Jean-Aan Koh

The pregnancy dermatoses are a group of heterogeneous inflammatory skin disorders which manifest primarily during pregnancy and/or in the immediate 6-week postpartum period. In 2006, Ambros-Rudolf CM et al. proposed a simplified and logical classification (Table 2.1) [1–3]. Before diagnosis of a dermatoses of

Table 2.1 Classification of the specific dermatoses of pregnancy

Pregnancy-specific dermatoses	Synonyms
1. Pemphigoid gestationis	Herpes gestationis Gestational pemphigoid
2. Polymorphic eruption of pregnancy	Pruritic urticarial papules and plaques of pregnancy (PUPPP) Toxic erythema of pregnancy Toxemic rash of pregnancy Late-onset prurigo of pregnancy Erythema multiforme of pregnancy
3. Atopic eruption of pregnancy	Prurigo of pregnancy Pruritic folliculitis of pregnancy Prurigo gestationis Early-onset prurigo of pregnancy Papular dermatitis of pregnancy Eczema in pregnancy
4. Intrahepatic cholestasis of pregnancy	Cholestasis of pregnancy Pruritus/prurigo gravidarum Icterus gravidarum Obstetric cholestasis Jaundice of pregnancy

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pregnancy is reached, the clinician needs to exclude other non-pregnancy-related dermatological conditions.

2.1 Atopic Eruption of Pregnancy

Synonym: Prurigo of pregnancy, Pruritic folliculitis of pregnancy, Prurigo gestationis, Early-onset prurigo of pregnancy, Papular dermatitis of pregnancy, Eczema in pregnancy.

2.1.1 Introduction

Atopic eruption of pregnancy (AEP) is an umbrella term that includes either exacerbation of already existing atopic dermatitis or other eczemas (20%) or first-ever onset of eczematous and/or papular eruption during pregnancy in an individual with strong personal or family history of atopy (80%). It is the most common specific dermatoses of pregnancy with an incidence between 1 in 50 and 1 in 200 pregnancies.

2.1.2 Etiopathogenesis

Atopic eruption of pregnancy is postulated to be triggered by pregnancy-related immunological changes. During a normal pregnancy, to avoid fetal rejection, there is reduced cell-mediated immunity and decreased Th1 cytokines (e.g., IL-2, IL-12, IFN-γ), with dominant humoral immunity and increased Th2 cytokine production (e.g., IL-4 and IL-10). This imbalance leads to an immune response skewed towards the Th2 pathway, leading to the appearance of the clinical features of atopic eruption in an atopic individual.

2.1.3 Clinical Features

Atopic eruption of pregnancy and polymorphic eruption of pregnancy can be differentiated clinically by the onset and morphology of rash. The onset of AEP is commonly early during the first trimester and the morphology of rash is either papular or eczematous, and unassociated with the striae gravidarum. Two-thirds of the patients present with an eczematous rash over typical atopic sites like the face, neck, and flexures of extremities known as the E-type of AEP (Fig. 2.1) [4]. The remaining one-third of patients present with small red papules and/or prurigo nodularis-like lesions scattered on the trunk and limbs known as the P-type of AEP (Figs. 2.2, 2.3 and 2.4) [4]. In some patients, the papules can be folliculocentric

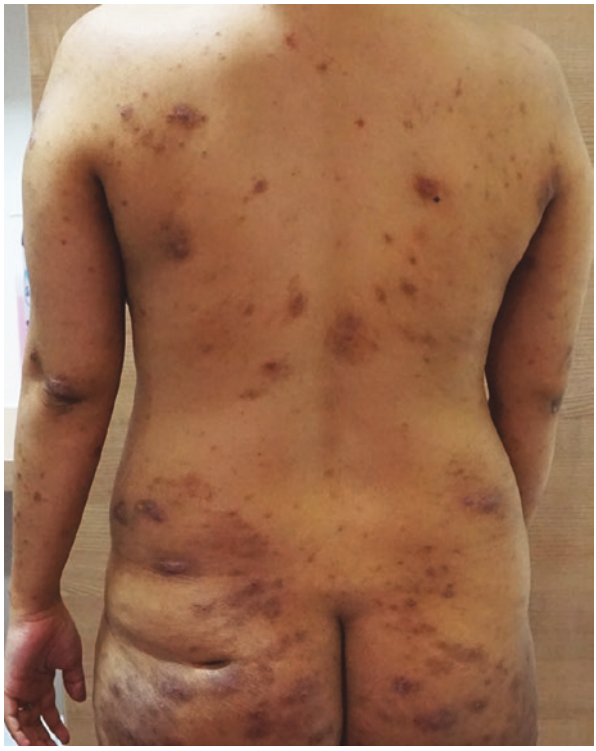

Fig. 2.1 Eczematous rash on the back and buttocks of a patient with atopic eruption of pregnancy

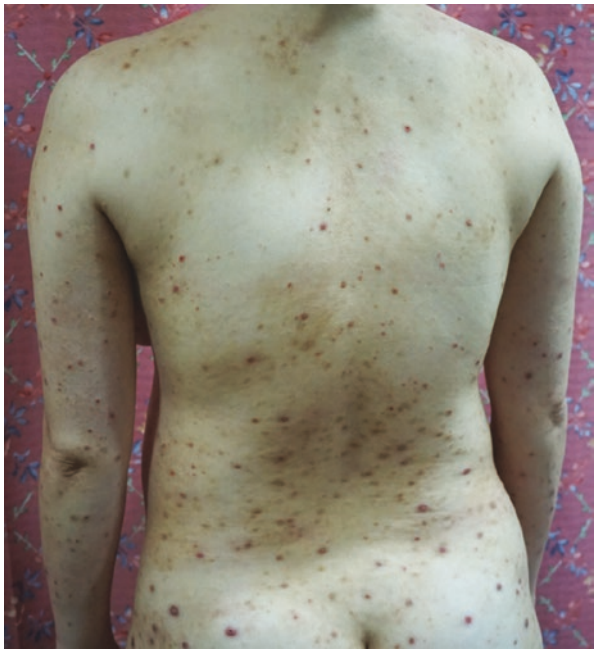

Fig. 2.2 Multiple excoriated, scaly, erythematous-to-hyperpigmented papules on the back, arms, and buttocks of a patient with atopic eruption of pregnancy

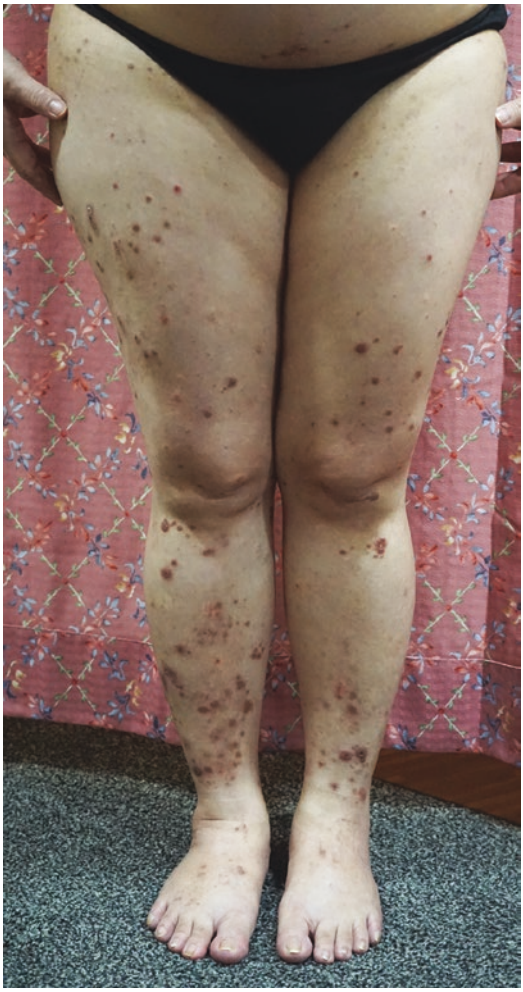

Fig. 2.3 Eczematous papules and plaques, with prurigo nodularis-like lesions on the legs of a patient with atopic eruption of pregnancy

resembling steroid-induced acne or pityrosporum folliculitis. The background skin is invariably xerotic. There is no associated poor fetal outcome except for the increased risk of development of atopic dermatitis in the infant. Recurrence in subsequent pregnancies is common.

2.1.4 Pathology

The histopathological features are that of a spongiotic dermatitis and include variable hyperkeratosis and focal parakeratosis, acanthosis, spongiosis, and a dermal infiltrate composed of lymphocytes, histiocytes, and scattered eosinophils.

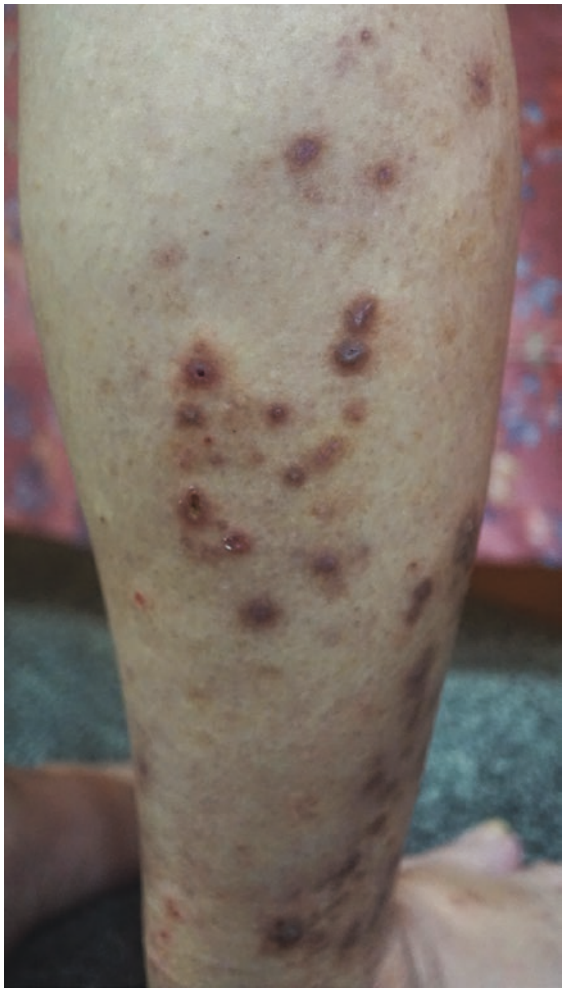

Fig. 2.4 Multiple excoriated, prurigo nodularis-like papules and nodules on the legs of a patient with atopic eruption of pregnancy

Laboratory findings are normal except for raised serum Ig E levels in 70% of cases [2]. Immunofluorescence studies are negative. Microbiological swab culture tests for bacteria and fungus can be sent if there is a follicular-based papule or a pustule to exclude infective causes.

2.1.5 Treatment

Treatment for atopic eruption of pregnancy is similar to treatment for eczema. Gentle skin care consisting of a tepid bath, use of soap-free cleansers or soap substitutes, and regular application of emollients is the cornerstone for management.

Patients will also benefit from topical corticosteroids, topical anti-itch formulations, and first-generation oral antihistamines, e.g., chlorpheniramine. A short course of oral corticosteroids may be considered in severe cases. Narrowband UVB can be considered as additional treatment in those with moderate or severe disease with suboptimal response to topicals.

2.2 Polymorphic Eruption of Pregnancy

Synonyms: Pruritic urticarial papules and plaques of pregnancy (PUPPP), Toxic erythema of pregnancy, Toxemic rash of pregnancy, Late-onset prurigo of pregnancy, Erythema multiforme of pregnancy.

2.2.1 Introduction

Polymorphic eruption of pregnancy (PEP) is a common benign self-limiting inflammatory dermatosis of pregnancy. The incidence is approximately between 1 in 160 and 1 in 250 pregnancies. There is no HLA association.

2.2.2 Etiopathogenesis

The etiopathogenesis is uncertain. The literature has shown a link to increased maternal weight gain and multigestational pregnancies. It has been postulated that sudden overstretching of the abdomen leads to connective tissue damage triggering an inflammatory response that manifests clinically as urticarial rash beginning within the striae distensae [5]. Some theories also postulate the role of increased levels of progesterone during multiple pregnancies leading to aggravated inflammatory response at the tissue level [5].

2.2.3 Clinical Features

Polymorphic eruption of pregnancy predominantly affects primigravidas generally during their third trimester (85%) or in their immediate postpartum period (15%) [2]. The eruption typically begins with intensely itchy urticarial papules and plaques along the striae distensae (Fig. 2.5) with classical "periumbilical sparing." It then spreads in a few days to the rest of the trunk, buttocks, and proximal extremities (Figs. 2.6 and 2.7) with sparing of the face, neck, palms, and soles. The eruption often evolves to become polymorphous, consisting of erythematous macules, tiny

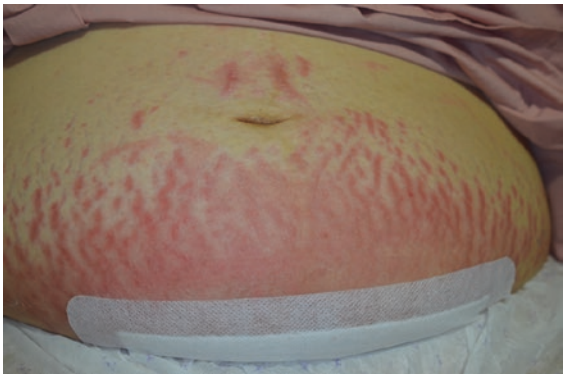

Fig. 2.5 Urticated plaques affecting the striae of a patient with polymorphic eruption of pregnancy

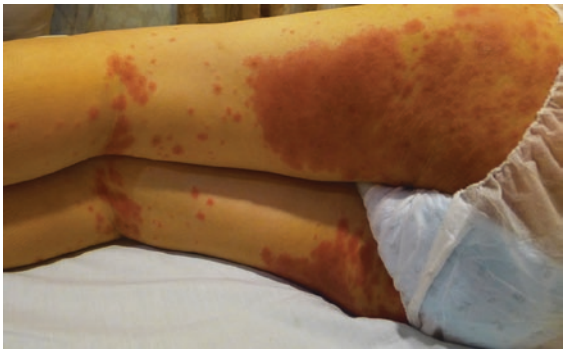

Fig. 2.6 Confluent urticated plaques on the legs of the patient with polymorphic eruption of pregnancy

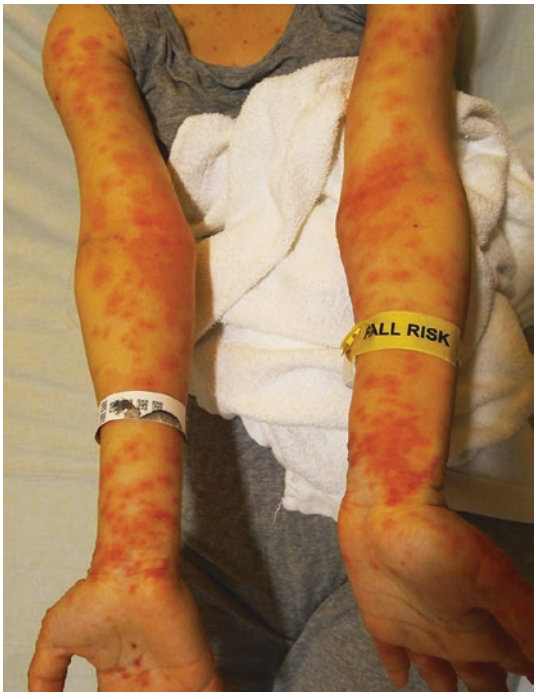

Fig. 2.7 Urticated plaques on the arms of a patient with polymorphic eruption of pregnancy

vesicles, eczematous plaques, or atypical targets. It generally subsides spontaneously in 4 to 6 weeks or soon after delivery without leaving behind any sequalae [4]. There is no associated fetal morbidity and recurrences are not common, except for multigestational pregnancies.

2.2.4 Pathology

The diagnosis of PEP is clinical, and skin biopsy is not routinely required. Histopathology is nonspecific and varies with various stages of clinical eruption. The skin biopsy findings consist of patchy parakeratosis, varying degrees of acanthosis, spongiosis, superficial to mid-dermal edema, and perivascular lymphocytic infiltrate with variable number of eosinophils and neutrophils [2, 5]. Direct immunofluorescence, indirect immunofluorescence, and routine biochemistry are essentially normal.

2.2.5 Treatment

The management of PEP is mainly for symptomatic relief. Most of the patients do well with the combination of topical corticosteroids, emollients, and oral antihistamines. In a small subset of patients with more severe and generalized disease, a short course of oral corticosteroids for 1 to 2 weeks is usually very effective.

2.3 Intrahepatic Cholestasis of Pregnancy

Synonym: Cholestasis of pregnancy, Pruritus/prurigo gravidarum, Icterus gravidarum, Obstetric cholestasis, Jaundice of pregnancy.

2.3.1 Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a rare pregnancy-specific dermatosis associated with a risk of poor fetal outcome in some cases. Early recognition and treatment are important to reduce fetal mortality and morbidity. There is a geographic and racial predisposition with the highest prevalence seen in South American Araucanian Indian women [2]. There is a positive family history in approximately 50% of affected individuals. There is a higher prevalence in twin pregnancies and after in vitro fertilization [5].

2.3.2 Etiopathogenesis

The etiopathogenesis of ICP is complex. The familial clustering suggests a genetic predilection. The key pathology is a defect in the excretion of bile acids, leading to increased serum levels. Raised serum levels of bile acids induce intractable pruritus in the mother and as these bile acids cross the placenta, may have deleterious effects on the fetus due to acute placental anoxia and cardiac depression [4]. The reason for this defect is a complex interplay between hormonal, environmental, and genetic factors. Recently, pathogenic variants in *ABCB4* gene encoding a protein necessary for bile acid excretion have been detected in some cases of ICP [4]. Other factors which have been shown to play a role are hepatitis B and hepatitis C infections, decreased serum levels of selenium, and cholestatic effects of estrogen and progesterone metabolites [2, 5].

2.3.3 Clinical Features

Patients with ICP typically present with sudden onset of severe pruritus often during their last trimester. The itch typically starts on the palms and soles and becomes generalized. There are no primary skin lesions. The cutaneous findings are mainly secondary to scratching which can range from minor excoriations (Fig. 2.8) to

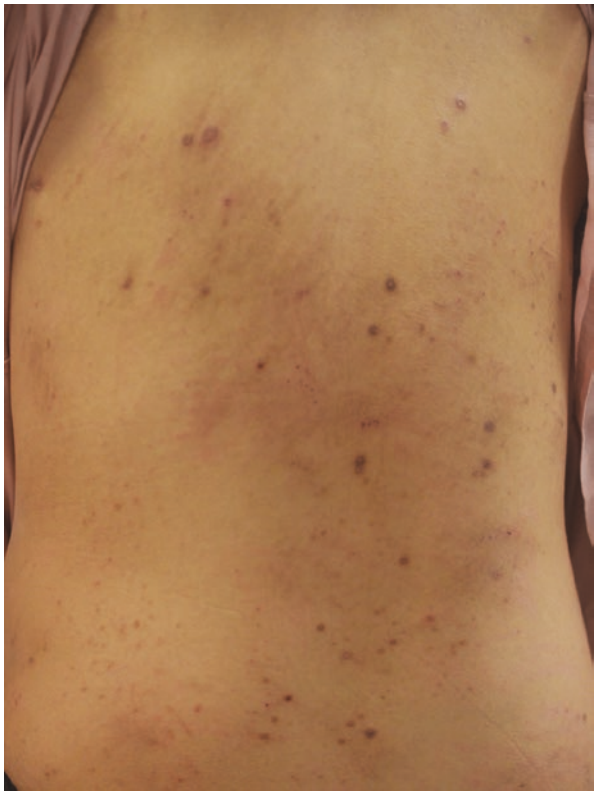

Fig. 2.8 Scratch marks and "prurigo-like" lesions on the back of a patient with intrahepatic cholestasis of pregnancy

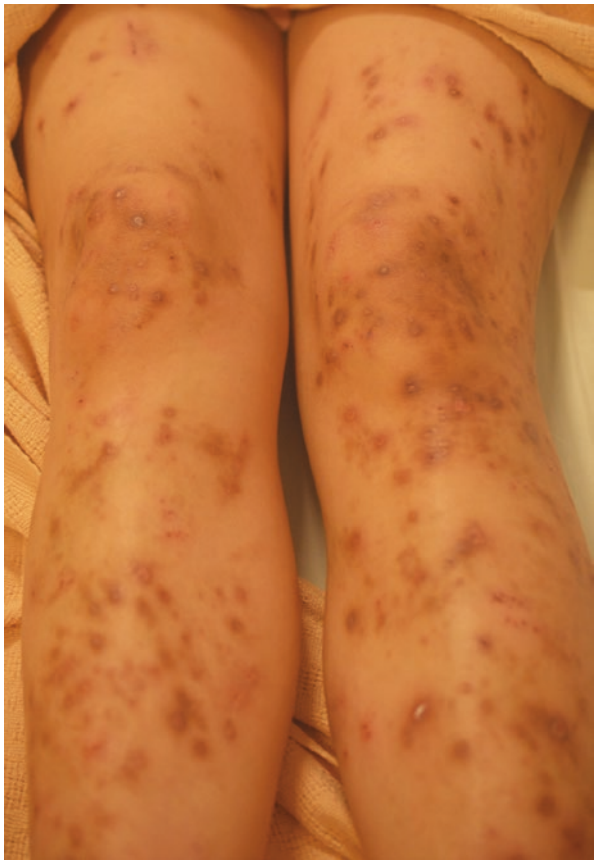

Fig. 2.9 "Prurigo-like" lesions in linear configuration on the legs of a patient with intrahepatic cholestasis of pregnancy

severe prurigo nodules in long-standing cases (Fig. 2.9). The skin changes tend to occur more commonly on the extremities but may affect the buttocks and abdomen. Patients may experience nonspecific symptoms like malaise, anorexia, and mild nausea. The prognosis for the mother is generally good. Pruritus may worsen as the pregnancy advances but classically resolves within a few days of delivery.

Jaundice is not a typical clinical sign of ICP but may be seen in 10% of cases with severe disease due to associated extrahepatic cholestasis. In such cases, patients are at increased risk of intra- and postpartum hemorrhage due to malabsorption of vitamin K [5]. Some may experience dark urine, light-colored stools, and steatorrhea.

The risk of recurrence of ICP in a subsequent pregnancy is high (40–60%) and can occur with oral contraceptive use. There is an associated increased risk for premature birth (20–60%), intrapartum fetal distress (22–33%), and stillbirths (1–2%). The risk correlates with higher bile acid levels, especially if levels exceed 40 μmol/l. Close obstetric surveillance and maternal counseling are essential to improve fetal outcomes.

2.3.4 Pathology and Investigations

Histopathology of the skin is nonspecific and immunofluorescence studies are typically negative. The key laboratory finding is raised total serum bile acids (>11 μmol/l). Liver function test may be normal (~30% of cases) or may show raised liver enzymes or raised conjugated bilirubin levels, especially in patients with jaundice. Ultrasonography of the liver and regular monitoring of prothrombin time are recommended in patients who develop jaundice.

2.3.5 Treatment

The main therapeutic goal is to reduce the serum bile acids and to minimize adverse fetal outcomes. Oral ursodeoxycholic acid (UCDA) is a naturally occurring hydrophilic nontoxic bile acid which has been shown to reduce serum bile acids, decrease the passage of maternal bile acids into the fetal circulation, and improve fetal prognosis. It should be started as early as possible, at a dose ~15 mg/kg/day or 1 g/day in 2–3 divided doses and can be stopped at the time of delivery. Although its use in pregnancy is considered "off-label," there have been no maternal or fetal adverse effects reported except for mild diarrhea. A multidisciplinary approach involving a dermatologist, obstetrician, hepatologist, and pediatrician in the care of patients with ICP is essential.

2.4 Pemphigoid Gestationis

Synonyms: Herpes gestationis, Gestational pemphigoid.

2.4.1 Introduction

Pemphigoid gestationis (PG) is a rare autoimmune bullous disorder associated with pregnancy. It is the most well-defined dermatoses of pregnancy with known etiopathogenesis. The incidence of PG is approximately 1 in 10,000 to 1 in 50,000 pregnancies and has shown a link with HLA-DR3 and -DR4 haplotypes. Rarely, PG has been reported in association with choriocarcinoma or hydatidiform mole [2].

2.4.2 Etiopathogenesis

Pemphigoid gestation is an autoantibody-mediated disease characterized by the presence of complement fixing IgG1 antibody against the noncollagenous (NC16A) domain of BP180 (BPAG 2 or Collagen XVII). It is postulated that an HLA

mismatch between mother and fetal tissue provokes an autoimmune response that targets the maternal skin.

2.4.3 Clinical Features

Pemphigoid gestationis most commonly manifests during the second or third trimester of pregnancy with mean onset at 21 weeks. Postpartum onset has been described in 25% of cases with the majority starting within hours or days of delivery. The onset is usually abrupt and starts as intensely pruritic urticarial papules and plaques over the abdomen, classically in a periumbilical distribution. This is followed by the development of clustered (herpetiform) vesicles and bullae on an erythematous base and in many instances, the eruption progresses centrifugally to affect the chest, back, and extremities. The mucous membranes are generally spared. The disease typically flares at the time of delivery in two-thirds of cases and before resolving spontaneously in weeks to months following delivery [6]. Scarring is usually not seen.

The disease can reoccur in subsequent pregnancies with a more severe course. In approximately 5 to 10% of cases, the neonate may develop a transient and limited form of a blistering eruption secondary to passive transfer of maternal autoantibodies which generally resolves without any intervention, after a few months when the maternal autoantibodies are eliminated. Early onset and severe forms of pemphigoid gestationis have been associated with increased risk of premature birth and small for gestational age babies.

2.4.4 Pathology

The histopathology and immunofluorescence findings of pemphigoid gestationis are similar to bullous pemphigoid. There is a subepidermal blister associated with an infiltrate of lymphocytes, histiocytes, and many eosinophils. Direct immunofluorescence from perilesional skin will show linear deposition of C3 (100% cases) and IgG (30% cases) along the basement membrane zone [3]. ELISA can be used in determining the levels of antibody titers against BP180-NC16A and this can help track disease activity and monitor response to therapy.

2.4.5 Treatment

The choice of treatment depends on the severity of the disease. In mild and limited forms, potent topical corticosteroids with oral antihistamines may be sufficient to control the disease. However, in severe cases with generalized blistering, oral

corticosteroids will be required for control of disease. Typically, prednisolone at a dose of 0.5 mg/kg/day is sufficient in most cases and can be rapidly tapered to a maintenance dose as soon as blistering is controlled. Rarely, the disease may have a refractory course requiring oral cyclosporine A or plasmapheresis during pregnancy.

2.5 Pustular Psoriasis of Pregnancy

Synonyms: Impetigo herpetiformis.

2.5.1 Introduction

Although pustular psoriasis of pregnancy (PPP) is not classified as a specific dermatosis of pregnancy, we will discuss it briefly as it is common and can have maternal fetal complications and should be diagnosed and treated early. It is considered a rare variant of generalized pustular psoriasis which occurs during pregnancy. There may be a positive personal or family history of psoriasis.

2.5.2 Etiopathogenesis

The etiology is still unknown but hormonal changes during pregnancy are suspected to play a role. Association with hypocalcemia and hypoparathyroidism has been suggested, although these findings may not be seen in many cases in clinical practice [7].

2.5.3 Clinical Features

PPP typically manifests during the late third trimester of pregnancy and mostly resolves in the postpartum phase. However, there is a high risk of recurrence in subsequent pregnancies and can persist after pregnancy in some patients. Clinically, it presents with erythematous plaques studded with sterile pustules typically beginning in the skin folds such as axilla and groin in a bilateral symmetrical distribution. Sheets of erythema and pustulation rapidly spread to involve the rest of the body sparing the face, palms, and soles (Figs. 2.10, 2.11 and 2.12). Pustules may come in waves and resolve with red brown pigmentation and fine desquamation (Fig. 2.13). These cutaneous lesions are often associated with systemic manifestations including high-grade fever, severe malaise, diarrhea, increased white blood cell count, and raised erythrocyte sedimentation rate (ESR). In severe cases, it can progress to full-blown erythroderma.

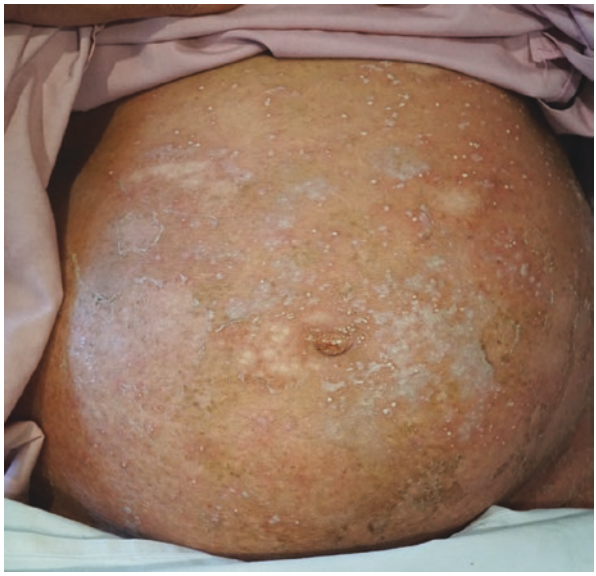

Fig. 2.10 Discreet pustules with superficial sheets of evolving pustulation and erythema affecting the abdomen of a patient with pustular psoriasis of pregnancy

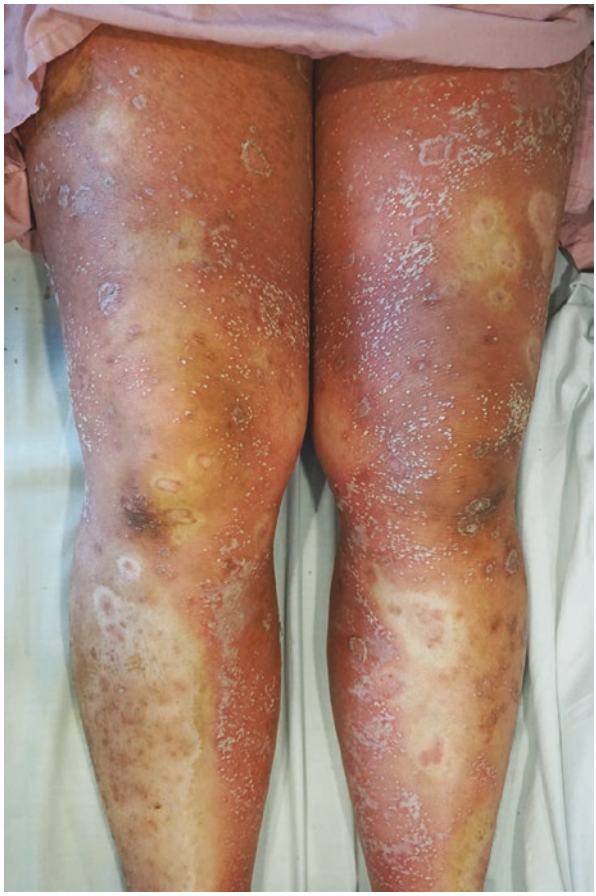

Fig. 2.11 Sheets of erythema and pustulation affecting the lower limbs of a patient with pustular psoriasis of pregnancy

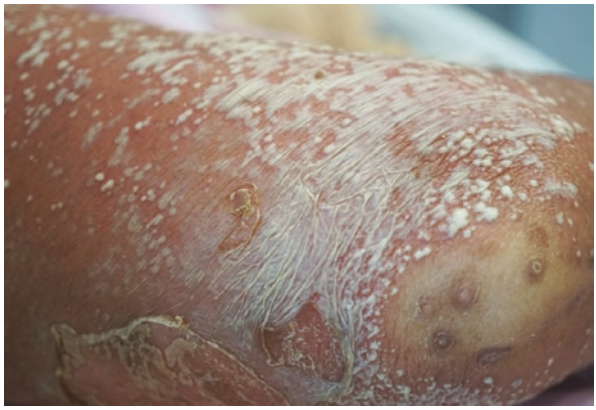

Fig. 2.12 Discreet and sheets of pustulation and erythema on the limb of a patient with pustular psoriasis of pregnancy

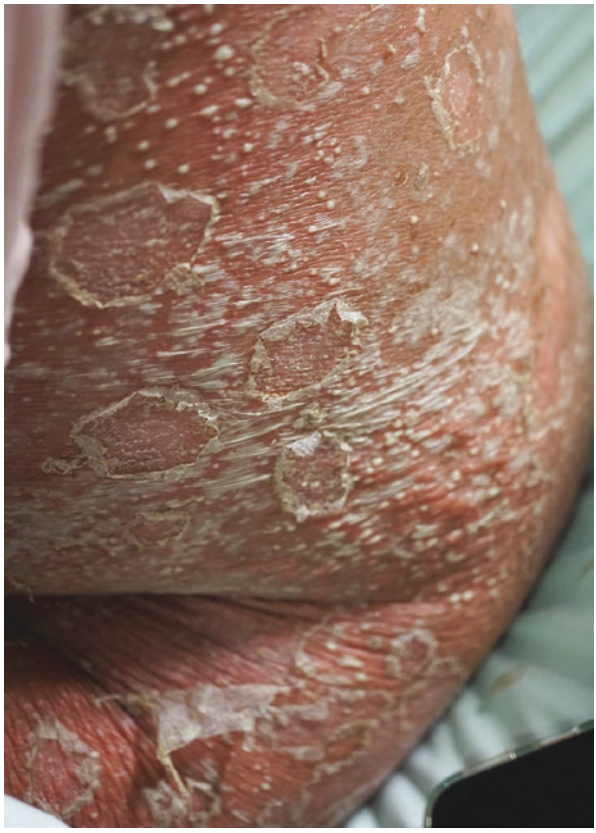

Fig. 2.13 Pustules and superficial scaling on the limbs of a patient with pustular psoriasis of pregnancy

Severe and extensive forms of PPP can be associated with placental insufficiency, leading to intrauterine growth restriction, low birth weight, and even stillbirth. Close fetal monitoring is crucial.

2.5.4 Pathology

The histopathology findings are the same as pustular psoriasis and are characterized by epidermal acanthosis, parakeratosis, varying degree of spongiosis, subcorneal and intraepidermal neutrophilic micro-abscesses (spongiform pustules of Munroe and Kogoj), and intense edema in the papillary dermis.

2.5.5 Treatment

The first-line treatment for PPP is systemic corticosteroids in the form of oral prednisolone. The dose may range from 20 to 60 mg per day based on disease severity and it should be continued in the postpartum period and gradually tapered off to avoid flares. In some corticosteroid refractory cases, there are reports of the use of other systemic therapies such as cyclosporine and biologics (TNF-alpha inhibitors). Other traditional systemic therapies for the treatment of psoriasis, like methotrexate and acitretin, are contraindicated in pregnancy and must be avoided.

References

1. Ambros-Rudolph CM, Müllegger RR, Vaughan-Jones SA, Kerl H, Black MM. The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. J Am Acad Dermatol. 2006;54(3):395–404.
2. Bolognia JL, Schaffer JV, Cerroni L, editors. Dermatology. 4th ed. China: Elsevier; 2018.
3. Lehrhoff S, Pomeranz MK. Specific dermatoses of pregnancy and their treatment. Dermatol Ther. 2013;26(4):274–84.
4. Ambros-Rudolph CM. Dermatoses of pregnancy - clues to diagnosis, fetal risk and therapy. Ann Dermatol. 2011;23(3):265–75.
5. Kroumpouzos G. Specific dermatoses of pregnancy: advances and controversies. Expert Rev Dermatol. 2010;5(6):633–48.
6. Kroumpouzos G, Cohen LM. Specific dermatoses of pregnancy: an evidence-based systematic review. Am J Obstet Gynecol. 2003;188(4):1083–92.
7. Trivedi MK, Vaughn AR, Murase JE. Pustular psoriasis of pregnancy: current perspectives. Int J Women's Health. 2018;26(10):109–15.

Chapter 3
Skin in Pregnancy

Shital Poojary and Kavya Badireddy

3.1 Physiological Skin Changes in Pregnancy

3.1.1 Introduction

Pregnancy or gravid state is associated with a temporary shift of hormonal, endocrinological, immunological, metabolic, and vascular factors leading to multitudinous systemic and cutaneous changes [1]. Physiological alterations in the skin and its appendages frequently appear in the early stages of gestation, causing significant impact on quality of life [2]. It is also imperative to distinguish the physiological changes from specific pregnancy dermatoses as some of the latter can cause serious risk to both the mother and the fetus or either of them [3]. Majority of the physiological skin changes resolve after child birth or require only conservative management [4]. Early recognition and accurate diagnosis of these changes are thus essential to improve the outcome in pregnant women while avoiding unnecessary treatment [5].

3.1.2 Pigmentation

Skin hyperpigmentation is one of the most common physiological changes seen during pregnancy and is observed in some form and intensity in all pregnant women, usually in discrete areas or patterns [6]. The new hormonal milieu of pregnancy with

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increased pituitary, ovarian, and placental hormones, i.e., melanocyte-stimulating hormone, β-endorphins, estrogen, progesterone along with bioactive sphingolipids enhanced tyrosinase activity is chiefly responsible for stimulating melanin production [1, 7]. These physiological pigmentary changes are more marked in skin of color; the intensity and distribution, however, is largely determined by genetic predisposition, environmental factors, and ultraviolet exposure [2].

Pigment accentuation of normally hyperpigmented anatomic sites is observed in almost all pregnant women and is among the first manifestations seen in pregnancy. This accentuated pigmentation is the result of an increase in number and sensitivity of melanocytes to hormonal stimulation in these regions.

It is most often appreciated in the nipple and areolar region [8] (Fig. 3.1). This hyperpigmented area gradually enlarges as pregnancy progresses, leading to the development of a new outer zone of pigmentation which is termed as secondary areola [9]. Genitals, perineum, axillae, inner thighs, and periumbilical skin also get affected. Skin folds and intertriginous sites can also become dark and pigmented.

Pigmentation fades postpartum; however, prepregnancy color may not be attained [1].

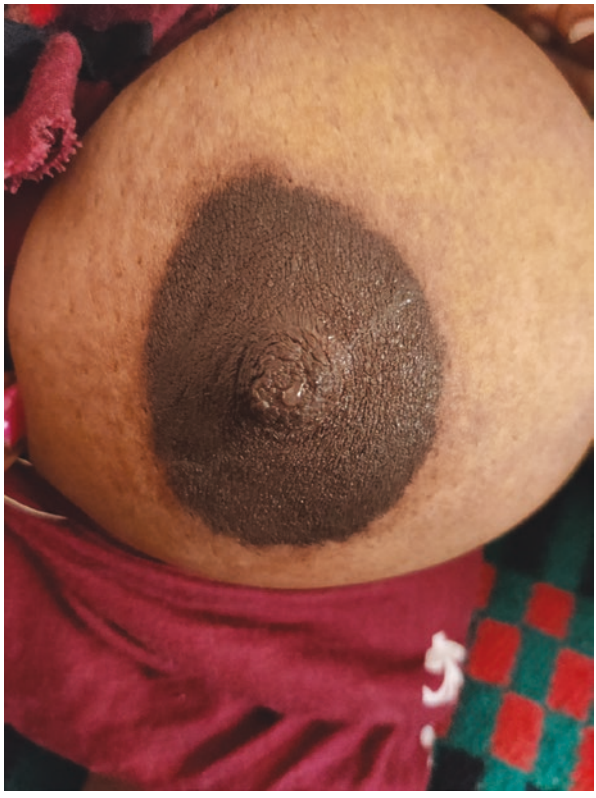

Fig. 3.1 Pigmentation of areola in pregnancy

Acanthosis nigricans can occur de novo in some pregnant women or there can be an exacerbation of pre-existing lesions when there is concomitant insulin resistance or gestational diabetes (Fig. 3.2).

Linea nigra refers to the hyperpigmentation of linea alba, a blended aponeurosis that runs vertically down the midline of the abdomen from the symphysis pubis to the xiphisternum with the umbilicus at or below its center [10]. The darkening and hyperpigmentation is generally more notable below the level of umbilicus; however it may also extend around and above it [8] (Fig. 3.3). There is frequent displacement of the umbilicus to the right, and this shift is known as the "ligamentum teres sign" [10]. Longitudinal melanonychia, benign linear pigmentation of the nail plate, may affect multiple fingers and/or toenails in pregnancy and is thought to result from the activation of nail matrix melanocytes. Pigmentation may fade or persist postpartum, sometimes recurring in following pregnancies. Irregular pigmentation or cuticular involvement warrants a thorough examination [11].

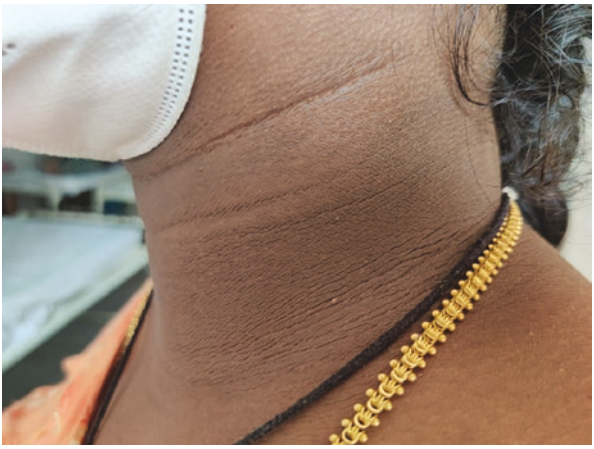

Fig. 3.2 Acanthosis nigricans in pregnancy

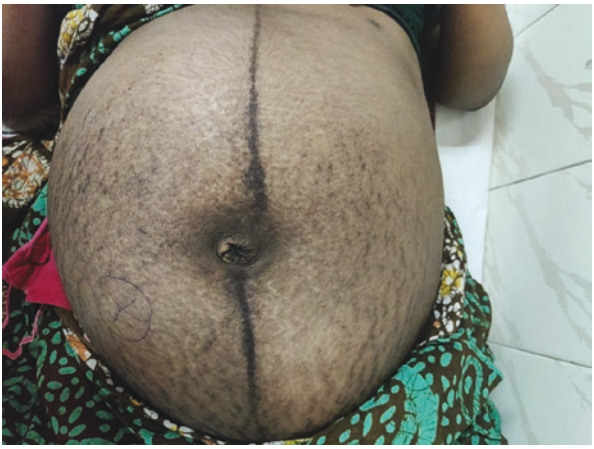

Fig. 3.3 Linea nigra, pigmentation of umbilicus and striae gravidarum

Pigmentary demarcation lines also known as Futcher's lines and Voigt's lines are sharp physiological lines demarcating areas of hyperpigmentation from normal skin [12]. Type B pigmentary demarcation lines are seen along the posterior aspect of lower limbs. They generally appear in the third trimester and regress after delivery [13]. The hormonal alterations, neurogenic inflammation secondary to trapping of cutaneous nerves by the enlarging uterus, genetic factors, and differential distribution of melanocytes on dorsal and ventral sides for better sun protection are possible factors that are likely to be involved in their development [14].

Freckles and scars that are fairly new also tend to darken during pregnancy. There are contradictory reports on the enlargement and darkening of melanocytic nevus in the gestation period and this area requires further research [15]. Any lesion with changes suspicious of melanoma should be immediately biopsied and assessed regardless of the site or gestational age [16].

Generalized mild hyperpigmentation occurs in pregnant women with Fitzpatrick skin type 1 or 2 [6].

3.1.2.1 Melasma

Pregnancy-related melasma commonly described as chloasma is characterized by light to dark brown, blotchy, irregular patches present symmetrically on photoexposed areas, especially face [17]. It usually starts to develop in the second trimester and reportedly affects 65–75% of pregnant women. It can occur on the malar, mandibular, or centrofacial regions of the face.

Nose and cheeks are the most frequently involved areas followed by the forehead, upper lip, and chin (Fig. 3.4). Forearms and other photoexposed areas can also sometimes get involved. Increased sun exposure, genetic predisposition, cosmetic usage, and elevated melanocyte-stimulating hormone, estrogen, and progesterone are the underlying causative factors [17]. Chloasma usually resolves completely after treatment within one year after delivery. Occasionally, spontaneous and complete remission may occur.

Some pigmentary sequelae are reported in about 30% of women. Pigmentation is found to be more persistent in dermal melasma and in women on oral contraceptives and may cause considerable impact on cosmetic appearance leading to psychosocial and emotional distress [18]. Melasma often tends to recur in subsequent pregnancies. Multiple pregnancies increase the possibility of melasma developing for the first time during pregnancy [17]. Sunscreen usage and prevention of photoexposure are strongly recommended during pregnancy to prevent the development or worsening of melasma [19]. Hydroquinone and topical tretinoin, though effective in treating melasma, are pregnancy category C drugs and better deferred during this period. Corticosteroids, chemical peels, and microdermabrasion can be tried after delivery. There is scarcity of literature on the usage of lasers during pregnancy [20].

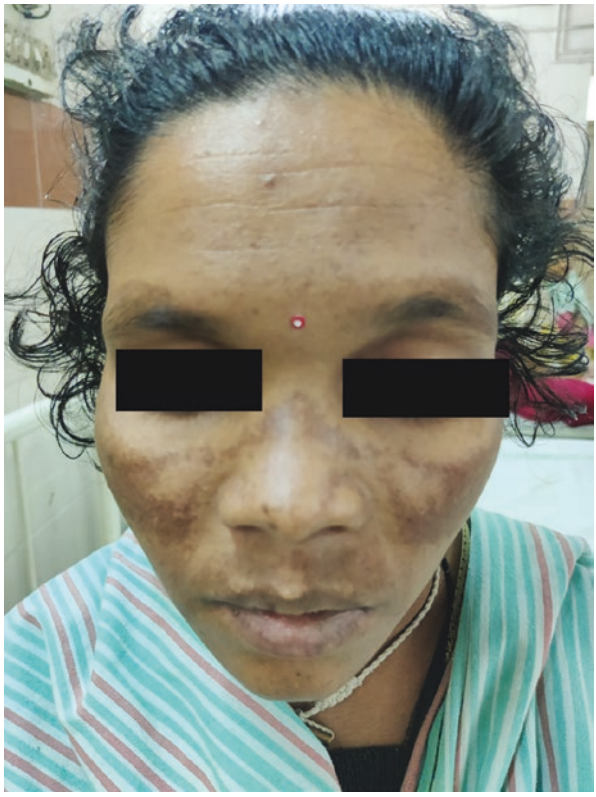

Fig. 3.4 Melasma in pregnancy

3.1.3 Vascular Changes

Vascular changes are congruent with pregnant state and arise in almost all pregnant women. Majority of these vascular changes resolve within few months after delivery. However, in some women these changes can lead to significant cosmetic consequences [21].

3.1.3.1 Varicosities

The physiological vascular adaptions of pregnancy secondary to elevated hormones and angiogenic factors lead to high circulating blood volume, increased proliferation and dilatation of cutaneous blood vessels, congestion, and hyperemia. These changes, together with progesterone-induced reduction of venous return secondary to partial compression of the inferior vena cava by enlarging the uterus, reduced plasma colloid osmotic pressure, and a hereditary predisposition are all responsible for the development of venous insufficiency, varicosities, and edema during pregnancy [21].

Varicosities involving the saphenous system, hemorrhoidal, vulvar, and vaginal networks occur in about 40% of pregnant women (Figs. 3.5 and 3.6). Of these, Varicosities of the lower limbs are the most frequent to occur and they characteristically present as edema, heaviness of legs, pain, night cramps, and paresthesias [22]. The skin surrounding the varicosities may also become hyperpigmented, itchy, and over a period of time develop eczematous changes resulting in varicose or gravitational eczema [23]. These symptoms tend to worsen with standing and with subsequent pregnancies.

Hemorrhoidal varicosities can bleed, become painful, and also commonly undergo thrombosis during pregnancy [24]. (Although uncommon in pregnancy, complications that can arise from varicose veins include venous ulcer, bleeding from the vein, inflammation or thrombophlebitis, deep vein thrombosis, and

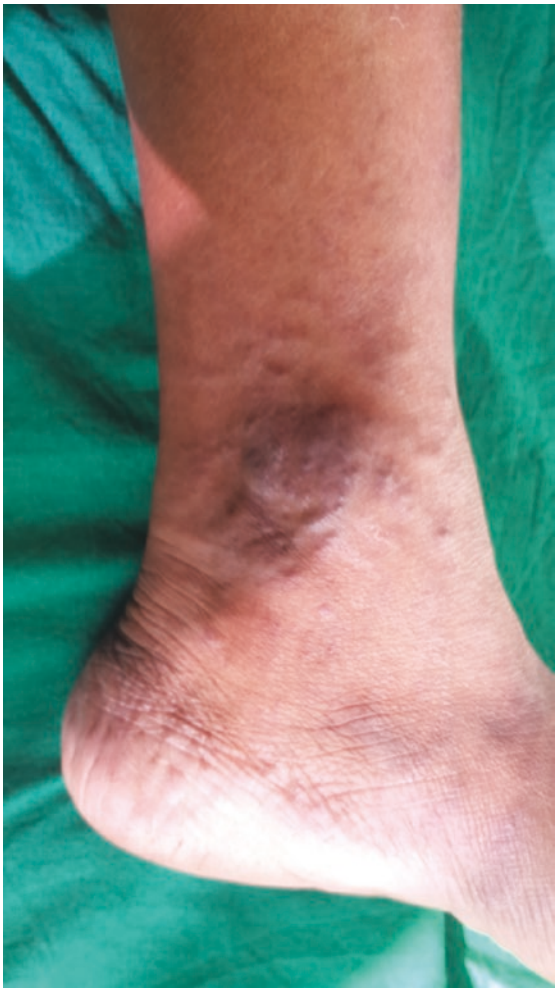

Fig. 3.5 Varicosities around ankle in pregnancy

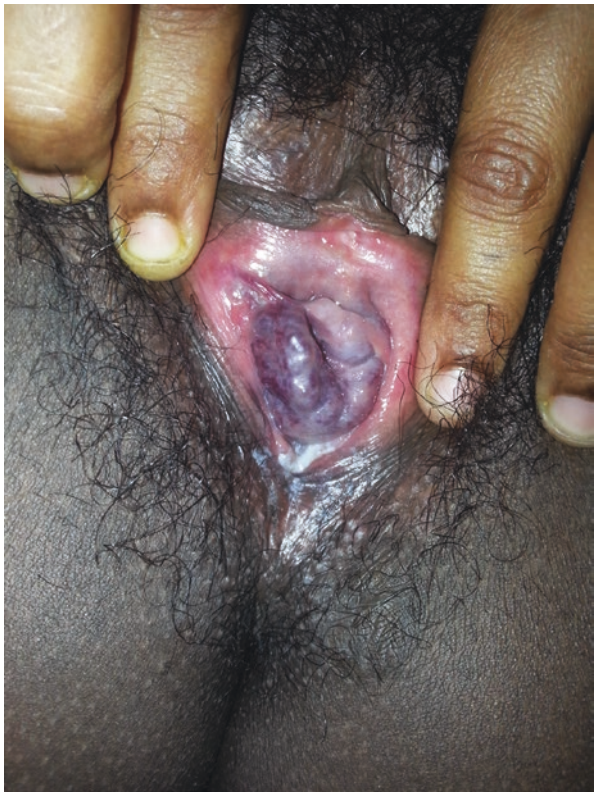

Fig. 3.6 Vulvar and vaginal varicosities in pregnancy

pulmonary embolism [25]) Varicosities improve three to four months post-delivery. Conservative measures like leg elevation, elastic compression stockings, and avoidance of prolonged standing suffice during pregnancy. Medical management with rutoside trihydrate has shown to alleviate the symptoms in severe cases. Sclerotherapy is hazardous and has to be strictly avoided during pregnancy [26]. Vein stripping and vascular surgery can be done postpartum [25].

3.1.3.2 Edema of Pregnancy

Nonpitting edema is found in 80% of pregnancies and occurs due to hormone-induced retention of salt and water, enhanced vascularity, and capillary permeability. Caval compression by the enlarging the uterus further exacerbates it [25]. It is usually noted during the third trimester and continues to progress with pregnancy. The edema is most conspicuous in the lower extremities and during early morning; however, edema may also manifest in periorbital area, hands, and face (Fig. 3.7). This edema is benign in nature and can be reduced by taking rest, leg elevation, use of compression stockings, and by sleeping in the left lateral decubitus position. The edema can also manifest in the complication of carpal tunnel syndrome.

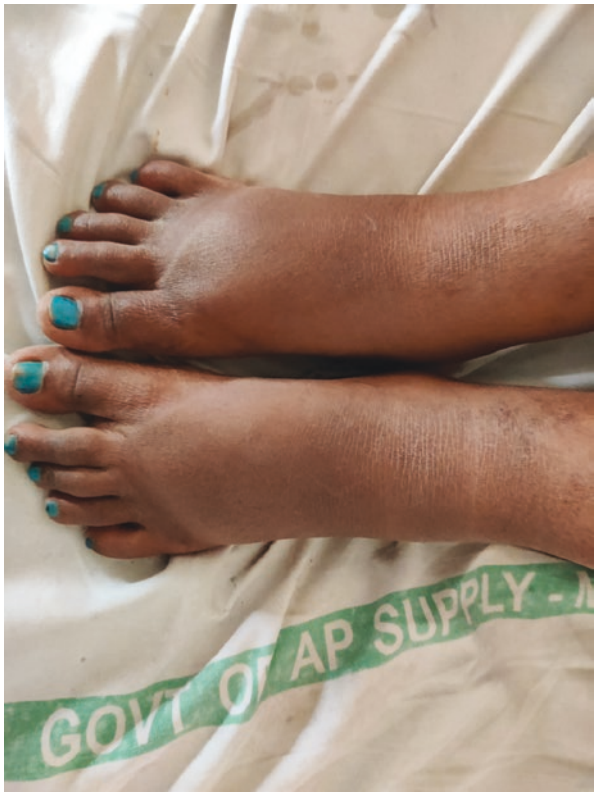

Fig. 3.7 Pitting edema, both legs in pregnancy

Persistent edema along with high blood pressure and proteinuria can be a sign of cardiac, renal, and preeclamptic edema and calls for further examination [27].

3.1.3.3 Spider Angioma

Spider angioma (syn: vascular spider, spider nevus, arterial spiders, nevi aranei) is the most common vascular change in pregnancy. It consists of a central, small, flat/raised, blanchable, faintly pulsating arteriolar telangiectatic puncta, surrounding erythema and extensions of fine thin-walled vessels that radiate outward like a spider's web. They commonly arise in the vascular territory of the superior vena cava such as the neck, face, throat, and arms during second and fifth months of pregnancy and continue to increase in number and size throughout pregnancy. Circulating plasma estrogen-induced anomalous dilatation of end vasculature is the main pathomechanism for their occurrence [28]. About 75% of these regress, although not completely by three months post-delivery. Recurrences in subsequent pregnancies are also reported. For the lesions that tend to persist, low voltage electrodessication at the center of the punctum gives good cosmetic outcome [29].

3.1.3.4 Palmar Erythema

Palmar erythema occurs commonly in the first trimester of pregnancy. It is often seen occurring together with spider angioma in the same patient. Increased estrogen, increased blood volume and flow, and genetic predisposition are all the possible underlying factors. It can either present as a localized area of erythema strictly confined to the thenar and hypothenar eminences or as mottled erythema involving the entire palm. Palmar erythema resolves quickly within a week post-delivery [30].

Multiple telangiectasias and unilateral nevoid telangiectasias may also develop secondary to increased estrogen levels [6]. Hemangiomas, subcutaneous hemangioendotheliomas, glomangiomas, petechiae and purpura may have an onset during pregnancy or already pre-existing lesions can exacerbate [4].

Cutis marmorata, a transient bluish mottling of the skin on cold exposure, can manifest on the legs in pregnancy due to elevated estrogen-induced vasomotor instability (Fig. 3.8). If cutis marmorata persists post-delivery, it is advisable to investigate for any underlying blood dyscrasia, collagen vascular disorder, or neoplastic disease [2]. Flushing, pallor, and paresthesias are other manifestations of vasomotor instability. Increased permeability and fragility of capillaries can result in purpura on the lower extremities in the latter half of pregnancy [21].

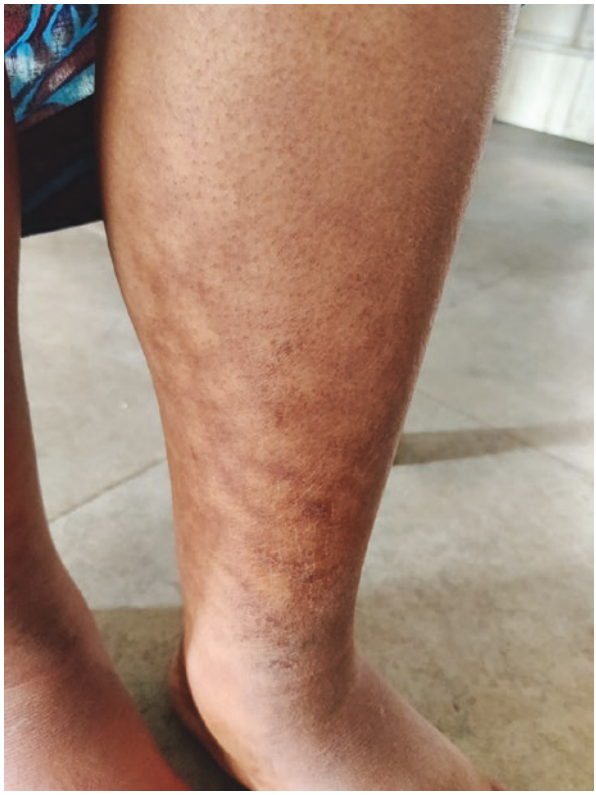

Fig. 3.8 Cutis marmorata in pregnancy

3.1.4 Connective Tissue Changes

3.1.4.1 Striae Distensae

Striae gravidarum is the most frequently noticed change affecting the connective tissue and is seen in 55% to 90% of women during the late second and early third trimester. They first appear as flat/raised pink to violet-red (striae rubra) bands along skin tension lines on the abdomen, breast, hips, and thighs [31]. They enlarge and become longer and wider with the progression of pregnancy, and over a period of months to years postpartum they gradually fade away forming atrophic, hypopigmented linear scars (striae alba).

Hormonal factors, increased maternal weight gain, genetic predisposition, and mechanical stress on the connective tissue are the causative factors of the abnormalities (Fig. 3.9) of elastic fibers, collagen, and other extracellular matrix components [32, 33]. Histologically, there is decreased adhesiveness between the collagen fibrils, increased ground substance, rupture, and retraction of elastic fibers within the reticular dermis [34]. Although mostly asymptomatic except for occasional itching and burning reported in a few, they can still be a substantial cause of cosmetic concern and decreased quality of life. Preventive measures such as application of

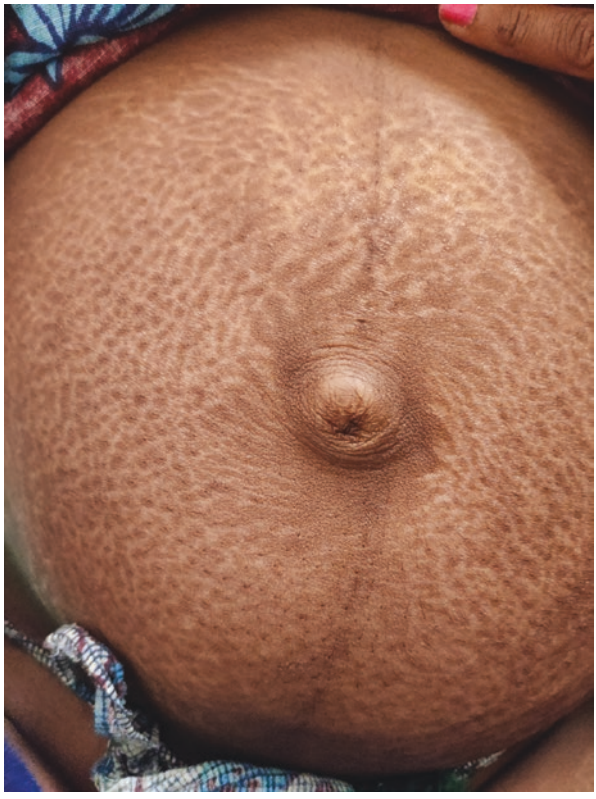

Fig. 3.9 Striae distensae

almond oil, olive oil, and hyaluronic acid have all been reportedly tried with limited success. Post-delivery treatment with topical tretinoin, glycolic acid, ascorbic acid or microneedling, microdermabrasion, radiofrequency ablation, fractional nonablative and nonfractional lasers can result in some improvement [35, 36].

Molluscum fibrosum gravidarum are benign, small, pedunculated, tan-to-brown, fleshy skin tags that develop on the face and in intertriginous areas during the second trimester [37].

Pregnancy leads to an increase in size and number of pre-existing neurofibromas. Also, eruptive neurofibromas appearing during pregnancy may be seen as an initial presentation of neurofibromatosis. Increased hypertensive and cerebrovascular complications are known to be associated with neurofibromatosis in pregnancy. In majority of cases, only partial regression of neurofibromas is seen postpartum. Complete resolution is not reported [38]. Increased estrogen levels cause worsening of keloids, cellulite, leiomyoma, and dermatofibroma during pregnancy [39].

3.1.5 Glandular Activity

The modifications of maternal immune functions and glandular functions by pregnancy have its repercussions on glandular skin diseases. Glandular dermatoses of sebaceous and eccrine origin are usually aggravated while those involving the apocrine glands are reported to improve during gestation [40].

3.1.5.1 Eccrine Glands

Increased thyroid activity and relative iodine deficiency in pregnancy give rise to increased eccrine gland activity in later stages of pregnancy. In addition, increased vasomotor activity due to altered functioning of the autonomic system and abnormal weight gain leads to excessive sweating leading to an increased development of hyperhidrosis, pompholyx, and miliaria. However, the adrenocortical activity results in increased suppression of palmar digital sweating [41]. These physiological adaptations do not have any definitive treatment and if they are too troublesome, aluminum chloride hexahydrate 20% solution in ethyl alcohol can be applied on sweaty areas every night for one to two weeks [1].

3.1.5.2 Sebaceous Glands

The nature of acne during pregnancy is highly unpredictable; it often improves during the first trimester but is known to exacerbate during the third trimester under the influence of elevated androgens in the pregnant mother and the resultant heightened sebum production [42–44] (Fig. 3.10). Pregnancy-related hormonal and immunologic changes lead to the development of more inflammatory lesions often involving the

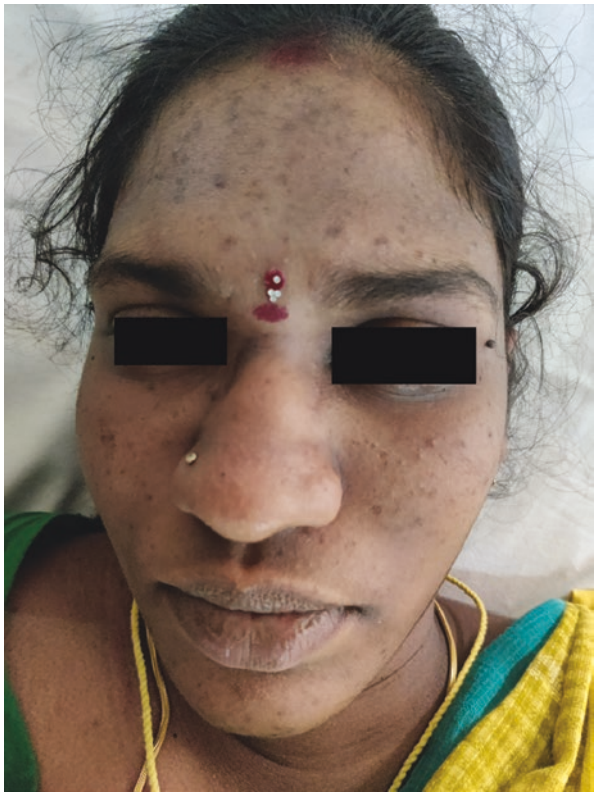

Fig. 3.10 Acne aggravated in pregnancy

trunk [42]. Women with prior acne have more propensity to manifest acne during pregnancy. Mild acne is treated with topical therapies such as benzoyl peroxide, azelaic acid, and topical antibiotics (clindamycin and erythromycin).

Oral erythromycin base or ethylsuccinate may be required to treat moderate to severe cases. Comedone extraction, mild superficial alpha-hydroxy acid peels, and microdermabrasion have been reported to cause no adverse effects. Salicylic acid is best avoided as systemic absorption is reported to occur. Safety data for laser modalities is inadequate [2].

3.1.5.3 Apocrine Glands

Fox-Fordyce disease and hidradenitis suppurativa are two apocrine disorders that were reported to have good remissions during pregnancy with chances of rebound post-delivery [45]. Apocrine glands are commonly found in the resting state and secrete less during pregnancy, and this effect on the functional activity of apocrine glands is the key reason behind the amelioration of apocrine gland disease in pregnancy.

3.1.6 Hair Changes

There can be increased or decreased hair growth under the influence of pregnancy hormonal changes. About 80% of scalp hairs are generally in the anagen phase of hair cycle. In pregnancy there is an even more increase in this number of anagen hairs because of decreased conversion of hairs from anagen to telogen phase [46]. Thus, hair is thicker and denser with increased shaft diameter throughout pregnancy [47]. Post-delivery, hormonal alterations cause all these anagen hairs to enter into the telogen phase simultaneously. Subsequently, shedding of this telogen hair causes diffuse hair loss (telogen effluvium) starting one to five months postpartum and may continue up to one to two years [48]. Mostly, there is excellent recovery with complete regrowth and reassurance is all that is required. Some women may rarely experience frontoparietal recession or male-pattern alopecia in late pregnancy. Complete regrowth of the shed hair does not usually happen in this minor group of patients [2].

3.1.6.1 Hirsutism

Male-pattern terminal and vellus hair growth involving the face, chest, lower abdomen, arms, and legs is seen in many pregnant women, particularly in women with darker hair [46]. Elevated ovarian and placental androgens influencing the pilosebaceous unit are thought to be responsible for the patterned hair growth. The terminal hairs are mostly permanent whereas the soft fine hairs regress to some extent within six months postpartum. Laser can be used to remove the persistent hair postpartum [49].

3.1.7 Nail Changes

Nail changes in pregnancy are seen in 2% to 40% of gravid women. Leukonychia, white spots on the nails, is the most common nail alteration reported and it can present as punctate, striate, partial, or total forms. Onychocryptosis (ingrown toenail), the second commonest nail change encountered, occurs due to increased weight gain. It causes paronychia with granulation tissue formation and tenderness of the involved digit. Onychoschizia (splitting of distal free end of nails), onycholysis, and brittleness of nail may arise due to accelerated growth and softening of the nail plate. Subungual hyperkeratosis, Beau's lines (transverse grooves on nail plate), and onychomycosis have also been reported. Koilonychia (spoon nail) is seen in anemic pregnant women with iron deficiency. Uniform, symmetrical melanonychia (pigmented nails) is often known to occur during pregnancy and it fades postpartum [50]. However, irregular pigmentation with cuticle involvement warrants a thorough

dermatological examination for evaluation of possible melanoma. Some studies have reported an increase in nail plate thickening rather than an increase in the nail growth [11].

3.1.8 Breast

The mammary gland/breast undergoes extensive anatomical and physiological changes to prepare for lactation. In early pregnancy, under the influence of elevated estrogen, vascular proliferation, increased blood flow, new duct formation and branching occur. Increased progesterone during the latter half of pregnancy induces lobular hyperplasia, involution of the breast's fibrofatty tissue, and distension of acini with colostrum. All these changes present clinically as progressive increase in the volume, firmness, nodularity of the breast tissue, tenderness, prominence of veins, striae, areolar and nipple enlargement, with/without nipple sensitivity [1] (Fig. 3.11).

Hyperkeratosis of the nipple and areola appears as bilateral, brown, pigmented, hyperkeratotic, hard warty crusts/plaques mostly involving the tip of the nipple (Fig. 3.12). These lesions tend to improve after delivery and can at times be persistent postpartum causing difficulty in breast feeding. Recurrence and worsening of the condition in subsequent pregnancies is also reported. In severe cases the treatment is challenging and unsatisfactory [51].

As discussed earlier, the nipple and areola may darken along with the formation of secondary areola and Montgomery's tubercles. Montgomery's tubercles represent hypertrophic sebaceous glands and are seen as circularly arranged small yellowish papules near the peripheral border of the areola (Fig. 3.13). Their secretions help lubricate the nipple-areolar complex and also serve as olfactory stimulus for the newborn to breast feed [10].

Fig. 3.11 Enlargement of nipple and areola

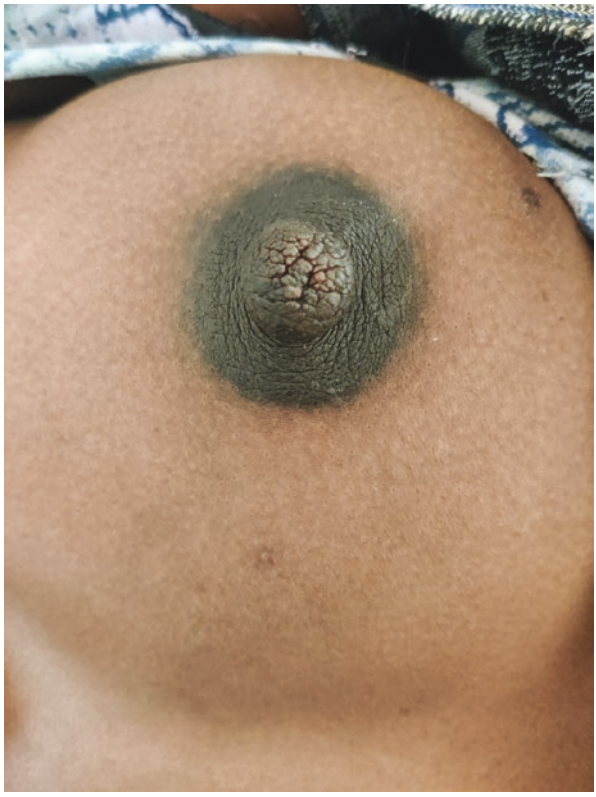

Fig. 3.12 Severe nipple hyperkeratosis with fissuring

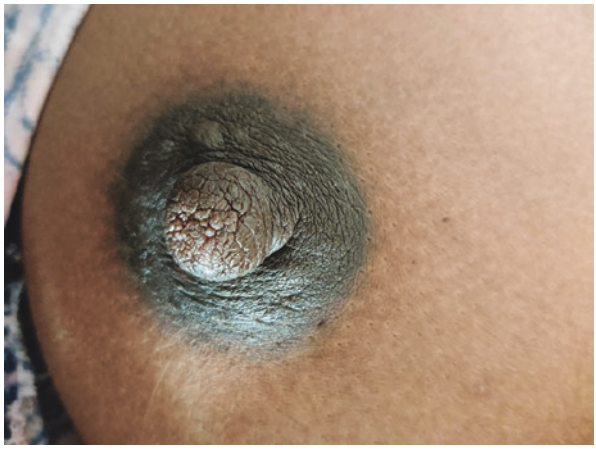

Fig. 3.13 Montgomery tubercles with nipple hyperkeratosis

3.1.9 Mucosa

Bluish-purple discoloration of the vaginal or cervical mucosa, known as the Chadwick's sign, is among the earliest signs observed during pregnancy. It occurs as a result of increased blood supply to the area [52].

Gingivitis is very common in pregnancy, affecting 30 to 100 percent of pregnant women. It usually first appears during the second month, increases through the eighth month, and disappears postpartum. Its development is initiated by dental plaque and exacerbated by endogenous steroid hormones. Significant worsening of pre-existing gingivitis or periodontitis is also known to occur in pregnancy [40]. The fluctuation in estrogen and progesterone levels exerts an influence on subgingival microbiota and ensues a spectrum of inflammatory response through alterations in chemotaxis, cytokine profile, release of proinflammatory enzymes and antioxidants from neutrophils, periodontal ligament cells, and gingival fibroblasts. Bleeding upon probing or mechanical stimulation, severe hyperplasia, increased periodontal probing depths, and gingival crevicular fluid flow are all the characteristic features of pregnancy gingivitis [6].

Pyogenic granuloma of the nasal or oral mucosa, a reactive inflammatory lesion, occurs in up to 5% of pregnancies and is therefore commonly referred to as "pregnancy tumor" and "granuloma gravidarum." Pregnancy hormonal fluctuations and exposure to low-grade irritants are the possible pathomechanisms behind its development. It has a potential for rapid growth and spontaneous bleeding. Expectant management is possible as it resolves after delivery. Maintenance of good oral hygiene and periodical dental check-ups during pregnancy are highly effective in combating this condition [53].

Hemangiomas, benign tumors of thin-walled blood vessels, have an increased incidence during pregnancy and can affect any organ or system. The increased estrogen levels aid in vascular proliferation and hemangioma formation [40]. Although most of these do not pose serious problems, hemangiomas of the central nervous system and abdominal viscera are reported to cause dangerous complications like severe blood loss, shock, and very rarely even maternal death [29].

Raised abdominal pressure and hormonal changes of pregnancy lead to the swelling and enlargement of external hemorrhoidal veins [29]. About 25% to 35% of pregnant women develop hemorrhoids and the incidence rises further up to 85% in the third trimester. Pruritus, burning, painful swellings at the anus, dyschezia, and bleeding are the symptoms associated with hemorrhoids. Spontaneous resolution of most of hemorrhoids occurs soon after delivery. Postpartum interventions such as vein stripping, hemorrhoidectomy, and sclerotherapy will be needed only for serious cases. Conservative measures will help relieve most symptoms during pregnancy and include administration of stool softeners and increasing the intake of liquids and fiber content of the diet. Proper bowel habits, hot sitz baths, astringent compresses, laxatives, suppositories, and topical anesthetic creams will also provide symptomatic relief. Appropriate management is however crucial to prevent more grave complications such as thrombosis and prolapse [54].

Nasal physiology is altered by hormonal changes during pregnancy; increased estrogen levels cause edema of the nasal mucosa, vascular congestion, and recurrent rhinitis (rhinitis of pregnancy) in 20% of pregnant females [55].

Tear film physiology is disturbed by pregnancy leading to the development of dry eye. Prolactin, epidermal growth factor, and transforming growth factor beta-1 induced direct destruction of acinar cells and immune reaction in the lacrimal duct cells are the hypothesized pathomechanisms responsible for dry eye. Dryness can be further exacerbated by dehydration [56]. Dry mouth from decreased salivary secretion may also develop [52].

3.2 Dermatologic Drugs in Pregnancy

During pregnancy drug prescriptions have to be personalized according to individual needs taking into consideration maternal and fetal risks. A thorough risk-benefit analysis is essential.

Factors affecting use of drugs in pregnancy:

- Timing of drug usage: Before conception, 1st/2nd/3rd trimester
- Essentiality to treat the dermatological disease
- Nature of the drug and adverse effects
- Risk assessment

In 2014: The US Food and Drug Administration (US FDA) issued the pregnancy and lactation labeling rule (PLLR) replacing the earlier guidelines with pregnancy categories W.E.F June 30, 2015. The older pregnancy categorization and new PLLR rule are depicted in Tables 3.1 and 3.2 respectively.

Table 3.1 Pregnancy categories according to the FDA

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits
N	Drug has not been classified

Table 3.2 New pregnancy and lactation labeling rule (PLLR)

Subsections	
Pregnancy	
1. Pregnancy exposure registry	
2. Risk summary	(a) Risk statement based on human data (b) Risk statement based on animal data (c) Risk statement based on pharmacology
3. Clinical considerations	(a) Disease-associated maternal and/or embryo/fetal risk (b) Dose adjustments during pregnancy and the postpartum period (c) Maternal adverse reactions (d) Fetal/neonatal adverse reactions (e) Labor or delivery
4. Data	(a) Human data (b) Animal data
Lactation	
1. Risk summary	(a) Presence of drug in human milk (b) Effects of drug on the breastfed child (c) Effects of drug on milk production (d) Risk and benefit statement
2. Clinical considerations	(a) Minimizing exposure (b) Monitoring for adverse reactions
3. Data	
Females and males of reproductive potential	
	1. Pregnancy testing *2. Contraception* *3. Infertility*

The new rule contains descriptive subsections for usage of drugs during pregnancy and lactation. In addition the new rule contains a summary of the risks involved with using different drugs and supporting data that enables physicians to make informed prescribing choices during pregnancy and lactation [57, 58].

3.2.1 Topical Dermatology Drugs in Pregnancy

During pregnancy, topical medications are often preferred over oral medications keeping in view the lesser risk of systemic side effects. However the safety of topical drugs should also be considered especially when higher concentrations are used or in cases of usage over long durations [59]. Safety of topical drugs in pregnancy is described in Table 3.3 including original FDA categories and risk description (PLLR).

Table 3.3 Topical dermatology drugs in pregnancy

Topical drug name	US FDA Category	Pregnancy and lactation labeling rule
Topical corticosteroid	C	Mild to moderate corticosteroids are safe to use for limited period in pregnancy Very potent corticosteroids for a long duration: Low birth weight babies
Nonsteroidal immunomodulators		
Tacrolimus	C	1. Poor systemic absorption due to large molecular size 2. Limited use on small areas permissible
Pimecrolimus	C	1. Lack of data in humans: Hence to be avoided 2. Can be used only if benefits outweigh risks and if no alternatives exist
Calcipotriene	C	1. Topical application: 6% of calcipotriene is absorbed (when applied on psoriatic plaques) 2. 5% on normal skin 3. Animal studies: Increased incidence of skeletal abnormalities 4. Limited human data with different recommendations on use: Most consider it to be safe to use in pregnancy on small areas
Crisaborole		1. Animal studies: No adverse effects reported 2. No data in pregnant women
Topical antifungals		
Ciclopirox	B	Animal studies: No adverse effects Limited human studies, likely compatible
Clotrimazole	B	Antifungal of choice for topical application and in pessary form
Miconazole	C	No adverse maternal and fetal events reported
Ketoconazole	C	Use safer alternatives such as clotrimazole and miconazole Use if benefits outweigh risks
Nystatin	C	No major adverse effects reported. Drug of choice for superficial candidiasis
Selenium sulfide	C	Can be used on limited area for limited period of time
Terbinafine	B	Systemic absorption is low. Permissible for use in small area
Topical antibiotics		
Clindamycin	B	Safe, no association with teratogenicity
Erythromycin	B	Limited data, no known fetal risks
Sulfacetamide	C	Limited data, no known fetal risks
Metronidazole	B	Human data: Low risk, permissible for use
Mupirocin	B	Use in small quantities and on limited area is not teratogenic
Bacitracin	C	Limited data, no known fetal risks
Polymyxin B	B	Limited data, no known fetal risks
Neomycin	C	Limited data, no known fetal risks
Retapamulin	B	Animal studies: Incomplete ossification after oral administration However, with topical application very low plasma concentration is achieved suggesting little to no risks

(continued)

Table 3.3 (continued)

Topical drug name	US FDA Category	Pregnancy and lactation labeling rule
Antiscabetic/antipediculocide		
Benzoyl benzoate	C	1. Benzyl alcohol, a metabolite of benzoyl peroxide, is associated with fatal intoxication in neonates or "gasping syndrome" from rinsing venous catheters. Hence, banned in the United States 2. No reported adverse outcomes in pregnancy
Crotamiton	C	Animal studies: Likely safe Limited human data
Lindane	C	Should be avoided, potentially neurotoxic
Malathion	B	To be avoided if possible
Permethrin	B	Drug of choice, first-line treatment for scabies and lice No evidence of adverse effects
Precipitated sulfur	C	Limited animal and human studies. Relatively safe. To be given only when benefits outweigh risks
Topical antiacne preparations		
Adapalene	C	1. Animal studies: No fetotoxicity, minimal increase in incidence of supernumerary ribs and delayed ossification 2. No human data 3. To be avoided in pregnancy
Azelaic acid	B	1. 4% absorbed systemically after one topical application 2. Animal studies: No teratogenic potential even in high doses 3. Limited human studies 4. Can be used only on small skin areas and to be avoided in the first trimester
Benzoyl peroxide	C	1. No animal/human data 2. Only 5% is absorbed systemically 3. Industrial use: Exposure: No indications of teratogenic effects 4. Some authors recommend use in limited areas
Tretinoin	C	1. Early case reports: Ear, CVS, and neurological complications 2. Larger studies: No teratogenic potential 3. Animal studies: Bone abnormalities 4. Avoid use in pregnancy
Tazarotene	X	1. Tazarotene: Category X; contraindicated in pregnancy 2. Approximately 6% of tazarotene is absorbed systemically after topical application 3. In animal studies: Reduced fetal body weights, reduced skeletal ossification, spina bifida, hydrocephaly, CVS abnormalities 4. Pregnancy test to be ordered before starting topical tazarotene in women of childbearing potential
Hair agents		
Minoxidil	C	1. Few case reports of fetal malformations: CVS, renal agenesis, esophageal atresia 2. Insufficient data 3. Use in pregnancy to be avoided
Hydroquinone	C	Human studies: No major fetal malformations or adverse effects. However it is advised to minimize exposure

Table 3.3 (continued)

Topical drug name	US FDA Category	Pregnancy and lactation labeling rule
Miscellaneous agents		
Anthralin	**C**	1. Animal studies: No data available 2. Human studies: No data available 3. Advised not to use in pregnancy
Salicylic acid	C	9–25% of the topically applied drug is absorbed systemically Not to be used in large amounts and under occlusion particularly in the third trimester due to reported adverse effects like closure of ductus arteriosus and oligohydramnios
Coal tar	C	1. Animal studies: High-dose maternal exposure resulted in perinatal mortality, and greater incidence of cleft palates, and small lungs in offspring 2. Human data: No reported teratogenic effects. Should ideally be avoided due to presence of mutagenic and carcinogenic hydrocarbons 3. No action required for incidental usage
Narrowband UVB Broadband UVB		1. Both are safe 2. Worsening of melasma reported, facial shielding depending on skin type 3. Decreased folic acid levels with both NBUVB and BBUVB known to occur, and folate deficiency in the first trimester could predispose to the development of neural tube defects (NTDs) 4. Folic acid levels to be measured prior to phototherapy and appropriate folic acid supplementation to be initiated
Methyl aminolevulinate	C	1. Animal data: Fetal ossification irregularities noticed 2. Human data: Limited
Liquid nitrogen		Safe, first-line treatment for human papilloma virus infection in pregnancy
Trichloroacetic acid	N	Safe, second-line treatment for human papilloma virus infection in pregnancy
Podophyllin	X	Strictly contraindicated. Heart, limb, and ear malformations, psychiatric complaints, and fetal and maternal deaths are reported to occur even though the systemic absorption is low
Camphor	C	1. Limited data in pregnant women 2. No adverse effects reported with external use in the first trimester 3. Safe for topical application
5-fluorouracil	X	1. Human data: About 6% of topically applied drug is absorbed systemically. Cleft lip, cleft palate, ventricular septal defects, and miscarriages are reported to occur 2. Absolutely contraindicated
Imiquimod	C	Minimal data available No teratogenic effects reported
Cantharidin	C	Limited human and animal data

3.3 Systemic Dermatologic Drugs in Pregnancy

3.3.1 Safety of Systemic Drugs in Pregnancy is Described in Table 3.4

3.3.1.1 **Biologicals in Pregnancy** (Table 3.5)

The existing evidence recommends the use of biologicals to treat psoriasis in pregnancy to circumvent any possible psoriasis-associated adverse outcomes. There is more data available on anti-TNF alpha agents compared to IL-12/23 and IL-17 inhibitors and hence anti-TNF alpha agents are preferred over the latter. The use of

Table 3.4 Systemic dermatology drugs in pregnancy

	Drugs	Category	Description of risk
I	Systemic immunomodulators		
	Systemic corticosteroids	C	Earlier studies have shown increased risk of cleft palate; hence steroids are to be avoided in the first trimester. However a recent study by Bandoli et al. did not show an increased risk of cleft abnormalities [60]. Steroids also have an increased risk of premature delivery, premature membrane rupture, intrauterine growth retardation, gestational diabetes, hypertension, preeclampsia, and eclampsia. Hence lowest effective steroid dose is recommended. 7.5 mg/day in prolonged usage. Avoid dosage > 20 mg/day
	Methotrexate	X	Methotrexate is a known teratogen and is absolutely contraindicated during pregnancy. Methotrexate is associated with miscarriage and congenital malformations, such as developmental delay and craniofacial, limb, cardiopulmonary, and gastrointestinal abnormalities. Methotrexate should be discontinued at least 3 months before conception
	Cyclosporine	C	Studies show no increased risk of fetal major malformations compared with the general population. However, there are reports of low birth weight and prematurity in babies of patients with complicated health status. Minimum possible dose should be administered with close monitoring of maternal blood pressure and renal function
	Hydroxychloroquine	C	Therapy of choice in pregnant patients with lupus. Studies have not found any increased risk of congenital anomalies
	Azathioprine	D	Risk of preterm delivery and low birth weight infants, and hematologic toxicities. Possible increased risk of atrial or ventricular septal defects. Can be used in pregnancy if benefits outweigh risks
	Cyclophosphamide	D	Cyclophosphamide embryopathy (growth restriction, ear and facial abnormalities, absence of digits, hypoplastic limbs, and developmental delay)

Table 3.4 (continued)

	Drugs	Category	Description of risk
	Mycophenolate mofetil	D	Contraindicated in pregnancy Teratogenic effects: Associated with miscarriages and congenital anomalies (microtia, external auditory canal atresia, cleft lip/palate, and finger, cardiac, renal, ocular, and central nervous system abnormalities), nonhormonal contraception to be used until 6 weeks after stopping treatment, as MMF lowers the efficacy of oral contraceptives
	Thalidomide	X	US boxed warning: May cause severe birth defects or embryo-fetal death Avoid pregnancy 4 weeks prior, during, and ≥4 weeks after therapy is discontinued
	Apremilast	C	No adequate studies in pregnant women. Animal studies have shown varying outcomes with one study showing increases in abortion/embryo-fetal death in monkeys BAD guidelines: Not to be taken in pregnancy Company prescribing information (FDA): Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
	Tofacitinib		Limited data available Use in pregnant women is to be avoided
	Acitretin	X	Contraindicated in pregnancy Known teratogen. Two forms of contraception advised, with avoidance of pregnancy 3 years after discontinuation
	Isotretinoin	X	Two methods of contraception or abstinence are essential at least 1 month prior, during, and 1 month after discontinuation. Associated with major fetal abnormalities, spontaneous abortions, premature births. Even a single dose can cause embryopathy
	Antihistaminics		The preferred choice in pregnancy is diphenhydramine and chlorpheniramine as these have been used for several years during pregnancy without much adverse effects. Loratadine, a nonsedating antihistamine, also has no major teratogenic risk Hydroxyzine may be associated with increased risk of congenital malformations Fexofenadine: No adequate data
	Chlorpheniramine	B	
	Diphenhydramine	B	
	Hydroxyzine	C	
	Cetirizine	B	
	Fexofenadine	C	
	Loratadine	B	
	Systemic antibiotics		
	Penicillins	B	Antibiotic of choice in pregnancy
	Cephalosporins	B	Older cephalosporins preferred
	Erythromycin Azithromycin	B	Safe in pregnancy Erythromycin estolate not to be used as it causes cholestasis
	Quinolones	C	To be avoided during pregnancy as it has been shown to cause damage to developing cartilage in experimental animal studies. Accidental administration is however not an indication for abortion
	Tetracyclines	D	Affects bone growth and causes teeth discoloration

(continued)

Table 3.4 (continued)

	Drugs	Category	Description of risk
	Rifampicin		No teratogenic effects. Can be used if benefits outweigh risks
	Sulfamethoxazole-trimethoprim	C	Possible increased risk of congenital malformations, preterm births. Avoid in G6PD deficiency
	Dapsone	C	No major risks to the fetus; however, risk of maternal anemia, and neonatal hyperbilirubinemia and hemolytic anemia. Use with caution
	Antifungals		
	Griseofulvin	C	Case reports of conjoined twins on use in pregnancy. Not to be used in pregnancy
	Itraconazole	C	Dose-related embryotoxicity and teratogenicity in the first trimester. In case of accidental use, fetal anomaly scan is essential. Risk of cardiovascular, skeletal, craniofacial, and neurodevelopmental defects
	Fluconazole	C	Dose-related embryotoxicity and teratogenicity in the first trimester. Risk of cardiovascular, skeletal, craniofacial, and neurodevelopmental defects. In case of accidental use, fetal anomaly scan is essential
	Ketoconazole	C	Dose-related embryotoxicity and teratogenicity in the first trimester. Risk of cardiovascular, skeletal, craniofacial, and neurodevelopmental defects. In case of accidental use, fetal anomaly scan is essential
	Terbinafine	B	Animal studies indicate low risk. Avoid use in pregnancy. If necessary can be used in the second trimester onwards
	Antivirals		
	Aciclovir	B	No adverse effects in pregnancy
	Valaciclovir	B	No adverse effects in pregnancy
	Famciclovir	B	Limited data available. Aciclovir and valaciclovir are preferred

anti-TNF alpha agents is restricted in the first half of pregnancy, and these drugs should not be used during the last trimester because of the risk of disseminated infections in infants following live vaccinations during that period [61].

Anti-TNF alpha agents (excluding certolizumab) are IgG1 antibodies or receptors attached to an Fc portion of an IgG1. IgG1 placental transfer is substantially increased in the third trimester [62].

Unlike adalimumab and infliximab, etanercept is a fusion protein and has minimal transfer across the placenta. Certolizumab is an Fc-free PEGylated TNF alpha inhibitor with negligible transfer across the placenta. The routine use of TNF alpha inhibitors during pregnancy is not recommended. They can nevertheless be used in severe and recalcitrant disease with caution.

Rituximab has been found to cause an increased risk of neonatal hematological abnormalities and is therefore not recommended for use in pregnancy. Transplacental passage of the drug gradually increases with due course of pregnancy and is minimal in the first trimester. It steadily increases by the second trimester and is

Table 3.5 Biologicals in pregnancy [65–74]

Name	Evidence and comments	2016 EULAR recommendation
Adalimumab	Data from usage in >500 pregnancies: No evidence of increased embryotoxicity, teratogenicity, or pregnancy loss [65] Manufacturer recommends contraception during therapy and within 5 months after end of treatment	If indicated, it can be used throughout pregnancy but preferred to stop at 20 weeks
Etanercept	Use in >300 pregnancies; no patterns of malformation or prematurity It is generally recommended over other antitumor necrosis factor alpha agents as it is a fusion protein However there is a single report of infant with VATER syndrome (vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, renal abnormalities, and limb anomalies) associated with use of etanercept during pregnancy [67] Increased rate of spontaneous abortion if etanercept is used during the first Trimester [68]	Therapy can be continued up to week 30–32 of pregnancy If indicated, it can be used throughout pregnancy
Infliximab	Usage in >1000 pregnancies: No evidence of increased incidence of malformation or prematurity [69]. However, manufacturer recommends contraception during treatment and for 6 months after last dose	Therapy can be continued up to week 20 of pregnancy
Ixekizumab	Limited clinical data of use in pregnancy. A study in animals showed no fetal adverse effects if administered within first 20 weeks of gestation but there were increased neonatal deaths when administered after 20 weeks of gestation [70]	
Ustekinumab	Limited data available [71–74]. Hence other biologicals are often preferred Manufacturer recommendation: Contraception in women of childbearing age group for at least 15 weeks after treatment	Insufficient evidence regarding the drug's safety during pregnancy May be used only if no other, safer options allow for adequate management of disease activity in the mother
Omalizumab	Limited clinical data available in pregnancy	
Certolizumab	Preferred biological in pregnancy A study on >1000 pregnant patients showed no teratogenicity or increase in fetal deaths [75]	EULAR task force advocated that further studies were warranted to confirm the safety of its use throughout pregnancy. If indicated can be used throughout pregnancy

(continued)

Table 3.5 (continued)

Name	Evidence and comments	2016 EULAR recommendation
Secukinumab	Limited clinical data available Animal studies have shown no adverse effects in fetus To be avoided during pregnancy Secukinumab should be stopped 19 weeks before conception (T1/2: 27 days)	
Dupilumab	Limited clinical data available. Dupilumab is a monoclonal IgG antibody; since IgG crosses the placenta, exposure to the fetus during pregnancy may occur	
Guselkumab	Since it is a monoclonal IgG antibody and can therefore cross the placenta; exposure to the fetus may occur if administered To pregnant women	
Rituximab	Not recommended in pregnancy Women to avoid pregnancy for at least 12 months after exposure due to long retention time Risk of B cell depletion and other cytopenias in neonate	Due to no sufficient data, it should be avoided if other therapy is available
Small molecules		
JAK inhibitor Tofacitinib	Animal studies: Membranous ventricular septal defects and skeletal/cranial malformations. Increase in post-implantation loss. Human studies did not show an increased risk to fetus on accidental exposures Current recommendation is to stop 2 months before conception [73]	
Apremilast	Insufficient data. To be avoided in pregnancy	

maximum by the third trimester and may also affect B-cell development in the fetus. Pregnancy should be avoided for at least a year post rituximab exposure.

It is recommended to avoid pregnancy for at least 12 months after rituximab exposure [63].

Ghalandari N et al. in a systematic review concluded that the risk of congenital fetal malformations with the use of infliximab, certolizumab pegol, and adalimumab in pregnancy is not significantly increased compared to the risk in general population. The risk in general population is about 2–5.5% [64]. The European Medical Agencies recently issued their conditional approval for the use of these drugs and etanercept during pregnancy based on the data obtained from pregnancy registries maintained by pharmaceutical companies.

Table 3.5 Depicts comments, Evidence, and EULAR (European League Against Rheumatism) Recommendations [64, 65]

3.3.2 Cosmetic Procedures in Pregnancy: Table 3.6 [76]

There is a relative dearth of data on the safety of cosmetic procedures in pregnancy. Thus procedures are often deferred until after delivery unless there is a strong therapeutic indication. Procedures are better performed with the patient lying in the left lateral decubitus position in order to avoid vascular compromise caused by pressure on the inferior vena cava.

Routine procedures such as biopsies and electrocautery can be performed in pregnant women.

Table 3.6 Cosmetic and surgical procedures in pregnancy

Procedure/drug	Pregnancy category	Comments
Local/topical anesthetics		
Lidocaine	B	1. Animal studies: No adverse events 2. Preferred choice in pregnancy 3. Safe when used in small amounts 4. Major concerns of lidocaine use during pregnancy: Accidental arterial injection and high-dose use of lidocaine as these can result in an increased risk of fetal cardiac and central nervous system toxicity Use of epinephrine should be limited as there is risk of uterine artery spasms with the administration of increased doses of epinephrine
Benzocaine, bupivacaine, mepivacaine, and tetracaine	C	Benzocaine can cause methemoglobinemia in infants Mepivacaine during the first trimester associated with congenital anomalies
Topical prilocaine	B	1. Animal studies: No adverse events 2. Preferred choice in pregnancy 3. Safe when used in small amounts
Chemical peels Glycolic acid peels: Lactic acid peels: Salicylic acid peels:	C	Relatively safe, limited dermal penetration Reports of safe use for gestational acne, limited dermal penetration Significant dermal penetration, limit use to small areas
Botox	C	Case reports of use in pregnancy have not reported any adverse effects in majority High doses of onabotulinum toxin (N600U) associated with systemic weakness. Insufficient evidence for definite recommendation
Fillers		Insufficient evidence for definite recommendation Not to be used in first trimester and after week 36
LASER		Insufficient evidence for definite recommendation Carbon dioxide and Nd YAG lasers have been used safely to treat condylomata acuminata in pregnant patients in several reports

With regard to cosmetic procedures, chemical peels, glycolic and lactic acid peels are considered safe whereas trichloroacetic and salicylic acid peels are recommended to be best avoided or used with caution.

There is scarcity of safety data on botulinum toxin A. Systemic absorption and transfer across placenta has been found to be minimal. Botulinum toxin A has been used for medical indications such as spasticity in pregnancy without any adverse effects.

Sclerotherapy is considered safe during pregnancy; however it should be avoided during the first trimester and late in pregnancy after 36 weeks. Laser therapy has been performed for patients with genital warts without adverse effects. Laser epilation may be avoided during pregnancy and other options such as waxing and shaving may be preferred.

References

1. Tyler KH. Physiological skin changes during pregnancy. Clin Obstet Gynecol. 2015;58(1):119–24.
2. Nussbaum R, Benedetto AV. Cosmetic aspects of pregnancy. Clin Dermatol. 2006;24(2):133–41.
3. Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol. 2001;45:1–19.
4. Rathore SP, Gupta S, Gupta V. Pattern and prevalence of physiological cutaneous changes in pregnancy: a study of 2000 antenatal women. Indian J Dermatol Venereol Leprol. 2011;77:402.
5. Kumari R, Jaisankar TJ, Thappa DM. A clinical study of skin changes in pregnancy. Indian J Dermatol Venereol Leprol. 2007;73(2):141.
6. Wong RC, Ellis CN. Physiologic skin changes in pregnancy. J Am Acad Dermatol. 1984;10:929–40.
7. Snell RS, Bischitz PB. The effect of large doses of estrogen and progesterone on melanin pigmentation. J Invest Dermatol. 1960;35:73–82.
8. Bieber AK, Martires KJ, Stein JA, Grant-Kels JM, Driscoll MS, Pomeranz MK. Pigmentation and pregnancy: knowing what is normal. Obstet Gynecol. 2017;129:168–73.
9. Wong RC, Ellis CN. Physiologic changes in the skin during pregnancy. J Am Acad Dermatol. 1984;10:929–40.
10. Barankin B, Silver SG, Carruthers A. The skin in pregnancy. J Cutan Med Surg. 2002;6(3):236–40.
11. Altan Ferhatoglu Z, Goktay F, Yasar S, Aytekin S. Morphology, growth rate, and thickness of the nail plate during the pregnancy. Int J Dermatol. 2018;57(10):1253–8.
12. Zieleniewski L, Schwartz RA, Goldberg DJ, Handler MZ. Voigt-Futcher pigmentary demarcation lines. J Cosmet Dermatol. 2019;18(3):700–2.
13. Chandran V, Kurien G, Mohan V. Pigmentary demarcation lines in pregnancy. Indian J Dermatol. 2016;61(1):127.
14. Nakama T, Hashikawa K, Higuchi M, Ishii N, Miyasato M, Hamada T, Hashimoto T. Pigmentary demarcation lines associated with pregnancy. Clin Exp Dermatol. 2009;34(8):e573–6.
15. Chan MP, Chan MM, Tahan SR. Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index. J Cutan Pathol. 2010;37:843–51.
16. Trayanova E, Chokoeva AA, Tchernev G, Patterson JW, Wollina U, Lotti T. Dysplastic nevi, melanoma and pregnancy- where is the relationship? J Biol Regul Homeost Agents. 2015;29(1 Suppl):87–90.
17. Bolanca I, Bolanca Z, Kuna K, Vuković A, Tuckar N, Herman R, Grubisić G. Chloasma--the mask of pregnancy. Coll Antropol. 2008;32(Suppl 2):139–41.

18. Filoni A, Mariano M, Cameli N. Melasma: how hormones can modulate skin pigmentation. J Cosmet Dermatol. 2019;18(2):458–63.
19. Sarkar R, Ghunawat S, Narang I, Verma S, Garg VK, Dua R. Role of broad-spectrum sunscreen alone in the improvement of melasma area severity index (MASI) and Melasma quality of life index in melasma. J Cosmet Dermatol. 2019;18(4):1066–73.
20. Sarkar R, Arora P, Garg VK, Sonthalia S, Gokhale N. Melasma update. Indian Dermatol Online J. 2014;5(4):426–35.
21. Bean WB, Cogswell R, Dexter M, et al. Vascular changes of the skin in pregnancy. Surg Gynecol Obstet. 1949;88:739–52.
22. Saliba Júnior OA, Rollo HA, Saliba O, Sobreira ML. Graduated compression stockings effects on chronic venous disease signs and symptoms during pregnancy. Phlebology. 2020;35(1):46–55.
23. Subbarao NT, Aradhya SS, Veerabhadrappa NH. Sclerotherapy in the management of varicose veins and its dermatological complications. Indian J Dermatol Venereol Leprol. 2013;79(3):383–8.
24. Avsar AF, Keskin HL. Haemorrhoids during pregnancy. J Obstet Gynaecol. 2010;30(3):231–7.
25. Bamigboye AA, Hofmeyr GJ. Interventions for leg edema and varicosities in pregnancy. What evidence? Eur J Obstet Gynecol Reprod Biol. 2006;129(1):3–8.
26. Coles CM, Werner RS, Zelickson BD. Comparative pilot study evaluating the treatment of leg veins with a long pulse Nd:YAG laser and sclerotherapy. Lasers Surg Med. 2002;30:154–9.
27. Benninger B, Delamarter T. Anatomical factors causing oedema of the lower limb during pregnancy. Folia Morphol (Warsz). 2013;72(1):67–71.
28. Bean WB. Vascular spiders and related lesions of the skin. 59-77:Springfield: Charles C. Thomas: 1958;94–110.
29. Henry F, Quatresooz P, Valverde-Lopez JC, Piérard GE. Blood vessel changes during pregnancy: a review. Am J Clin Dermatol. 2006;7(1):65–9.
30. Bean WB, Cogswell R, et al. Vascular changes of the skin in pregnancy; vascular spiders and palmar erythema. Surg Gynecol Obstet. 1949 Jun;88(6):739–52.
31. Thomas RG, Liston WA. Clinical associations of striae gravidarum. J Obstet Gynaecol. 2004;24:270–1.
32. Chang ALS, Agredano YZ, Kimball AB. Risk factors associated with striae gravidarum. J Am Acad Dermatol. 2004;51:881–5.
33. Poidevin LOS. Striae gravidarum: their relationship to adrenal cortical hyperfunction. Lancet. 1959;274:436–9.
34. Watson REB, Parry EJ, Humphries JD, Jones CJ, Polson DW, Kielty CM, et al. Fibrillin microfibrils are reduced in skin exhibiting striae distensae. Br J Dermatol. 1998;138:931–7.
35. Rangel O, Arias I, Garcia E, Lopez-Padilla S. Topical tretinoin 0.1% for pregnancy-related abdominal striae: an open-label, multicenter, prospective study. Adv Ther. 2001;18:181–6.
36. Jimenez GP, Flores F, Berman B, Gunja-Smith Z. Treatment of striae rubra and striae alba with the 585-nm pulsed-dye laser. Dermatol Surg. 2003;29:362–5.
37. Templeton HJ. Cutaneous tags of the neck. Arch Dermatol Syph. 1936;33:495.
38. Terry AR, Barker FG 2nd, Leffert L, Bateman BT, Souter I, Plotkin SR. Neurofibromatosis type 1 and pregnancy complications: a population-based study. Am J Obstet Gynecol. 2013;209(1):46.e1–8.
39. Muallem MM, Rubeiz NG. Physiological and biological skin changes in pregnancy. Clin Dermatol. 2006;24(2):80–3.
40. Motosko CC, Bieber AK, Pomeranz MK, Stein JA, Martires KJ. Physiologic changes of pregnancy: a review of the literature. Int J Womens Dermatol. 2017;3(4):219–24.
41. MacKinnon PCB, MacKinnon IL. Palmar sweating in pregnancy. J Obstet Gynaecol Br Commonw. 1955;62:298–9.
42. Van Pelt HP, Juhlin L. Acne conglobata after pregnancy. Acta Derm Venereol. 1999;79:169.
43. Ratzer MA. The influence of marriage, pregnancy and childbirth on acne vulgaris. Br J Dermatol. 1964;76:165–8.

44. Burton JL, Shuster S, Cartlidge M. The sebotropic effect of pregnancy. Acta Derm Venereol. 1975;55:11–3.
45. Cornbleet T. Pregnancy and apocrine gland diseases: hidradenitis, Fox-Fordyce disease. AMA Arch Dermatol Syphilol. 1952;65:12–9.
46. Lynfield YL. Effect of pregnancy on the human hair cycle. J Invest Dermatol. 1960;35:323–7.
47. Nissimov J, Elchalal U. Scalp hair diameter increases during pregnancy. Clin Exp Dermatol. 2003;28:525–30.
48. Gizlenti S, Ekmekci TR. The changes in the hair cycle during gestation and the postpartum period. J Eur Acad Dermatol Venereol. 2014;28:878–81.
49. Liu K, Motan T, Claman P. No. 350-hirsutism: evaluation and treatment. J Obstet Gynaecol Can. 2017;39(11):1054–68.
50. Erpolat S, Eser A, Kaygusuz I, Balci H, Kosus A, Kosus N. Nail alterations during pregnancy: a clinical study. Int J Dermatol. 2016;55(10):1172–5.
51. Higgins HW, Jenkins J, Horn TD, Kroumpouzos G. Pregnancy-associated hyperkeratosis of the nipple: a report of 25 cases. JAMA Dermatol. 2013;149:722–6.
52. Ramos ES, Martins NR, Kroumpouzos G. Oral and vulvovaginal changes in pregnancy. Clin Dermatol. 2016;34:353–8.
53. Oakes RE, Frampton SJ, Scott PM. Granuloma gravidarum: management. J Obstet Gynaecol. 2012;32(8):805.
54. Vazquez JC. Constipation, haemorrhoids, and heartburn in pregnancy. BMJ Clin Evid. 2010;1411
55. Giambanco L, Iannone V, Borriello M, Scibilia G, Scollo P. The way a nose could affect pregnancy: severe and recurrent epistaxis. Pan Afr Med J. 2019;34:49.
56. Morya AK, Gogia S, Gupta A, Prakash S, Solanki K, Naidu AD. Motherhood: what every ophthalmologist needs to know. Indian J Ophthalmol. 2020;68(8):1526–32.
57. Koh YP, Tian EA, Oon HH. New changes in pregnancy and lactation labelling: review of dermatologic drugs. Int J Womens Dermatol. 2019;5(4):216–26.
58. Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: part I. Pregnancy J Am Acad Dermatol. 2014;70(3):401.e1–14.
59. Patel VM, Schwartz RA, Lambert WC. Topical antiviral and antifungal medications in pregnancy: a review of safety profiles. J Eur Acad Dermatol Venereol. 2017;31(9):1440–6.
60. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin N Am. 2017;43(3):489–502.
61. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010;4:603–5.
62. Eworuke E, Panucci G, Goulding M, Neuner R, Toh S. Use of tumor necrosis factor-alpha inhibitors during pregnancy among women who delivered live born infants. Pharmacoepidemiol Drug Saf. 2019;28(3):296–304.
63. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117:1499–506.
64. Ghalandari N, Dolhain RJEM, Hazes JMW, van Puijenbroek EP, Kapur M, Crijns HJMJ. Intrauterine exposure to biologics in inflammatory autoimmune diseases: a systematic review. Drugs. 2020;80(16):1699–722.
65. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795–810.
66. Grunewald S, Jank A. New systemic agents in dermatology with respect to fertility, pregnancy, and lactation. J Dtsch Dermatol Ges. 2015;13(4):277–89.
67. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. J Rheumatol. 2006;33:1014–7.

68. Verstappen SM, King Y, Watson KD, Symmons DP, Hyrich KL. BSRBR control Centre consortium. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology biologics register. Ann Rheum Dis. 2011;70:823–6.
69. Ostensen M. Safety issues of biologics in pregnant patients with rheumatic diseases. Ann N Y Acad Sci. 2014;1317:32–8.
70. Clarke DO, Hilbish KG, Waters DG, Newcomb DL, Chellman GJ. Assessment of ixekizumab, an interleukin-17A monoclonal antibody, for potential effects on reproduction and development, including immune system function, in cynomolgus monkeys. Reprod Toxicol. 2015;58:160–73.
71. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Spontaneous abortion during ustekinumab therapy. J Dermatol Case Rep. 2012;6:105–7.
72. Gisbert JP, Chaparro M. Safety of new biologics (Vedolizumab and Ustekinumab) and small molecules (Tofacitinib) during pregnancy: a review. Drugs. 2020;80(11):1085–100.
73. Gerosa M, Argolini LM, Artusi C, Chighizola CB. The use of biologics and small molecules in pregnant patients with rheumatic diseases. Expert Rev Clin Pharmacol. 2018;11(10):987–98.
74. Wils P, Seksik P, Stefanescu C, Nancey S, Allez M, Pineton de Chambrun G, et al. PREGNANCY-GETAID study group. Safety of ustekinumab or vedolizumab in pregnant inflammatory bowel disease patients: a multicentre cohort study. Aliment Pharmacol Ther. 2021;53(4):460–70.
75. Clowse MEB, Scheuerle AE, Chambers C, Afzali A, Kimball AB, Cush JJ, et al. Pregnancy outcomes after exposure to certolizumab pegol: updated results from a pharmacovigilance safety database. Arthritis Rheumatol. 2018;70(9):1399–407.
76. Trivedi MK, Kroumpouzos G, Murase JE. A review of the safety of cosmetic procedures during pregnancy and lactation. Int J Womens Dermatol. 2017;3(1):6–10.

Chapter 4
Skin Changes in Menopause

Preethi B. Nayak and Vivek M. Pai

4.1 Introduction

Skin is significantly affected by the aging process, as well as menopause. The changes which occur on the skin during menopause are due to the effects on skin's individual components [1]. Menopause is defined as either permanent cessation of menses or lack of menses for 12 consecutive months. The major change that occurs during menopause is cessation of estrogen production by ovaries, and major source of estrogen from conversion of adrenal androgen to estrogen by the action of aromatase enzyme in peripheral tissues [2].

4.2 Physiological Changes

Effects of Estrogen on Structural Component of Skin.

Estrogen receptors are seen on skin's cellular components [1]. With changes in structure and functions, the skin becomes thinner. The quality of skin decreases its efficacy with aging due to the synergistic action of time, photoaging, hormonal deficiency, decline in metabolic activity, and environmental factors [3].

It is difficult to distinguish between changes which are specific to aging and those due to estrogen deprivation; however estrogen might lead to accelerated aging of skin [3].

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4.2.1 Collagen

Atrophy of collagen fibers is a major factor of aging skin. Thickened, basophilic clumped collagenous material is suggestive of partial degradation of collagen, along with significant decrease in quantity of dermal collagen. The aging of collagen main occurs due to a decrease in the number of immature reducible cross-links between collagen molecules and an increase in nonreducible collagen. There is a reduction in enzymes which helps in post-translational collagen processing, reduction in fibroblasts which synthesize collagen and vessel supply of skin. All these attribute to increase in laxity and wrinkling. There is a strong correlation between loss of collagen and estrogen deficiency, since as much as 30% of collagen loss occurs in the first five years of menopause [3].

4.2.2 Elastin

Elastin fibers are closely interwoven with collagen fibrils, leading to recoil after stretching and prevention of overstretching. Degenerative changes in dermal elastic fibers occur during premature menopause in young women [3].

4.2.3 Elasticity

There is progressive increase in extensibility and reduction in skin elasticity in aging of skin over the face [3].

4.2.4 Water

A good amount of water content is required for a healthy skin, which is dependent on epidermal hydration and cutaneous evaporation. Dermal glycosaminoglycans decrease with age; these glycosaminoglycans are associated with high water-binding capacity and are essential to maintain normal skin hydration [3].

4.2.5 Thickness of Skin

The thinning effect is due to decrease in collagen, water, and glycosaminoglycans, which is seen in the postmenopausal years [3].

4.2.6 Blood Flow

The structural integrity and functioning of capillary blood vessels are very important for healthy skin. The rich capillary network in the dermal papillae is responsible for flush seen following menopause. Peripheral microcirculation also decreases significantly at menopause, especially at the nailfold capillaries [3].

4.3 Sebaceous Glands and Hair

There is a decrease in sebum secretion with aging. Also, there is an increase in facial hair and a decrease in pubic/body hair. Estrogen is also an important regulator of hair follicle growth and cycles. It is known that androgens have a role in the pathophysiology of female pattern hair loss (FPHL), but hair miniaturization in women can also be caused by nonandrogen signals as well. The hormonal changes of menopause lead to decreased growth rate, hair diameter, and percentage anagen. Hair density is affected by chronological age. The compounded effect of these changes may lead to a heightened perception of decreased scalp coverage in middle-aged women. It has been shown that the estrogen-receptor pathway regulates the telogen-anagen follicle transition under the influence of estrogens. The length of the hair follicle's life cycle is increased, owing to the prolongation of the anagen phase of the hair growth cycle. Conversely, with plummeting estrogen levels postpartum, significant loss of hair occurs. Decrease in estrogen levels is known to induce hair fall; hence hormone replacement therapy/topical estrogens are proposed to be used in hair fall [4–6].

4.4 Wound Healing

As aging occurs, the skin becomes more fragile and susceptible to trauma, and there is a decrease in transforming growth factor (TGF)-β. The estrogen induces TGF-β secretion by dermal fibroblasts and enhances the quality and rate of wound healing [3].

The effect of menopause on physical characters of skin is depicted in Fig. 4.1.

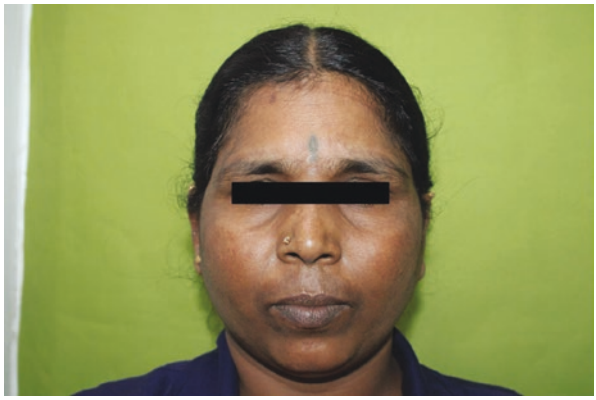

Fig. 4.1 Various skin changes seen at perimenopausal age

4.5 Skin Thickness

There is age-related thinning due to a decrease in collagen, water, and glycosaminoglycan content. The skin thickness usually increases up to the age of 35–49 years, followed by thinning [5].

4.6 Elasticity and Distensibility

Aging in skin, mainly over the face, is associated with reduction in skin elasticity and increase in extensibility [5].

4.7 Wrinkles

There is age-related loss of connective tissue in skin, leading to loss of tonicity and increased distensibility, which causes progressive deepening of facial creases. Hormone replacement therapy is suggested to increase in collagen content and elasticity, causing decreased wrinkling [5].

4.8 Blood Flow

The structural and functional integrity of capillary blood vessels along the cutaneous circulation is required to maintain core temperature [5].

Menopause denotes an estrogen-deficient hormonal condition, due to which the skin reflects a conspicuous decline in physical attributes [2]. The decrease in

functional follicles number leads to increase in levels of circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) during and after menopause, leading to reduction in levels of estrogen and progesterone [7]. There is abundance in estrogen receptors in epidermis as well as dermis, and to a lesser extent progesterone receptors, leading to significant changes in skin during menopause due to the impact of hormones [7].

The symptoms a woman experiences during menopause is called as climacteric syndrome. Climacteric syndrome can be classified as physical or psychological in nature. Vasomotor symptoms, palpitations, headaches, urogenital symptoms, bone and joint pain, tiredness, disturbed sleep, breast tenderness, and skin aging are the physical symptoms. Depression, loss of memory, poor concentration, irritability, loss of confidence, and tiredness are the psychological symptoms. Alopecia and hirsutism seen during menopause are physical symptoms which cause significant psychological impact [7].

Dermatological problem occurring more commonly during menopause:

Vulvovaginal problems—atrophic vulvovaginitis, vaginitis of uncertain etiology, lichen sclerosus, dysesthetic vulvodynia.

General dermatological problems—hirsutism, recession of the frontal and frontoparietal hairline, postmenopausal frontal fibrosing alopecia, menopausal flushing, oral discomfort, drying of the skin, keratoderma climactericum [8].

4.9 Estrogen-Deficient Skin: Role of Topical Estrogen

Estrogen receptors are found in the skin, with the density of receptors being highest on the genitalia, face, and lower limbs. More estrogen receptors are found in females compared with males. Fewer estrogen receptors are found on the vulva compared with the vagina. The p29 protein found in the cytoplasm of estrogen-sensitive cells is present in the epidermis. A gradient of concentration exists which is highest in the stratum granulosum. Action of estrogen on collagen, elastic fibers, and hyaluronic acid has been demonstrated. Estrogen therefore exerts its effect on both epidermal and dermal components of the skin [8, 9].

Beneficial effects of estrogen on the skin:

Epidermal—decreased atrophy, increased water-holding capacity of the stratum corneum, increased barrier function.

Dermal—increased dermal thickness, increased turnover of hyaluronic acid, increased dermal water content, increase in type III collagen, morphological improvement of elastic fibers—increased number, thickness, and/or vertical orientation of fibers.

General cutaneous effects—increased thickness (7–15%), decreased slackness, decreased extensibility, increased DNA repair capacity (25%), decreased drying and wrinkling of the skin [8].

4.9.1 Topical Estrogen

Estrogens are steroids that are synthesized from cholesterol in the ovary in premenopausal women and in the peripheral tissue postmenopausally.

Two estrogen receptors (ERs), α and β, have predominantly been identified in the skin. Histologically, their relative expression levels start to decline from the perimenopausal years onward as women enter an estrogen-deficient state. Both ERs bind to estradiol with similar affinity; however, the expression profiles of ER-α and ER-β are tissue-specific, with ER-β more widely distributed within the skin than ER-α. Interestingly, ER-α activation is a main driver of reproductive cancers, which makes the selective targeting of ER-β a promising new avenue for targeted intervention [9].

Many studies have shown that upon entering menopause, women detect a swift commencement of skin aging symptoms. One of the first symptoms experienced is increased skin dryness, followed by decreased firmness and elasticity. These symptoms correspond with structural and architectural changes, such as decreased sebum production, collagen content, dermal thickness, and elastin fibers [9–11].

Estrogen helps to retain and restore skin moisture through the promotion of sebum secretion, primarily by regulating the expression of insulin-like growth factor receptors and increasing the production of insulin-like growth factors from fibroblasts, which in turn induces lipogenesis in human sebocytes and leads to moisture retention. Additionally, estrogen therapy elevates the levels of mucopolysaccharides and hyaluronic acids in the dermis to keep the skin hydrated, which improves the barrier function of the stratum corneum and optimizes the surface area of corneocytes [9–11].

Although systemic hormone replacement therapy can reverse signs, such as skin and vaginal dryness and atrophy, the various risks (mainly hyperplasia or cancer of the endometrium, and concern regarding increased risk of breast and ovarian cancer) preclude its use to treat skin disorders [9]

4.10 Cutaneous complication of Hormone Replacement Therapy

Hypersensitivity—sensitivity to adhesives in patches.

Pigmentation—increased incidence of melasma.

Immunological effects—raised levels of anti-DNA antibodies, induction of antiphospholipid antibodies, increased risk of developing SLE, no deterioration in cutaneous disease of SLE among HRT users, dose-dependent estrogen effect on production of IL-1.

Uncommon cutaneous adverse effects—acanthosis nigricans, erythema multiforme, photosensitivity, pompholyx, spider telangiectasia, stomatitis, urticaria [8].

Because maintaining youthful skin is strongly desired by a large portion of today's population, studies that evaluate approaches to reverse skin changes in menopause through alternative medicine and topical therapy have expanded [9].

Fuchs et al. used 0.01% estradiol cream for 6 months over the face (temple hairline)—epidermal thickness significantly increased by 23% compared with controls; markers of skin aging (rete peg pattern, epidermal thickness) significantly improved [12].

Schmidt et al. used 0.3% estriol cream or 0.01% estradiol cream for 6 months over the face—skin aging symptoms (vascularization, firmness, elasticity, moisture, wrinkle depth, and pore size) improved in both groups, but the effects of the topical estriol group were slightly superior to those of the estradiol group with regard to extent and onset [13].

Creidi et al. used 1 g Premarin cream (0.625 mg conjugated estrogen/g of cream) for 24 weeks over the face—skin thickness and fine wrinkles significantly increased in the treatment group compared with placebo; improvement in roughness, laxity, and mottled pigmentation but did not reach statistical significance between the groups [14].

Patriarca et al. used 0.01% micronized 17B-estradiol gel for 16 weeks over the face—epithelial and dermal thickness significantly increased compared with baseline, amount of collagen significantly increased compared with baseline, and keratinocyte proliferation and epidermal thickness increased [15].

Patriarca et al. used 0.01% 17-beta estradiol gel for 24 weeks over the face; hyaluronic acid concentration significantly increased [16].

Masuda et al. used 0.06% estradiol gel (l'estrogel) for 24 weeks over arms leading to fineness of texture (measured by digital microscope) increased in application site (forearm) and cheek (unapplied site) [17].

Silva et al. used 0.01% 17-beta estradiol for 24 weeks over the face leading to Types I and III facial collagen significantly increased at the end of treatment [18].

Although an absence of systemic effects after topical estrogen application has been described by many investigators, few had contrasting results. For instance, Masuda et al. described a decreased incidence of hot flashes in postmenopausal women after application of a gel formulation that contained 0.06% estradiol gel, suggesting that topical applications could indeed exhibit systemic effects via blood circulation in addition to exerting local action on the application site [9, 17].

In general, the systemic absorption of local or topical estrogen therapies is thought to be quite low and does not increase the risk of venous thromboembolic events, as seen with systemic estrogen therapies. Thus, whether the application of topical estrogens may potentially result in unwanted systemic effect is currently unclear, and topical estrogens are not widely used to treat estrogen deficiency [9].

The effects of estrogen deficiency on the skin are an important endogenous cause of aging skin in women. Clinically, topical estrogen products can be used cosmetically to improve skin dryness, texture, and elasticity and reduce wrinkles. However, concerns exist with regard to the safety of topical estradiol. Thus, more research is needed to support the use of topical agents to prevent and treat estrogen deficiency.

References

1. Raine-Fenning NJ, Brincat MP, Muscat-Baron Y. Skin aging and menopause. Am J Clin Dermatol. 2003;4(6):371–8.
2. Lephart ED, Naftolin F. Menopause and the skin: old favorites and new innovations in cosmeceuticals for estrogen-deficient skin. Dermatol Ther. 2020;26:1–7.
3. Calleja-Agius J, Brincat M. The effect of menopause on the skin and other connective tissues. Gynecol Endocrinol. 2012;28(4):273–7.
4. Mirmirani P. Hormonal changes in menopause: do they contribute to a 'midlife hair crisis' in women? Br J Dermatol. 2011;165:7–11.
5. Brincat MP, Muscat Baron Y, Galea R. Estrogens and the skin. Climacteric. 2005;8(2):110–23.
6. Bolognia JL, Braverman IM, Rousseau ME, Sarrel PM. Skin changes in menopause. Maturitas. 1989;11(4):295–304.
7. Blume-Peytavi U, Atkin S, Gieler U, Grimalt R. Skin academy: hair, skin, hormones and menopause–current status/knowledge on the management of hair disorders in menopausal women. Eur J Dermatol. 2012;22(3):310–8.
8. Wines N, Willsteed E. Menopause and the skin. Australas J Dermatol. 2001;42(3):149–60.
9. Rzepecki AK, Murase JE, Juran R, Fabi SG, McLellan BN. Estrogen-deficient skin: the role of topical therapy. Int J Women's Dermatol. 2019;5(2):85–90.
10. Hall G, Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. J Am Acad Dermatol. 2005;53(4):555–68.
11. LePillouer-Prost A, Kerob D, Nielsen M, Taieb C, MaitrotMantelet L. Skin and menopause: women's point of view. J Eur Acad Dermatol Venereol. 2020;34(6):e267–9.
12. Fuchs KO, Solis O, Tapawan R, Paranjpe J. The effects of an estrogen and glycolic acid cream on the facial skin of postmenopausal women: a randomized histologic study. Cutis. 2003;71(6):481–8.
13. Schmidt JB, Binder M, Demschik G, Bieglmayer C, Reiner A. Treatment of skin aging with topical estrogens. Int J Dermatol. 1996;35(9):669–74.
14. Creidi P, Faivre B, Agache P, Richard E, Haudiquet V, Sauvanet JP. Effect of a conjugated oestrogen (Premarin®) cream on ageing facial skin. A comparative study with a placebo cream. Maturitas. 1994;19(3):211–23.
15. Patriarca MT, Barbosa de Moraes AR, Nader HB, Petri V, Martins JR, Gomes RC, et al. Hyaluronic acid concentration in postmenopausal facial skin after topical estradiol and genistein treatment: a double-blind, randomized clinical trial of efficacy. Menopause. 2013;20(3):336–41.
16. Patriarca MT, Goldman KZ, dos Santos JM, Petri V, Simões RS, Soares JM Jr, et al. Effects of topical estradiol on the facial skin collagen of postmenopausal women under oral hormone therapy: a pilot study. Eur J Obstet Gynecol Reprod Biol. 2007;130(2):202–5.
17. Masuda Y, Hirao T, Mizunuma H. Improvement of skin surface texture by topical estradiol treatment in climacteric women. J Dermatol Treat. 2013;24(4):312–7.
18. Silva LA, Carbonel AA, de Moraes ARB, Simões RS, Sasso GRDS, Goes L, et al. Collagen concentration on the facial skin of postmenopausal women after topical treatment with estradiol and genistein: a randomized double-blind controlled trial. Gynecol Endocrinol. 2017;33(11):845–8.

Chapter 5
Acne in Women

Evangeline B. Handog and Maria Juliet E. Macarayo

5.1 Introduction

Acne vulgaris has been a foe that haunts both the physician and the patient. It strikes its wrath across all ages and genders. What has been known as an affliction of the early teen age life is now affecting women beyond this age group (i.e., pre- and postmenopausal women). Considered a lingering inflammatory skin disorder of the pilosebaceous glands, it predilects the face at all times, with the back, chest, and arms similarly affected but to a lesser degree. Its severity is variable and may manifest with comedones, papules, pustules, or nodulocystic lesions.

Local and international disease incidence and prevalence reports revealed that it has been one of the top ten reasons for consultation in both private and nonprivate dermatology clinics and institutions. In the Philippine Dermatological Society alone, from its 7-year data (2015–2021), acne vulgaris ranked first with an incidence between 6.6% and 35.1% [1]. Acne persisting into adulthood among women was shown in an early survey done by Collier et al., where 50.9% was seen in ages 20–29 years and 26.3% among 40–49 years [2].

ACNE can be an acronym for "**A**cne is a **C**hronic **N**asty **E**xperience". Suffice to say that it negatively affects the quality of life of almost every acne sufferer. The chronicity of the disease, the high cost of treatment draining the patient's finances,

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the time spent in adhering to treatment, and the variability of results from exacerbations to relapses are some of the valid reasons why anxiety and depression are seen among acne patients.

5.2 Adult Female Acne (AFA)

AFA has been considered a particular subtype of acne, distinct from acne vulgaris or adolescent acne. On top of the differences in the clinical presentation and etiopathogenesis, the chronicity of this type of acne is noteworthy since it may last until the postmenopausal period. Management may be more complicated, given that women in this age group have more sensitive and less oily skin. This complexity is further compounded by the fact that they face more challenges in their lives (i.e., workload, stress, sleep disorders, more dietary supplements intake, and use of contraceptive methods) [3].

5.2.1 Definition

About two-thirds of visits made to the dermatologists for acne are female patients and most of them are women who are older than 25 years [4]. Acne may even continue incessantly or recurrently and may even persist after the fifth decade of life [5]. Thus, ADULT FEMALE ACNE (AFA) has been described.

Three types of AFA have been defined: persistent acne, late acne, and recurrent acne; the latter starts in adolescence, improves for a variable period of time, and reappears in adulthood. Zeichner et al. suggested two categories of AFA: acne seen from 25 to 44 years of age and those seen over 45 years of age in the perimenopausal period [6].

5.2.2 Clinical Presentation

It came to be known that the AFA lesions, predominantly papules and pustules, were located mostly on the following areas: mandibular, perioral, chin, and anterior cervical region. However, studies also showed that the presentation can be comedonal and the trunk can be affected as well. The skin of AFA patients may be less tolerant to topical medications as the skin may be more sensitive than that of adolescents. Hence, postinflammatory hyperpigmentation may be a common sequela [7–9] (Fig. 5.1).

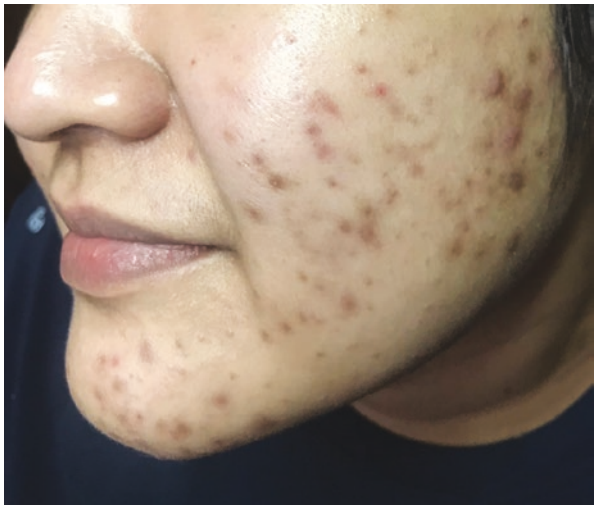

Fig. 5.1 Adult female acne in a 34-year-old single Asian female (Courtesy of Dr. Maria Juliet Macarayo)

5.2.3 Etiology

An interplay of the four key factors in the pathogenesis of acne is still in place: follicular hyperkeratinization leading to comedogenesis, overproduction of sebum under androgen control, follicular colonization by Cutibacterium acnes, and inflammatory mechanisms that may be innated and acquired [10]. But the precise causation of AFA has not yet been entirely elucidated. Dreno et al. suggest that several triggers or aggravating factors are likely, such as exposure to ultraviolet radiation, stress, obesity, diet, smoking, sleep disorders, cosmetics, medications, excessive skin washing, possible resistance to *C. acnes*, and endocrine deficiency diseases [11].

5.2.3.1 Genetics

The estimated background lifetime risk of developing acne is about 85 to 90% [12] and being genetically predisposed to developing acne vulgaris may play an important role in influencing the number, size, and activity of the sebaceous glands [13]. Though the true role of genetics is yet to be made clear, Lasek noted that two-thirds of acne cases among adult patients recounted a history of at least one first-degree relative who also suffers from acne [14]. Goulden later suggested that the daughters of adult female acne patients are at a significantly higher risk of developing acne as an adult ($P < 0.001$) [13].

5.2.3.2 Hormones

Androgens play a role in the etiopathogenesis of acne vulgaris. In AFA, there is an increase in the number of sebocyte and keratinocyte receptors whose sensitivity to circulating androgens are augmented. The hyperactivity of the enzymatic organization in the sebocytes and keratinocytes associated with the metabolism of androgenic hormones (i.e., 5-alpha reductase, 3-beta-hydroxysteroid dehydrogenase (3-βHSD), and 17-hydroxysteroid dehydrogenase) leads to an elevated prehormone peripheral conversion of dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and testosterone into more potent androgenic hormones testosterone and dihydrotestosterone (DHT). Clarke et al. report that testosterone, DHEA-S, and DHT stimulate sebaceous gland growth and sebum production, with DHT being 5 to 10 times more potent than its precursor, testosterone, and less likely to be metabolized by aromatase into estrogen [15].

Estrogens act reversely by inhibiting the secretion of androgens, modulating the genes involved in the growth of the sebaceous gland and deterring their function. The estrogen/androgen ratio determines the activity of the sebaceous gland [15]. The worsening of the disease in the premenstrual period in 60% to 70% of women, as well as in premenopausal, pregnancy, and during the use of progestin-only contraceptives, happens because there is a relative increase of the hormones with greater androgenic activity, in relation to estradiol [3].

During stressful periods, the sebaceous gland, which is a neuroendocrine organ, can be further stimulated by neuropeptides and hormones such as melanocortins and corticotropin-releasing hormone (CRH) [3]. CRH increases the expression of 3-βHSD mRNA, the enzyme responsible for the conversion of dihydroepiandrosterone (DHEA) to testosterone. Other regulators of sebum production include histamine, retinoids, vitamin D, and insulin-like growth factor 1 (IGF-1) [5].

5.2.3.3 Other Factors

5.2.3.3.1 Epidermal Barrier Function

Del Rosso et al. report that epidermal barrier function loss may be an important factor in the setting of adult acne. A disrupted epidermal barrier leads to a transepidermal water loss that may set the cascade of inflammation leading to acne formation [16, 17].

5.2.3.3.2 Diet

Dairy products and foods with a high glycemic load were noted to increase insulin and insulin-like growth factor-1 (IGF-1) levels. The mammalian target of rapamycin complex 1 (mTROC1) is then stimulated, triggering the processes such as increased protein and lipid synthesis, cell proliferation, proliferation of keratinocytes,

sebaceous gland hyperplasia, sebaceous lipogenesis, insulin resistance, and increased body mass index [18]. The gonads and sebaceous glands, with receptors for both insulin and IGF-1, stimulate the production of androgens, such as testosterone, and inhibit the action of aromatase that converts testosterone to estradiol [19].

5.2.3.3.3 Drugs

Certain medications such as corticosteroids, benzodiazepines, lithium, cyclosporine, ramipril, isoniazid, iodides, bromides, vitamin B-type complexes, serotonin uptake inhibitors, epidermal growth receptor inhibitors, and progestin contraceptives have all been associated with the development of acne.

Corticosteroids stimulate hyperkeratinization and increase the expression of toll-like receptor-2 (TLR 2) [20].

Norgestrel and levonorgestrel, which are first-generation progestins, have androgenic effect similar to testosterone [21–23]. Levonorgestrel intrauterine devices and implants, subcutaneous etonogestrel, and long-acting methods with progestin alone have been noted to produce a negative effect on acne or may trigger acne in predisposed women [24–26].

5.2.3.3.4 Stress

Stress can result in increased levels of cortisol due to the release of proinflammatory cytokines and CRH. Even sleep deprivation associated with women's modern lifestyle and stress have an important impact on the hypothalamic-pituitary-adrenal axis and in the increased secretion of stress-related hormones [3].

5.2.3.3.5 Cosmetics

Earlier data suggested that cosmetics trigger acne in as many as 62% of adult female acne cases [27]. However, as part of coping up with the presence of acne, the use of cosmetics form part of these women's way to get back their self-esteem that is already low [28]. Cosmetic use is not entirely prohibited. What is essential is education on the use of noncomedogenic and nonacnegenic cosmetics, to avoid acne flares [28, 29].

Skin care products (i.e., moisturizers, toners, and sunscreens) are commonly used along with acne medications [30]. Zeichner reports that application of a moisturizer before topical acne medications did not interfere with efficacy and enhanced the tolerability of the drug [31].

5.2.3.3.6 Tobacco

There is a close relationship between smoking and the occurrence of AFA. Acne prevalence in the general population was shown to be higher among smokers compared to nonsmokers [32]. A similar inclination was shown among adult women ages 25 to 50 years who are smokers. They were shown to have a higher prevalence of comedonal acne [33]. Yang et al.'s study showed that tobacco is the main factor responsible for the appearance of noninflammatory acne in this age group, with a significant difference between female smokers and nonsmokers. Micro- and macrocomedones with just few inflammatory lesions were seen among smokers, described as "smoker's face." Nicotine stimulates the sebaceous gland which is sensitive to acetylcholine. Acetylcholine leads to cellular modulation and differentiation, and hyperkeratinization is induced. Sebum production and composition is altered, antioxidant agents are reduced, and peroxidation of sebum components, such as squalene, is increased [34]. Whether tobacco worsens pre-existing acne or causes new acne in those with a genetic predisposition is not clear [6].

5.2.3.3.7 Endocrine Diseases

The association of acne with an endocrinopathy characterized by hyperandrogenism may present with other clinical signs, such as hirsutism, seborrhea, alopecia, menstrual disorders, ovulatory dysfunction, infertility, early puberty, metabolic syndrome, and virilization. The main endocrinopathies that occur with hyperandrogenism are PCOS, late congenital adrenal hyperplasia or dysfunction, and more rarely, tumors of the ovary, adrenal gland, pituitary gland, and hypothalamus [35]. It is worthwhile to note that in most AFA patients showing no signs of clinical or laboratory hyperandrogenism, slightly elevated levels of S-DHEA have been observed [36].

5.2.4 Role of Polycystic Ovary Syndrome (PCOS)

5.2.4.1 Definition

Polycystic ovary syndrome (PCOS) is the most common hormonal imbalance with an unknown etiology in women in their reproductive years [37]. The first definition of PCOS was given in 1990 by the National Institute of Health (NIH). The criteria included a combination of oligo-anovulation and clinical or biochemical signs of hyperandrogenism [38]. Rotterdam consensus in 2003 included ultrasonographic evidence of polycystic ovaries as one of the characteristics of PCOS [39]. Dermatological manifestation of hyperandrogenism, namely acne vulgaris, hirsutism, and androgenic alopecia, is included as one of its cardinal criteria [40] (Fig. 5.2).

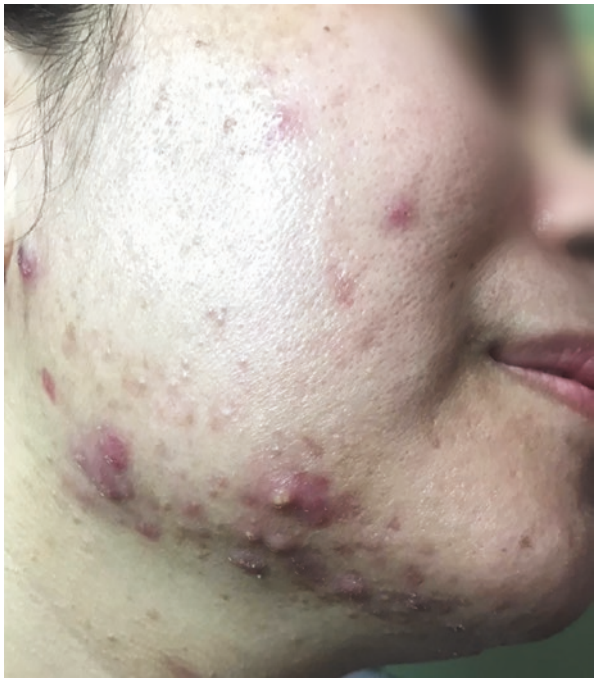

Fig. 5.2 Acne with PCOS in a 40-year-old married Asian female (Courtesy of Dr. Maria Juliet Macarayo)

5.2.4.2 Epidemiology

There are various reports from different parts of the world regarding the prevalence of PCOS. An earlier study noted that its frequency may be higher in women younger than 35 years of age [41]. According to the NIH and Rotterdam criteria, 6–10% of women were affected by PCOS and that women of reproductive age between 15 and 49 years are affected by PCOS and endocrinopathies [42]. Among South Asian patients living in the United Kingdom, prevalence of PCOS was lower than that of hirsutism [43, 44].

5.2.4.3 Manifestations and Pathophysiology

Playing a key role in the pathophysiology of PCOS are the ovarian, neuroendocrine, and metabolic dysfunctions. PCOS, hyperandrogenism, hyperinsulinemia, and insulin resistance are well interrelated. The critical role of chronic low-grade inflammation in PCOS cannot be overlooked [45].

Clinical indicators of hyperandrogenism are acne vulgaris, hirsutism, and androgenic alopecia, virilization, clitoromegaly, infertility, increased muscle mass, and decreased breast size [46, 47]. Hyperandrogenism in relation to the ovaries as a source may be due to PCOS or ovarian tumors (benign or malignant); with regard to the adrenals as source, may be due to adrenal hyperplasia (congenital or

noncongenital) or adrenal tumors (benign or malignant) [48]. Suggestive of virilization are disorders of severe insulin resistance, androgen-secreting tumors, and androgenic substance abuse [49].

Metabolic disturbances including obesity and insulin resistance were found in 60–80% of women with PCOS. According to Housman et al., the risk for multisystemic consequences, including type 2 diabetes mellitus, cardiovascular disease, endometrial cancer, obstructive sleep apnea, nonalcoholic steatohepatitis, and psychiatric disorders is high in women with PCOS [50]. Hyperinsulinemia and peripheral insulin resistance occur frequently in women with PCOS. The former influences an increase in the concentration of plasma IGF-1 while IGF Binding Protein-Like 3 (IGFBP-3) is lowered. This imbalance culminates in the hyperproliferation of keratinocytes. The increased IGF-1 leads to the inhibition of aromatase, averting the conversion of testosterone to estrogen. Also, a decrease in the hepatic production of sex hormone binding globulin (SHBG) favors the elevation of the free androgens that constitute its active form [35].

Metabolic syndrome is common among women with acne, obesity, and PCOS. Criteria for metabolic syndrome include the following: (a) abdominal obesity (circumference of the waist) > 88 cm, (b) triglycerides >150 mg/dL, (c) HDL <50 mg/dL, (d) blood pressure > 130/> 85 mm Hg, (e) high glycemia = 110-126 mg/dl, and (f) glycemia 2 h after the glucose tolerance test = 140–199 mg/dL [35, 51].

Velija-Asimi reported that the imbalance of estrogen and progesterone levels may be involved in the growth of ovarian cysts. Characteristic among PCOS women is the chronic secretion of estrogen without the cyclic pattern that complements the ovulatory cycle. Serum estradiol (E2) levels were noted to be variable but serum estrone (E1) was frequently higher than that of E2. In addition, though serum progesterone levels are low in PCOS women, 17-hydroxyprogesterone values were described to be significantly elevated in women with PCOS [52].

Inflammation processes are involved in ovulation and may be linked to the visceral adipose tissue as a host to this process. With abdominal obesity more common among women with PCOS, production of inflammatory cytokines, monocyte chemoattractant proteins (MCPs), and recruitment of the immune cell can lead to an inflammatory response in adipocytes [53].

In the latest study of Tsvetanova et al. among female patients of the reproductive age, a relationship was established between acne vulgaris, PCOS, and autoimmune thyroid disease (AITD) [54]. Moreover, often seen with PCOS are fertility disorders, cardiovascular problems, and psychological effects on the quality of life, including anxiety and depression [55].

Hyperandrogenism, being one of the most important diagnostic features of PCOS, must be readily detected by the dermatologist for proper diagnosis and correct management of the disorder. Irregular menses plus hirsutism, acne, seborrhea, and less commonly hair loss should make one suspect of PCOS [50].

5.2.4.4 Evaluation Considerations

It cannot be more emphasized that a thorough medical history, a complete physical examination, and a comprehensive review of systems are vital to evaluate any patient with acne. It is imperative that the social history, medications and supplement use, tobacco and illicit drug use, menstrual history (i.e., age of menarche, regularity of menses, history of infertility), and prior/current acne treatments must not be missed [56].

5.2.4.5 Laboratory Investigations

In suspected PCOS, the following criteria should be checked: (1) presence of menstrual alterations (amenorrhea or oligomenorrhea), (2) clinical and/or biochemical hyperandrogenism, as well as (3) ultrasonographic changes (≥12 follicles with 2–9 mm diameter or increase in ovarian volume > 10 cm^3). In the revised consensus of 2004, the presence of two of the three criteria confirmed the diagnosis [57, 58].

Although PCOS is the most common cause of increased androgens in adult women, endocrine testing is only needed in patients who have other signs or symptoms of hyperandrogenism [59]. And in the presence of other clinical signs of hyperandrogenism, most authors suggest acquiring of the patient's plasma concentrations of free and total testosterone, DHEA-S, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Free androgen index (FAI) may be requested, as well, since a high concentration was noted among PCOS women [60].

When suspecting PCOS, a transvaginal ultrasound must be carried out for visualization of the ovaries. These examinations should always be performed in the follicular phase, preferably between the first and fifth day of the menstrual cycle and the collection should be done in the morning, between 8 and 10 am. It is not, however, recommended to perform these when hormonal contraceptives are in use [35].

Testing for thyroid function may be warranted in some cases. Clinically diagnosed thyroid diseases with hormonal or autoimmune dysfunction were more frequently seen in patients with acne vulgaris than in patients without acne [40, 61].

Other than these laboratory parameters, care and screening are required for these already troubled women, as they are at high risk for depressive disorders, disorganized eating behavior, and impaired quality of life [62].

5.2.4.6 Treatment

5.2.4.6.1 Nonhormonal

Change in the lifestyle for PCOS patients is most important. Diet and exercise can lead to weight loss and can improve fertility and metabolic abnormalities. Aiming to have a normal body mass index (normal value 18.5 to 24.9) is ideal. Glucose control is a must.

Treatment for acne usually involves the standard therapy, depending on its severity. This may include topical medicaments such as retinoids, antibiotics, benzoyl peroxide, and dapsone. Oral options may be isotretinoin or antibiotics. Chemical peeling can be offered as a procedural adjunct. Management of hirsutism may include application of eflornithine cream or procedures such as bleaching, shaving, waxing, electrolysis, and laser hair removal. Use of minoxidil scalp solution may help in dealing with androgenetic alopecia.

5.2.4.6.2 Hormonal*

Hormonal treatment of PCOS includes combination estrogen and progesterone oral contraceptives (COCs), antiandrogen drugs (i.e., spironolactone, cyproterone acetate, drospirenone, and flutamide), inhibitors of peripheral androgen conversion (e.g., finasteride), and insulin-sensitizing agents (e.g., metformin) [63].

See Role of Hormonal Treatment for Female Acne

5.2.4.6.3 Other Drugs

Metformin

Most drugs for the management of PCOS act through increasing insulin sensitivity and the reduction of insulin levels. Metformin is the most widely used insulin-sensitizing drug. It leads to an increase in insulin sensitivity by upregulation of lethal-7 microRNA (let-7 family miRNAs) [64]. It can steer the inhibition of hepatic glucose production and a reduction of glucose uptake. By decreasing insulin levels, metformin diminishes the activity of cytochrome P450c-17α, causing a decline in androgens' synthesis, and hence, lowering the levels of plasma androgens [65]. It also plays an anti-inflammatory role by impeding phosphorylation of the inhibitory protein I kappa B (IκB), thereby activating the kappa enhancer binding protein NF kappa B (NF-κB) [66].

Metformin's positive effects on the menstrual cycle led to its being administered to young women needing improvement of their ovulatory cycle and hyperandrogenic symptoms such as hirsutism, acne, and weight gain [67]. However, its gastrointestinal side effects may not be well tolerated such that it is often used as a second-line option after spironolactone, and is best reserved for patients with glucose intolerance, insulin resistance, or who are trying to conceive [68].

Thiazolidinediones

Thiazolidinediones (TZDs) suppress gluconeogenesis by increasing peripheral glucose uptake and decreasing hepatic glucose production. Troglitazone was effective for hirsutism in patients with PCOS, but is no longer available because of

hepatotoxicity. Currently, pioglitazone and rosiglitazone are being used, but both are not without side effects. Both carry associated cardiovascular risks and hepatotoxicity [63, 69].

5.2.4.7 Prognosis

PCOS seems to have a long prodromal phase with detectable abnormalities throughout the life cycle of affected women. Approximately, 25% to 30% of women with PCOS may show impaired glucose tolerance by the age of 30 and 8% may develop type 2 diabetes. Women with PCOS are seen to have more extensive coronary artery disease by angiography. The presence of hypertension and the chronic anovulation can predispose them to endometrial, ovarian, and breast cancer [70].

5.2.5 Role of Hormonal Treatment in Women

5.2.5.1 The Hormones Implicated in Acne Pathogenesis

The following hormones are implicated in the pathogenesis of acne vulgaris: androgens, estrogens, progesterone, insulin and IGF-1, corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), melanocortins, glucocorticoids, and growth hormone (GH) [71].

Androgens are the most important of all the hormones regulating sebum production. Its excess can be suspected when there is a sudden onset of acne presenting with cysts and nodules that are quite widely distributed. Hormonal imbalance is still possible even in women with normal menstrual periods [72].

Beginning at puberty, sebum production and acne formation are stimulated by androgens in both sexes. Potent androgens such as **testosterone and DHT** mediate the secretion of sebum. Sources for DHEA and androstenedione production are the adrenal glands and ovaries. DHEA is predominantly produced by the adrenal glands, while androstenedione is produced by the ovaries and adrenal glands in equal proportions. Of interest, 5 α-reductase enzyme in the infundibular sebocytes can convert the testosterone to the 5–10 times more active DHT [73]. While testosterone, SDHEA, and DHT stimulate sebaceous gland growth and sebum production, estrogens have the opposite effect.

Estrogens influence the genetic control of the sebaceous glands and sebocyte formation. As estrogens increase the production of SHBG by the liver, free serum testosterone level is decreased, counteracting the action of testosterone in the sebocytes [74]. High-dose estrogen which exerts a negative feedback on the gonadal axis can result in the reduction of the sebaceous gland size, thereby causing a decrease in sebum formation [74, 75]. In this manner, the estrogen/androgen ratio dictates the activity of the sebaceous gland [15].

Progesterone inhibits 5 α-reductase which is required to convert testosterone to the more potent DHT. This hormone, whose receptors are expressed in basal epidermal keratinocytes, causes menstrual flare and sebum exacerbations [72].

Insulin stimulates the growth and maturation of the sebaceous glands through the upregulation of GH receptors on the sebocytes. Highly glycemic index foods result in insulin release which in turn produces androgen and sebum production [76].

Corticotrophin-releasing hormone (CRH) from the hypothalamus shares its role in targeting the sebaceous glands and inducing lipogenesis. It enhances androgen bioavailability by stimulating the conversion of DHEA to testosterone [77].

Melanocortin is one of the breakdown products of proopiomelanocortin. Sebocyte receptors for melanocortin (MC-1R and MC-5R) serve to regulate sebocyte differentiation and lipogenesis [78].

The different **pituitary hormones** have their own roles to play. ACTH serves as a stimulator of sebum production. GH activates sebocytes differentiation and stimulates conversion of testosterone to DHT via 5 α-reductase. LH aids in regulating ovarian androgen secretion. Increased secretion of Prolactin in the adrenal glands leads to prolactin receptors acting up to the fast formation of acne lesions [48, 79].

Hormonal treatment of acne may therefore come into place in the following setting: premenstrual severe flare-ups, when oral contraception is desirable, acne not responding to conventional treatment, PCOS, late-onset acne (acne tarda), and ovarian or adrenal hyperandrogenism [80].

5.2.5.2 Endocrinal Evaluation in Patients with Suspected Hormonal Acne

Bettoli et al. stressed that hormonal evaluation is not mandatory for those who experience short bouts of onset and offset of their acne, and for those who respond well to standard treatments. However, assessment might be necessary in the more resistant cases and for those who fail to respond to conventional therapies. This includes patients with acne that is: (a) late-onset (presenting in the third decade) or early-onset (prepubertal/premenstrual), (b) resistant to therapy, (c) stress-exacerbated, (d) with signs of hyperandrogenism, virilization (clitoromegaly, deepened voices, and masculine features), PCOS or hyperinsulinemia (obesity in the trunks, skin tags, and acanthosis), and (e) with lesions distributed more on the lower third of the face along the chin and jaw lines [81].

It is important to note that many patients with hormonal acne might not have a raised level of circulating testosterone in their blood. Also, some women with raised androgen levels can still have normal menstrual patterns. The reason for this may lie on the small portion of the testosterone (1–2%) being free and able to bind to the androgen receptors to induce action [82].

On the other end, patients exhibiting normal levels of both total and free testosterone but with definite signs of hyperandrogenism can be explained by the fact that there is an increased sensitivity of the receptors to androgen at the pilosebaceous unit or there is an increased activity of the 5 α-reductase enzyme that results in the overproduction of DHT [83].

5.2.5.3 Laboratory Tests in Patients with Suspected Hormonal Acne

For patients whose acne requires endocrine evaluation, this must be done at the early menstrual phase (follicular phase). Oral contraceptives should be terminated and stopped one month before laboratory investigations, to avert false positive results [81].

Testosterone (free and total): minimal to modest elevations of >200 ng/dL are suggestive of a benign ovarian or adrenal cause; with greater elevations above this level, neoplasia of ovarian or adrenal origin should be suspected [84]. Normal test results show total testosterone levels of 15–70 ng/dL for women. It may vary from 8 to 48 ng/dL (females 19–49 yo) and 2 to 41 ng/dL (females ≥50 yo). For free testosterone, normal levels are as follows: 1–6 pg/mL (31–40 yo), 1–4 pg/mL (41–50 yo), and <3 pg/mL (≥51 yo).

Androstenedione: secreted equally by the ovaries and adrenals and follows a circadian rhythm making early morning samples the best to analyze [85]. Normal levels in women are between 0.7 and 3.1 ng/mL.

DHEA: high levels of DHEA >8000 ng/dL should raise concern of adrenal tumors, while levels of DHEA-S between 4000 and 8000 ng/dL indicate benign adrenal hyperplasia [85]. DHEA is derived mostly from the adrenal glands and converted to DHEA-S in the adrenal glands and liver. Elevated DHEA-S levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels of ≥600 mcg/dL can suggest the presence of an androgen-secreting adrenal tumor [86].

SHBG: decreased levels of SHBG lead to free unbound testosterone in excess, resulting in more manifested signs [87]. The normal ranges for SHBG concentrations in adults are 10–57 nmol/L (males) and 18–144 nmol/L (nonpregnant females).

Prolactin: elevated prolactin could point out to hypothalamic or pituitary causes for further assessment and investigation. Normal level for nonpregnant females is 2–29 ng/mL and for pregnant females, 10–209 ng/mL [88].

17-Hydroxy progesterone: elevated (>200 ng/dL) in congenital adrenal hyperplasia or nonclassic congenital adrenal hyperplasia due to deficiency or absence of 21 α-hydroxylase [81].

Luteinizing hormone (LH): **follicle-stimulating hormone (FSH) ratio**: a ratio of >2 is indicative of possible PCOS [81].

Fasting and postprandial insulin: overweight and obese patients should be checked for insulin levels [87].

Serum cortisol: high levels are an indication of adrenal neoplasia [87]. Normal levels are as follows for the adults/elderly: if taken at 8:00 AM, 5–23 mcg/dL (138–635 nmol/L); if taken at 4:00 PM, 3–13 mcg/dL (83–359 nmol/L).

ACTH stimulation or dexamethasone suppression test: should be carried out for further evaluation. Androgen from ovarian sources will be disinclined to respond to both tests. Adrenal-sourced androgens are reactive to both tests: an increase following the ACTH stimulation and a decrease in response to dexamethasone suppression test [81].

5.2.5.4 Hormonal Agents

Hormonal therapy in acne is given to suppress androgen production from the ovaries, adrenals, and pituitary and also to inhibit androgen receptors (ARs) on the sebaceous glands. It is not indicated as monotherapy [89].

Along with topical or systemic antibiotics in severe pustular and moderate nodulocystic acne cases, hormonal treatment is recommended by the European guidelines. It can also be an alternative to starting therapy with isotretinoin. It is, however, absolutely contraindicated for comedonal acne. Its usage with antibiotics, benzoyl peroxide, azelaic acid, and even retinoids is allowed. It usually takes about 3 months before one sees improvement and benefits from treatment [90].

Recommendations for hormonal treatment by the work group of Zaenglein et al. stated that estrogen-containing combination oral contraceptives are effective for inflammatory acne in females and that spironolactone, for a select set of females with acne, may be useful. They also support the use of a short-course of oral corticosteroid therapy for patients with severe inflammatory acne while starting standard acne treatment [82].

5.2.5.4.1 Combination Oral Contraceptive Pills (COC)

First approved by the FDA for contraception in the United States in 1960, **combination oral contraceptive** pills (COCs) contain both an estrogen and a progestin component. They prevent ovulation and pregnancy by inhibiting gonadotropin-releasing hormone and, subsequently, follicle-stimulating and luteinizing hormones. COCs are needed to start follicular maturation and for ovulation.

The COCs approved by USFDA are *ethinyl estradiol/norgestimate*, *ethinyl estradiol/norethindrone acetate/ferrous fumarate*, *ethinyl estradiol/drospirenone*, and *ethinyl estradiol/drospirenone/levomefolate*.

Based on their antiandrogenic properties, COCs decrease androgen production at the level of the ovary and also increase SHBG, binding free circulating testosterone and rendering it unavailable to bind and activate the androgen receptor. The activity of 5-a-reductase is reduced, thereby blocking the androgen receptor [91–93].

Numerous randomized controlled trials showed that COCs reduce both inflammatory and comedonal lesion counts. However, determining which COC is consistently superior in the treatment of acne is difficult. Palli et al. evaluated the effectiveness of drospirenone 3 mg/ethinyl estradiol 0.02 mg in the treatment of moderate truncal acne. Result showed significant reductions in inflammatory, noninflammatory, and total acne lesions compared to placebo [94].

Like any other drug, there are risks when taking COCs:

Venous thromboembolic events (VTEs) have been implicated with COCs, usually with higher doses of ethinyl estradiol. However, some progestins have been associated as risk factors for VTE.

The risk of **myocardial infarction (MI)** is also increased in COC users, more so in the presence of cigarette smoking, diabetes mellitus, and hypertension. Both

ischemic and hemorrhagic stroke in COC users were noted, but quite uncommon in women of reproductive age [92, 95, 96].

There is increased risk of **breast cancer** in some women taking COCs. Notably, this increased risk of breast cancer is greatest in women 34 years of age, when the overall incidence of breast cancer is at its lowest. Gierisch et al. however noted that the duration of COC use or a positive family history of breast cancer did not appear to be added risks [97]. Though **cervical cancer** may be increased in COC users, the risk declines after the COC is discontinued and the increase in risk disappears after 10 years of nonuse [98].

Within two years of first having menstruation or in patients who are 14 years of age, the use of COC for acne should be avoided unless it is clinically warranted. The development of peak bone mass occurs during adolescence and young adulthood. The addition of low-dose estrogen COCs early in the teen years may weaken the buildup of bone mass [99].

The FDA has approved COC use for females 14 years (e.g., drospirenone and drospirenone/levomefolate) or 15 years (e.g., norgestimate and norethindrone/ferrous fumarate) and older. Noncontraceptive benefits of COCs, in addition to the improvement of acne, include regulation of the menstrual cycle, lessening of menorrhagia and associated anemia, and a decrease in the formation of benign ovarian tumors. There has been decreased risks for colorectal, ovarian, and endometrial cancers [92, 100].

A comprehensive acne treatment regimen may include COCs. They may be used in combination with other oral acne medications like spironolactone [101]. The tetracycline class of antibiotics were shown not to affect the effectiveness of the COCs; hence they may be used in conjunction with COCs [102, 103]. Rifampin and griseofulvin are the only anti-infectives that may interact with COCs, lessening their effectiveness [101].

Before initiating the use of a COC, a Papanicolaou smear and a bimanual pelvic examination may still be done but are no longer deemed mandatory since both procedures do not identify women who should not take a COC.

5.2.5.4.2 Spironolactone

Spironolactone is an aldosterone receptor antagonist with a potent antiandrogen activity.

It decreases testosterone production by competitively inhibiting the binding of testosterone and DHT to androgen receptors in the skin [104–106]. It may also inhibit 5-a-reductase and increase SHBG.

The usual dosage for the treatment of acne is 50–200 mg daily, taken after a meal. Despite the long use of spironolactone in acne and due to the limited number of literature studies, the efficacy of spironolactone remains to be considered intermediary [107].

In a study by Shaw et al., spironolactone given at 50 to 100 mg daily, either as monotherapy or as adjunctive therapy, led to 66% of the subjects being clear or

markedly improved, with favorable tolerability at these lower doses [108]. Among Asian women, 200 mg daily for 8 weeks with the dose tapered by 50 mg every four weeks over a total of 20 weeks showed clinical improvement rated as good to excellent [106].

With the available evidence, experience, and expert opinion, work group supports the use of spironolactone in the management of acne for select women. It is well tolerated with the side effects being dose related. The most common side effects include diuresis, menstrual irregularities, and breast tenderness; less common are breast enlargement, fatigue, headache, and dizziness [109, 110]. It is pregnancy category C with animal studies having shown feminization of a male fetus early in gestation. There is also an increased risk of hypospadias. Oral contraceptives should be used with spironolactone due to the risk of birth defects and for the reduction of side effects [111].

It is generally safer and well accepted to use spironolactone in women. In men, side effects as impotence, decreased libido, and gynecomastia limit its use [112]. Hyperkalemia, a serious side effect, is rare in young healthy individuals as long as they have normal hepatic, adrenal, and renal functions. However, potassium monitoring should be done frequently and on a regular basis while on spironolactone and the drug should be immediately stopped if hyperkalemia ensues.

Topical spironolactone 5% has been investigated for its local antiandrogen effects but much larger controlled studies are required to assess its efficacy and safety in the future [113].

5.2.5.4.3 Flutamide

Flutamide, a nonsteroidal selective androgen receptor blocker, is mainly used in the treatment of prostate cancer. Adalatkah et al. have noted its effectivity to treat acne, androgenetic alopecia, and hirsutism [114]; however, its indication for acne is not yet approved by the USFDA [82].

The dose can range from 62.5 mg daily to 250 mg twice daily [115]. Combined with a triphasic COC, flutamide at 250 mg twice daily reduced acne by 80% compared with spironolactone 50 mg twice daily/COC, which reduced acne by only 50% after 3 months of therapy [116].

Dose and age-related side effects noted were breast tenderness, gastrointestinal problem, decreased libido, pseudohermaphrodite condition and signs of feminization in the male fetus [117], as well as idiosyncratic fatal hepatitis [118].

5.2.5.4.4 Prednisone

Prednisone which is given at 0.5 to 1 mg/kg/day is indicated for the treatment of the systemic and cutaneous manifestations of acne fulminans. It is also recommended for the treatment and prevention of isotretinoin-induced acne fulminans-like

eruptions. There is a need to slowly taper the dose over several months while transitioning to isotretinoin or oral antibiotics in order to minimize relapses. Because of adverse effects, its long-time use is prohibited [119].

Bettoli et al. reported that oral corticosteroids, if used in high doses, might help patients with inflammatory signs of acne despite any hormonal causes. Low-dose steroids suppress adrenal activity in patients with proven adrenal hyperactivity [81].

Long-term use of more than 6 months is not recommended. It is mandatory to monitor blood sugar and signs of osteoporosis. ACTH stimulation test should be used every 2 months to test for risk of adrenal suppression [120].

5.2.5.4.5 Cyproterone Acetate (CPA)

Cyproterone acetate, one of the earliest and most studied antiandrogens, may also exhibit properties of being a progestin. When used as a monotherapy, in doses of 50–100 mg/day from days 1 to 10 of the menstrual cycle, acne improvement was rated to be from 75% to 90% [121, 122].

5.2.5.4.6 Drospirenone

Drospirenone is the only progestin approved by the USFDA. It blocks the androgen receptors and is truly antiandrogenic, even without the addition of estrogen [95].

5.2.5.4.7 GRH Agonists

Gonadotropin-releasing hormone agonists, analogs of GRH, impedes the ovarian cyclic release of LH/FSH. This leads to an induced state of anovulation, with the end results of suppressing both estrogen and androgen production [123]. It can be administered as a nasal spray, through subcutaneous or intramuscular injections, or as a subcutaneous implant [124].

5.2.5.4.8 Cortexolone 17α-Propionate

Cortexolone 17α-propionate cream is a topical steroidal antiandrogen agent with a strong antiandrogen activity and mild anti-inflammatory properties [125]. The medication was approved by the US Food and Drug Administration (FDA) for the treatment of acne in August 2020.

5.3 Acne in Pregnancy

In as much as there is a myriad of researches on all aspects of acne vulgaris across the globe, there is still a paucity of knowledge on the special population of pregnant women suffering from this disease.

5.3.1 Epidemiology

Some researches dealing with skin changes and diseases in pregnancy showed a small percentage of this population having acne vulgaris (0.1–10%) [126–129]. In the past decade, three interesting studies focused on acne in pregnancy. Dreno's French study was a cross-sectional questionnaire on 378 patients conducted in 18 months [130], Yang's Taiwanese study was a 12-month prospective longitudinal study on 35 patients [131], and Kutlu's more recent prospective cross-sectional study involved 295 patients in Turkey within a span of 4 years [132]. Included subjects were 18 years old and above and the mean age in years were similar for all: 29.8 ± 4.8 [130], 28.5 [131], and 27.06 ± 4.88 [132].

As of late, acne in adult women has caught much attention [2, 7, 31, 133, 134] and in this essence, acne among pregnant women has been claimed to share many common points with this new population [130–132].

A previous history of pre-pregnancy acne was noted in the majority [130, 131] if not all of the subjects [132]. Among the 86.6% of these patients in Dreno's study, 35.1% reported relapse of cured acne and 51.5% had continuous acne since adolescence [130]. The latter category comprised 94.3% in the study of Yang [131]. Similarly, Kutlu's study revealed a high percentage of persistent acne (71.2%) with the remaining 25.8% having adult-onset acne [132].

5.3.1.1 Factors to Consider Among Pregnant Women with Acne

5.3.1.1.1 Previous History of Pre-pregnancy Acne

Earlier reports showed that women bearing a previous history of acne had a higher incidence of acne while pregnant, with worsening on the face and notable extension to the trunk [130]. However, a recent study revealed that acne severity while pregnant had no correlation with the onset of acne pre- or postpuberty. Also, though there was a high number of pregnant acne patients reporting persistent or adult-onset acne, the same group did not find a significant relationship between the history of adult-onset acne and acne severity [132].

5.3.1.1.2 Menstrual Cycle History

Women with irregular menstrual cycles (oligomenorrhea or polymenorrhea) were reported to have significantly more severe to very severe acne than those with normal menstruation in the study of Kutlu. However, further analysis in the same study showed no statistical significance between acne severity and the length of menstruation periods before pregnancy. Also, though premenstrual worsening of acne was reported in more than 50% of the study population of Kutlu, they found no relationship between acne severity in pregnancy and perimenstrual worsening of acne [132]. Similarly, in another study, a history of dysmenorrhea did not affect the severity of facial acne [131].

5.3.1.1.3 Age of Pregnant Women with Acne

In the study of Dreno and Kutlu involving a bigger number of subjects, they observed that younger patients (≤25 yo) tended to have more severe to very severe facial acne while pregnant; also, truncal acne was noted to be higher in this age group [130, 132].

5.3.1.1.4 Gravidity/Parity

Gravidity, defined as the number of times a woman has been pregnant, was noted to have a negative effect on the severity of acne. Older primigravidas (≥25 yo) were reported to have a higher number of facial acne lesions during the second and third trimesters in the study of Yang [131]. Submandibular, chest, and upper back involvement were noted to be significantly higher in the third trimester [132].

Parity, on the other hand, is defined as the number of times the woman has given birth to a fetus with a gestational age of ≥24 weeks. Though acne was reported in previous pregnancies, no correlation between acne severity and parity was shown [130, 132].

5.3.1.1.5 Distribution of Acne Lesions

Facial acne was common among the pregnant patients in the three aforementioned studies, but only 35.2% was noted among the French subjects compared with a much higher percentage among the patients in Taiwan and Turkey [130–132].

The degree of involvement on the different parts of the face varied. The mandibular region was significantly involved [130–132] but the cheeks were most affected in the Taiwanese and Turkish studies [131, 132]. Truncal acne was noted in 52.8% [132] and 87.2% [130] of the pregnant subjects, being significantly higher in the third trimester [132].

Even if the three studies differ in the distribution of facial acne among pregnant women, similarities to adult female acne were substantiated with the perioral and mandibular areas being affected in both sets of patients.

5.3.1.1.6 Severity of Acne Lesions

Acne severity was generally mild to moderate among pregnant patients, most notable in the second trimester [131, 132]. While inflammatory lesions predominated in the French study, with nodules and cysts more notable in those with a history of continuous acne [130], severe or very severe acne was not recorded by Yang et al. among its Taiwanese subjects [131] and only 13.9%, most common in the third trimester, was noted in the study done in Turkey [132].

Interestingly, while Yang et al. noted that higher numbers of inflammatory facial acne in the second and third trimesters were associated with the woman being a primigravida and with the newborn bearing a female gender and having a low birth weight for gestational age [131], Kutlu et al. found no correlation between acne severity and the newborn's birth weight [132].

Acne severity in pregnancy was found to have no significant relationship with the onset of acne pre- or postpuberty nor with history of adult onset of acne [132].

In an earlier study, no association between severity of facial acne and body mass index (BMI) at the first maternal visit and maternal weight gain throughout pregnancy was disclosed [131] but in a more recent research, it was noted that women with higher BMI for pregnancy showed significantly more severe to very severe acne [132].

5.3.1.1.7 Medical Conditions

Prior polycystic ovary syndrome (PCOS) was noted among 26 (8.8%) pregnant patients with acne. Among this subset of patients, variable severity of acne was noted, with 18 (69.2%) having mild to moderate acne and 8 (30.8%) with severe to very severe acne; truncal acne was higher in the third trimester [132].

Only 3.7% of the pregnant patients with acne in the Turkish study exhibited gestational diabetes mellitus. The acne severity of this subset of patients was mild. No statistical correlation between acne severity and gestational DM was established [132].

A small number (11.9%) of pregnant acne patients was reported to have androgenetic alopecia of different stages (Ludwig stage 1–3). The analysis showed no significant correlation between acne severity and stage of AGA [132].

Pregnant women with hirsutism (12.2%) had a higher prevalence of severe acne in pregnancy but there was no correlation of acne severity and degree of hirsutism [132].

History of thyroid diseases was also not associated with the severity of facial acne [131].

5.3.1.1.8 Smoking/Alcohol Consumption Continued While Pregnant

Smoking was noted to be continued while pregnant in a small percentage of women in Kutlu's study (7.5%) with a median of 20 cigarettes per day for 1 year. However, the authors did not find any correlation between acne severity and smoking during pregnancy. None reported alcohol consumption during pregnancy [132].

5.3.1.1.9 Effect of Previous Medications on Acne in Pregnancy

No link between the course of acne and the previous use of contraceptives was noted [130].

In the study involving pregnant Turkish women, 70.2% reported receiving acne treatment before pregnancy. Of these, 37.7% received systemic therapies (antibiotics, spironolactone, oral contraceptive pills, or isotretinoin). Of the 32 patients who received oral isotretinoin prior to pregnancy, only two had severe to very severe acne during pregnancy, while those whose acne was treated pre-pregnancy with oral antibiotics presented more with severe to very severe acne while pregnant [132].

5.3.2 Pathogenesis

Pregnancy, with its associated physiological changes, whether it be hormonal, metabolic, and emotional, is known to initiate the onset of skin diseases specific to pregnancy or modify existing skin diseases [131, 135]. Acne vulgaris can be quite unpredictable in its course during pregnancy [136] and the changes in the multifactorial nature of acne while a woman is pregnant are not much explored.

5.3.2.1 Gestational Hormone Status

During pregnancy, hormonal changes are noted and considered part of the gestational process: human chorionic gonadotropin production peaking at week 12, progesterone and estrogen production from the corpus luteum, and even alterations in thyroid function causing a higher yield of gonadotropins and adrenocorticotropic hormone [137]. Progressive elevation of serum androgens [138] is noted as well, with testosterone (T) levels peaking at birth [139]. Nonpregnant levels of testosterone among women with no PCOS were observed to be <50 ng/dL (1.7 nmol/L) [138]. An age-related decrease in serum T and its adrenal precursor dehydroepiandrosterone sulfate (DHEA-S) was also noted among women aged 20–49 years old without complaints of any sexual dysfunction, from 51.5 to 33.7 ng/dL and 195.6 to 140.4 μg/dL, respectively [140]. Pregnancy levels of serum T are in the 50–120 ng/dL (1.7–4.2 nmol/L) range [138].

In nonpregnant women, free testosterone comes from the adrenals (25%), ovary (25%), and a higher percentage (50%) from the peripheral conversion of androstenedione which includes the skin and adipose tissue [141]. In the early phases of pregnancy, the maternal ovary appears to be the prime source of the increased production of testosterone, with contribution from the adrenal glands and adipose tissue. However, during the main course of pregnancy, the central testosterone production comes from the fetoplacental unit [142].

Although maternal serum T is increased during pregnancy by 70% [132], its effects are offset by the increased sex hormone binding globulin (SHBG)-bound androgens in the serum [139] and the very high increase in progesterone levels (10–100-fold) [143] which may inhibit binding of testosterone to the androgen receptor and conversion of testosterone to dihydrotestosterone. Also, the placenta bears a great capacity in the conversion of androgens to estrogens, affording metabolism of the increased androgen production during pregnancy. Moreover, an increase in estradiol levels (10–50-fold) was noted during pregnancy [143].

These physiological surges still do not completely explain the occurrence of acne in pregnancy since not all pregnant women have acne during pregnancy [130–132]. However, acne worsening in the third trimester may be accorded to the increased maternal androgen concentrations and the resultant effects on sebum production [144].

In the studies on acne in pregnancy, the majority of the patients had mild to moderate acne. Hormones-wise, the significant escalation of beta-human chorionic gonadotropin in the first trimester may stimulate androgen production and thus induce acne [145]. By the second and third trimesters, the excessive progesterone levels may worsen the acne due to the spur in sebum production and keratinocyte proliferation [48, 146–148]. Excessive amounts of prolactin noted during the third trimester may be contributory to the state of acne by increasing sebosecretion in the skin, partly by way of androgen-dependent routes [48].

5.3.3 Management of Acne in Pregnancy

Treating acne in any stage of a person's life is challenging enough, whether one is a neonate, an adolescent, or an adult. Every phase encounters hurdles and the question of adherence to therapy. What more during pregnancy and lactation?

As safety and efficacy of the medications both for the mother and the fetus at any point in time must always be the priority when considering treatment options, limitations in the usage of commonly effective drugs exist. As guidelines in the management of acne have evolved through the years, weight on the correct choice of treatment for pregnant women has always been emphasized (Fig. 5.3).

Prudence dictates us to be knowledgeable of the US-FDA Pregnancy Risk Categories [48, 146] (Table 5.1) before any acne drug can be administered to this special set of population. Though this categorization has moved on to a more elaborate Pregnancy and Lactation Labeling Rule (PLLR) since 2015 [149, 150],

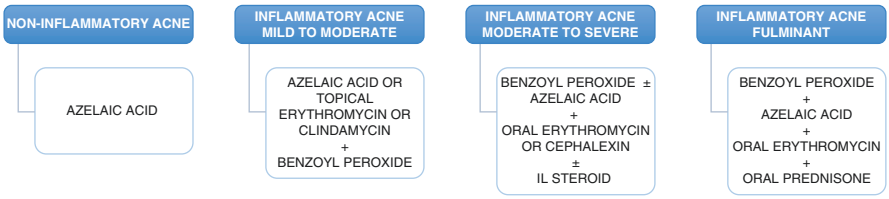

Fig. 5.3 Treatment options for acne in pregnancy. (Adapted from Chien AL, Qi J, Rainer B, et al. Treatment of acne in pregnancy. J Am Board Fam Med 2016;29:254–62)

Table 5.1 US-FDA pregnancy categories prior to PLLR

Category	Recommendation	Animal/human studies	Drugs for acne
A	Controlled studies showed no risk to humans	Pregnant women studies: Adequate, well-controlled, and have not shown an increased risk of fetal abnormalities	None
B	No evidence of risk in humans	Animal studies: No evidence of harm to the fetus Pregnant women studies: No adequate and well- controlled studies or	Topical Azelaic acid Topical & Oral Erythromycin Topical clindamycin Oral amoxicillin Oral cephalexin Oral azithromycin Oral metronidazole
		Animal studies: Shown an adverse effect Pregnant women studies: Adequate, well-controlled have failed to demonstrate a risk to the fetus	
C	Risks cannot be ruled out in humans	Animal studies: Shown an adverse effect Pregnant women studies: No adequate and well- controlled studies or	Topical benzoyl peroxide Topical salicylic acid Topical sodium Sulfacetamide Topical Dapsone Topical tretinoin Topical Adapalene Topical TCA Topical aminolevulinic acid Oral Trimethroprim-sulfamethoxazole Oral prednisone Oral zinc sulfate
		Animal studies: None conducted Pregnant women studies: No adequate and well-controlled studies	
D	Clear evidence of risks in humans However, the potential benefits of therapy may outweigh the potential risks	Pregnant women studies: Adequate, well-controlled, or observational, have demonstrated a risk to the fetus	Oral Tetracyclines Oral spironolactone Oral minocycline Oral doxycycline

Table 5.1 (continued)

Category	Recommendation	Animal/human studies	Drugs for acne
X	Contraindicated in human pregnancy	Animals or pregnant women studies: Adequate, well-controlled, or observational, have demonstrated positive evidence of fetal abnormalities	Topical Tazarotene Oral isotretinoin
NA	Pregnancy rating not available		Topical glycolic acid Topical lactic acid Topical Jessner's solution Topical Clascoterone Oral zinc gluconate

majority of the studies still use the long-known lettered categories for practical reasons [131, 132, 151, 152]. Manufacturer-wise, all products, over-the-counter or prescribed, should ideally bear pregnancy/lactation warnings [153].

5.3.3.1 Topical Agents

The use of topical agents is a mainstay for the treatment of all types of acne vulgaris in pregnant women. Noninflammatory/comedolytic acne and inflammatory mild to moderate acne are best treated with topical agents alone [130–132, 152].

5.3.3.1.1 Maybe Recommended Are the Following

Azelaic Acid

*Pregnancy Category B.

It is a naturally occurring saturated 9-dicarboxylic acid with a broad antimicrobial coverage including *C. acnes* and acts by interrupting mitochondrial respiration and production of DNA [154]. It is comedolytic, mildly anti-inflammatory with antityrosinase activity [146]. Only a minimal amount (<4%) is available systemically after topical application; hence it is noted to be pregnancy low risk [150]. A significant change from its baseline levels in breast milk is not expected [155] such that small doses are unlikely to pose a lactation risk [10].

At 15%–20%, it is an effective antiacne agent for pregnancy with a good evidence rating [156, 157] and can be recommended for mild acne with noninflammatory lesions [10, 146, 158, 159].

Combined with topical benzoyl peroxide, erythromycin, or clindamycin, it can be used for inflammatory lesions [146, 158]. An added advantage is the absence of reported *C. acnes* resistance from prolonged use of azelaic acid [146].

Benzoyl Peroxide

*Pregnancy Category C.

An organic peroxide by origin, benzoyl peroxide is a broad-spectrum bactericidal agent lethal to *C. acnes* in vitro, inhibiting triglyceride hydrolysis and reducing inflammation in acne lesions. It has comedolytic and keratolytic activities added to its antiacne effects. Approximately 5% is absorbed systemically, completely metabolized into benzoic acid (a food additive) which is rapidly cleared by the kidneys with no expected systemic toxicity [154]. Note that exposure to benzoic acid in the diet is greater than exposure from topical application [160]. Though there are no adverse reports in lactation [10], it remains unknown if benzoyl peroxide is excreted in breast milk, hence caution in administering to nursing females [150]; it has been labeled as compatible with lactation [160]. It is considered safe to use during pregnancy, best used for inflammatory acne [146], and helps prevent the development of resistance when used in conjunction with antibiotics [160, 161].

Salicylic Acid

*Pregnancy Category C.

This lipid-soluble phenolic aromatic acid acts as a keratolytic/desmolytic and comedolytic antiacne agent [161]. Systemic absorption is minimal (9–25%) and teratogenic potential is very low [136]. Salicylate toxicity may arise with the widespread application of highly concentrated salicylic acid on hyperkeratotic skin but no reported cases in association with the use of salicylic containing acne products [162]. It can be used by pregnant and lactating females with a caution to use on localized areas for a limited length of time and under no occlusive dressings [153, 160].

Sodium Sulfacetamide

*Pregnancy Category C.

Sodium sulfacetamide is an aniline-derived synthetic molecule that inhibits dihydropteroate synthetase leading to a decrease in folic acid formation [154]. Its use in acne derives from its being antibacterial and anti-inflammatory [154], with a skin absorption of only about 4% after topical application [160]. There are no reports of congenital anomalies with sulfacetamide [151], and it is deemed compatible with lactation [160].

Topical Antibiotics—Erythromycin and Clindamycin

*Pregnancy Category B.

While erythromycin is a macrolide having its origin directly from *Streptomyces erythraeus*, clindamycin is an artificial derivative of lincomycin, an antibacterial isolated from *Streptomyces* species [154]. Both reduce the amount of *C. acnes* in the

sebaceous follicles through inhibition of bacterial protein synthesis, leading to suppression of inflammatory acne [146].

Being the most commonly prescribed among topical antibiotics to treat inflammatory acne, bacterial resistance has been recorded with monotherapy and long-term use. Concomitant use of benzoyl peroxide however was shown to improve therapeutic efficacy [154, 163, 164].

Though the effect of chronic use of these topical antibiotics is not available [146], still this combination of either topical erythromycin or clindamycin and benzoyl peroxide can be used for pregnant females with inflammatory acne [156, 157].

Both are lactation compatible [160].

5.3.3.1.2 To Be Used with Caution

Topical Dapsone

*Pregnancy Category C.

A synthetic sulfone with antimicrobial and anti-inflammatory properties, it exerts its effect by inhibiting dihydropteroate synthetase [154]. As an antiacne agent, it has shown significant efficacy on inflammatory lesions [165]. The risks of maternal anemia, neonatal hyperbilirubinemia, and hemolytic anemia have been linked with oral dapsone among those with glucose-6-phosphate dehydrogenase deficiency; these however are low with topical dapsone [159].

It must be noted that although the topical application of dapsone did not result in systemic toxicity even if used for a year [166], safety data among pregnant women is scarce; hence, it should be used with caution [159].

5.3.3.1.3 Not Recommended Are the Following

Topical Retinoids (Tretinoin, Adapalene, Tazarotene)

Its capacity to modulate keratinocyte differentiation leads to its comedolytic and anti-inflammatory effect [146]. Only small amounts of topical tretinoin and adapalene are absorbed systemically; hence it is unlikely to lead to congenital malformations [167]. This was supported by Kaplan's meta-analysis on pregnancy outcomes following first-trimester exposure to topical retinoids where major increases in the rates of spontaneous abortions, congenital malformations, prematurity, and low birth weight were ruled out [168].

However, with a questionable risk-to-benefit ratio, avoidance is still recommended in pregnant women [146, 160].

Tretinoin

*Pregnancy Category C.

Also known as all-trans retinoic acid, it is a naturally occurring retinoid. Being the earliest of the retinoids to be discovered, much studies have been done on its safety and efficacy profiles among the general population.

Among pregnant women, only minimal amounts are absorbed systemically and among lactating women, minimal amounts found in breast milk were considered not to be harmful to infants [155].

Adapalene

*Pregnancy Category C.

It is a synthetic retinoid that is more chemically stable and lipophilic than tretinoin [169].

Only trace amounts were shown to be systemically absorbed [169] but excretion in breast milk is unknown [142]. Yet, with no controlled studies among pregnant patients, use is not advocated.

Tazarotene

*Pregnancy Category X.

Tazarotene is a synthetic retinoid prodrug rapidly converted in the tissues to the active metabolite tazarotenic acid [169, 170]. Even if systemic absorption is only at 6% [155], its reported retinoid-like malformations in experimental animals led to its not being recommended in pregnant women [170].

Trace amounts were noted to be excreted into human milk but the risk to a nursing infant is unknown [155, 170]; limited human data suggest potential toxicity hence not recommended in the lactation phase.

5.3.3.1.4 No Pregnancy/Lactation Rating

Clascoterone

The 2020 FDA-approved 1% androgen receptor inhibitor decreases sebum production and inflammation. It is readily metabolized at application areas to an inactive form, ideally limiting systemic activity [171].

Though adverse events were observed in some animal studies following subcutaneous administration, information relating to topical clascoterone exposure in pregnancy is limited since recent trials excluded pregnant patients. It is not known if the drug is present in breast milk [172].

5.3.3.2 Systemic Agents

Oral agents may be used for moderate to severe inflammatory acne and recalcitrant-to-treatment acne in pregnancy.

5.3.3.2.1 May Be Given, as the Situation Calls for

Oral Antibiotics

To date, the penicillin and erythromycin group of antibiotics have a history of safety of administration during pregnancy. But judicious use is imperative and the benefits must outweigh the risks. It is recommended that intake be done only during the second and third trimesters when organogenesis is complete and duration limited to less than six weeks [146].

Macrolide Erythromycin (250 mg-500 mg, 2-4× a day)

*Pregnancy Category B.

It is the antibiotic of choice throughout pregnancy, with preference for the erythromycin base or ethylsuccinate. The estolate form causes maternal hepatotoxicity during the second trimester and is contraindicated during pregnancy [146, 150, 160]. Single doses cross the placenta poorly, leading to low concentrations in the fetal tissue [146]; hence, it is lactation compatible [170].

Macrolide Azithromycin (Variable Dosing; 250 mg 3× a Day)

*Pregnancy Category B.

Azithromycin is an erythromycin-derived antibiotic [53] that has an off-label indication for the treatment of acne [146]. There is no suggestion that azithromycin poses an embryo-fetal risk of developing toxicity, based on human pregnancy data. An increase in the risk of pyloric stenosis has not been associated with this drug [170], hence deemed compatible to be used in pregnancy [160, 173]. Though excreted in small amounts in breast milk, studies have not shown any adverse effects, hence compatible to use in lactation [155, 170].

Beta-Lactam Amoxicillin (250–500 mg 2× a Day)

*Pregnancy Category B.

Amoxicillin is an aminopenicillin, known to cross the placenta [170]. Though it can be considered as an option for treating resistant acne and is generally not known to be teratogenic [173] there are reports of increased risk of oral clefts if used early in pregnancy [174] and increased risk of neonatal necrotizing enterocolitis in women at risk of preterm delivery [173]. Concentrations in the human milk are <1% and considered compatible to use during lactation [155, 170].

Beta-Lactam Cephalexin (500 mg 2× a Day)

*Pregnancy Category B.

Cephalexin is a first-generation cephalosporin that is found to be safe in pregnancy and lactation [155, 160, 170, 173]. It is anti-inflammatory; thus it can be used

for acne in pregnancy but resistance to staphylococcus developing with its use may be a concern [146].

Nitroimidazole Metronidazole (250 mg 2× a Day)

*Pregnancy Category B.

An oral synthetic antiprotozoal and antibacterial agent, it is not a first-line treatment for acne and is rarely used for uncomplicated acne vulgaris. But for refractory and very severe acne, it may be considered as one of the last options when the condition is unresponsive to the customary line-up of oral antibacterials [152]. It is being used safely for other nondermatological conditions during pregnancy [175] and Briggs branded it as low risk as per human data; however, lactation-wise, with limited human data available, potential toxicity exists with divided dosing, hence must be taken with caution [170].

Trimethoprim-Sulfamethoxazole (TMP/SMX) (160/800 mg 2× a Day)

*Pregnancy Category C.

Also known as cotrimoxazole, it is a combination of a dihydrofolate reductase inhibitor (TMP) and a dihydropteroate synthetase inhibitor (SMX), synergistically acting as a selective folate antagonist [176].

The combination increased the risk of cardiovascular defects with first-trimester exposure, preterm birth, low birth weight, and miscarriage but the primary danger is its use near delivery when the risk of neonatal hyperbilirubinemia increases [160].

It is secreted into the breast milk in low concentrations but still must be used with caution [150].

Only consider TMP-SMX as an alternative antiagent if the aforementioned antibiotics do not work and when benefits prevail over the risks.

5.3.3.2.2 Oral Corticosteroids

Prednisone (≤20 mg/day for not more than 4 Weeks)

*Pregnancy Category C.

Prednisone, an intermediate-acting nonfluorinated corticosteroid, is favored for use in pregnancy since its route towards the embryo is limited by placental enzymes [177]. The absolute risk of orofacial cleft noted during the first trimester is low [160].

For pregnant women having fulminant nodular cystic acne, it may be appropriately given after the first trimester, more specifically during the third trimester, at ≤20 mg/day for not more than 4 weeks [146, 157, 158, 160].

It is labeled as compatible with breastfeeding [155, 170].

5.3.3.2.3 Supplements

Zinc (Zn Gluconate < 75 mg/Day)

*Zinc sulfate (23% zinc)—Pregnancy Category C.

*Zinc gluconate (14% zinc)—not formally categorized.

Zinc is a trace element with antibacterial, anti-inflammatory, antisebum properties [146] that was shown to be effective for mild to moderate inflammatory acne in some studies [178]. Though the recommended dietary allowance during pregnancy is 11 mg/day, the French study of Dreno on pregnant women with acne noted zinc gluconate to be given at 30 mg/day by a majority of the dermatologists [130]. Combining topical antibiotics with the intake of zinc salts has been shown to decrease the risk of bacterial resistance [7, 179].

Of the studies involving more than 2500 pregnant women given zinc at variable doses, there was no mention of risk for fetal abnormalities nor fetal harm at doses <75 mg/day [179].

5.3.3.2.4 Contraindicated

Tetracyclines

*Pregnancy Category D.

Tetracycline binds to calcium orthophosphate and its deposition in the teeth is permanent [146]. Exposure after the twentieth week of gestation leads to yellow-stained deciduous teeth which still darken in time [173]. Bone deposition led to a small fetal size and inhibition of fibular growth [146, 173].

It is best to be avoided during pregnancy especially after the first trimester; acute fatty liver of pregnancy can be an outcome [173].

It is, however, lactation compatible and the possibility of dental staining at this stage of lactation may be remote [170].

Spironolactone

*Pregnancy Category D.

An antiandrogen that inhibits 5-alpha reductase and antagonizes androgen receptors, this drug must be avoided due to the increased risk of male fetus feminization and hypospadias [160].

Though there is a possibility of suppression of milk during lactation, it is deemed compatible with breastfeeding [170].

*Isotretinoin**

*Pregnancy Category X.

Isotretinoin, a vitamin A isomer, is the only systemic retinoid FDA approved for acne vulgaris, specifically for severe recalcitrant nodular acne [170, 180]. Its

effectivity to reduce sebum production and normalize keratinization has been well recorded.

However, pregnancy-wise, the drug is contraindicated. It has been associated with major fetal abnormalities, spontaneous abortions, premature births, and low IQ scores, among others [146, 150]. Embryopathy has been reported even with single doses [150]. Isotretinoin is highly lipid-soluble and if taken during the lactation phase, concentrations in the milk would be substantial and may lead to infantile retinoid toxicity [155].

**Further discussion on isotretinoin can be found in the latter part of this chapter.*

5.3.3.3 Procedural Options

Procedural options serve as adjuncts to topical and oral agents in the management of acne in pregnancy.

5.3.3.3.1 Intralesional Steroid Injection for Cystic Acne Lesions

Few data are available on the transplacental transfer of intralesional steroid and if used with caution, it is unlikely to pose additional risk to the fetus [146].

5.3.3.3.2 Chemical Peels

Glycolic Acid

*No Pregnancy Categorization available.

No published reports on adverse effects during pregnancy and is deemed safe to use [181, 182].

There is limited dermal penetration with in vitro studies showing that ≤27% is absorbed into the skin, depending on the pH, concentration, and time [182].

Lactic Acid

*No pregnancy categorization.

Dermal penetration is limited and the 2% concentration has reports of safe use for gestational acne [182].

Salicylic Acid

*Pregnancy Category C.

There is a significant dermal penetration of up to 25% when treating large areas or when used under occlusion [181]. If to be used, must be cautiously applied on only small areas [182].

Jessner's Solution

*No pregnancy categorization.

There is a deficiency of reports on its use during pregnancy. However, since this solution is a combination of resorcinol, salicylic acid, and lactic acid, caution is the key to its utilization as a peeling agent [182].

Trichloroacetic acid (TCA)

*Pregnancy Category C.

Lee et al. reported possible dermal penetration of TCA since it can be absorbed through ocular and oral mucosal surfaces [181]. TCA in maternal urine correlated with fetal growth retardation [183]. It must therefore be used with caution or not used at all during pregnancy. During lactation, it may unlikely appear in breast milk and is considered safe to use during breastfeeding. Application must be avoided on areas that may come in contact with the infant's skin [184].

5.3.3.3.3 Photodynamic Therapy (PDT)

Aminolevulinic acid (ALA)

*Pregnancy Category C.

Topical ALA-PDT may directly induce injury to the sebaceous glands, thereby impeding further manufacture of sebum. The growth of *C. acnes* is ideally stopped. Also, modifications on keratinocyte shedding and hyperkeratosis may lead to a decrease in the follicular blockade. PDT has emerged over many years as a form of alternative therapy for the treatment of acne, with variable results among the general population.

The risk to pregnant women cannot be totally ruled out since animal reproduction studies have not been done. The amount that is excreted in breast milk is unknown, hence caution for nursing mothers [185].

Narrowband Ultraviolet B Phototherapy

Its use in the treatment of acne is based on its anti-inflammatory capacity [186].

Short-term treatment for pregnant patients deemed likely safe [152] but caution on use during the early stages of pregnancy must be observed since the highest risk for folate deficiency occurs early in pregnancy [152, 161].

5.4 Isotretinoin in Women

Isotretinoin (13-cis retinoic acid), a first-generation retinoid, was initially produced 67 years back (1955), intended primarily for keratinizing conditions, and subsequently explored for its impressive effect on acne vulgaris. Fifteen years later (1970s),

it was established to be a greatly valuable drug for acne vulgaris especially for the cystic type; however, approval by the USFDA as a treatment for severe nodulocystic acne came after another 12 years (1982) [180]. Classically reserved for nodulocystic acne, it has become the drug of choice by dermatologists even for moderate to severe acne [187], as it targets all the four key factors in acne pathogenesis [188] and has the best impact on improving the quality of life of acne patients [189, 190].

Adherence to therapy has been an issue in achieving therapeutic success in the management of acne across all ages and gender. Treatment simplification, correct patient selection, and use of isotretinoin for increased acne severity may contribute to increased compliance [187]. It was shown in the study of Hayran et al. that treatment satisfaction was higher among females and patients using oral isotretinoin [191].

Apart from isotretinoin's primary indication for nodulocystic acne, it has been used for severe acne cases where oral antibiotics of 6–8 weeks with topical retinoids and benzoyl peroxide have failed and for patients prone to severe acne scarring and manifesting severe psychological or physical distress due to their acne condition [192, 193]. And for many years, many experts are stepping up for its utilization not only in cases failing conventional therapy [194] but also for patients with mild to moderate acne desiring rapid improvement and for patients manifesting over seborrhea [195].

5.4.1 What Pharmacokinetics Tell us

Isotretinoin is a naturally occurring retinoid in the human serum readily produced after the consumption of vitamin A. Bioavailability after intake is approximately 25%, enhanced when it is taken with food since it is highly lipophilic. It is extensively bound to plasma proteins and rapidly distributed to both the epidermis and dermis, with enterohepatic circulation playing an important role in its pharmacokinetics. Upon termination of intake at doses of 0.5–1 mg/kg/day, isotretinoin returns to its endogenous concentrations within 2 weeks [196].

It suppresses sebum production by ultimately causing apoptosis of the sebocytes, which may be dosage-dependent [197]. As a result of this sebosuppression, a resultant decrease in the size of the pilosebaceous unit ensues together with the decrease in the number of *C. acnes*. Reduction in the inflammatory process has been reported to be brought about by a decrease in the expression of monocyte toll-like receptor-2 (TLR2), inhibition of neutrophil and monocyte chemotaxis, and decline of sebum matrix metalloproteinases (MMPs) [196].

5.4.2 Where Isotretinoin Stands in the Management of Acne Vulgaris

That isotretinoin must be the first-line treatment for very severe acne consisting of cystic and conglobate lesions is approved by many experts [198, 199]. Its use has been highly successful in clearing acne lesions and sustaining remission periods as proven by multiple studies in the past and present.

For facial and truncal acne, known and applied by many dermatologists is the practice of giving it at 0.5–1.0 mg/kg for 4–6 months with the goal of achieving a cumulative dose of 120–150 mg/kg to lessen relapse and increase remission rates [199]. With the goal of not only reaching but maintaining remission states, this cumulative dose may be applicable to a more moderate degree of acne but not for those with severe acne. Thus it has been suggested that isotretinoin must be continued until full clearance is achieved with an extension of another month, with the dosage varying per individual [199].

Interestingly, in the recent study of Kutlu et al. among pregnant women with acne, among the 32 women who received isotretinoin as a systemic acne treatment before pregnancy, only two manifested severe to very severe acne while pregnant. The authors equated this effect to isotretinoin's capacity to produce long-lasting atrophy and apoptosis of the sebaceous glands [132].

5.4.3 Opening the Doors to Other Modes of Dosaging

A usual initiating dose of 0.25–0.5 mg/kg/day that may gradually be increased depending on the patient's tolerance and response to the medication [10, 195, 200] and taken for 6 months was deemed practical for Asian patients [10].

Various modes of regimens have been explored from 0.3 to 0.4 mg/kg/day, 20 mg every other day or 5 mg/day with claims of efficacy and fewer side effects hence better treatment adherence [5]. Fallah et al., in their recent review on practical prescribing of isotretinoin, encountered only a small group of patients who needed dosages of ≥0.5 mg/kg/day. They claimed that, in their experience, starting doses between 5 and 20 mg once daily with increments in time depending on the response of the patient allowed clearance of the acne without even reaching the 0.5 mg/kg/day dosing. Upon improvement of the acne, patients were put on alternate day 10 mg. Achieving the required cumulative dose was not their endpoint. Instead, once acne clearance is reached, isotretinoin is continued for another 2–3 months, with a total duration of 8–12 months [196].

Low-dose maintenance for persistent acne in adults may be considered among Asians but with caution (teratogenicity, hepatotoxicity, hyperlipidemia) [10]. Pulse therapy of every 1–3 weeks has however been noted to produce higher relapse rates [10, 201, 202].

5.4.4 The Need for Monitoring Laboratory Parameters

A 2016 systematic review and meta-analysis done by Lee et al. on the laboratory monitoring among standard acne patients aged 9–35 years old, given the standard isotretinoin doses of ≥40 mg/day, revealed that monthly monitoring may not be necessary since the proportion of patients having laboratory abnormalities was low

[203]. This standpoint was in agreement with the results of a recent retrospective analysis done for those isotretinoin takers ≥35 years old whose baseline laboratory test results were within normal limits [204].

The Singapore guideline recommends performing liver function tests, serum cholesterol and triglycerides pretreatment, after 6–8 weeks of treatment, and every 6 months for long-term therapy [10]. However, more frequent monitoring of these laboratory parameters may be needed for adult women who are overweight, obese, or who have hormonal abnormalities [5] due to a higher risk of this population having elevated cholesterol and triglycerides [205].

5.4.5 Dealing with Pertinent Concerns when Taking Isotretinoin

5.4.5.1 Pregnancy

Isotretinoin is Pregnancy Category X and serves as an outright contraindication for pregnant patients.

For female patients who are not pregnant but may be pregnant at any point, a pregnancy test pretreatment is a good precautionary measure and contraception must be discussed if they are to take isotretinoin. Ju et al. recommended that a strict contraceptive regimen be done a month prior, during, and three months after isotretinoin intake [195]. Oon et al. deem it better to start intake at the start of the next menstrual cycle [10].

Isotretinoin's teratogenic potential and risk of retinoid embryopathy led to risk management programs (RMP) across the globe [206]. Most popular among the RMPs is the iPLEDGE program being mandated by the USFDA. Pregnancy prevention requirements set during the course of therapy were either sexual abstinence or the use of two contraceptive methods simultaneously. For those choosing the latter method, both a primary and secondary method are required. Primary contraception includes subdermal hormonal implant, permanent surgical contraception (i.e., vasectomy, tubal ligation, or salpingectomy), intrauterine device (hormonal or not), depot medroxyprogesterone injection (DMPI), and the hormonal contraceptive pill, patch, or ring. Secondary contraception includes barrier methods (i.e., male latex condom, diaphragm, cervical cap) and the vaginal sponge. Unacceptable methods under iPLEDGE are progestin-only contraceptive pills, female condoms, fertility awareness-based methods, and withdrawal [207]. Given the scenario where not all are in agreement as to what contraception to use or adherence is compromised, noncompliance remains to be a serious concern and isotretinoin-exposed pregnancies are still being reported [82, 208]. To offset this, knowledge as to the necessity and efficiency of available contraceptive methods must be made known and reiterated to both doctor and patient. In the recent study done by Barbieri et al., it was shown that the primary tier 1 contraceptive methods like subdermal hormonal implant and IUDs used alone and primary tier 2 methods like COCs or DMPI used

in combination with barrier methods showed effectiveness of >99%. Monotherapy using tier 1 is possible, making the contraception process simpler thereby increasing compliance. And for those inclined to utilize the tier 2 contraception, emphasis must be made that a secondary form of contraception must accompany its use to ensure effectivity [207].

5.4.5.2 Adverse Effects

Zaenglein et al. have meticulously listed the several adverse effects and toxicities affecting the following systems: cardiovascular, central nervous, skin, endocrine, gastrointestinal, hematologic, hepatic, musculoskeletal, oculo-otic, and respiratory [82]. Serious side effects are numerous but experienced rarely [195] in the usual clinical setting. Experienced by almost all is the mucocutaneous dryness, especially of the lips. Lip dryness may, however, be an indicator of the effectiveness of drug dosage [195]. Less common are eye dryness, musculoskeletal pain, elevated serum lipids, and transaminases. Prepubertal usage may lead to premature closure of the epiphysis, bone hyperplasia, and osteoporosis; hence it is recommended starting at age 12 years and above [82].

5.4.5.3 Acne Flare

Acne flare, or as patients call it as "acne purging," has been noted by some within the first month of intake of isotretinoin. Though Borghi et al. noted only a small fraction of less than 15% among takers having this flare [209], this has been a concern over the years. To deal with this, experts agreed that initiating a low dose (0.2–0.5 mg/kg/day [10], 5–10 mg daily [196]) may reduce the likelihood of acne flare. A systemic corticosteroid may be considered to be given (prednisone 0.25–0.5 mg/kg/day tapered within 4–6 weeks) for those who are at high risk of flaring or scarring [196]. Though this flare may be transient, some develop severe reaction such that there may be a need to even discontinue isotretinoin [195].

5.4.5.4 Dermatological Procedures while on Isotretinoin

Performance of any elective procedure has been recommended to be delayed for 6–12 months after termination of isotretinoin intake due to previous incidences of delayed wound healing or keloid formation. This delay has been questioned with reports of the safety of various dermatological procedures while on or recently done with isotretinoin. While deferring the use of laser or light devices has inadequate data to support such recommendation [196], full face dermabrasion and mechanical dermabrasion using rotary devices must still be avoided immediately after finishing the isotretinoin course [210]. Superficial chemical peels, however, can be performed while on isotretinoin [196].

5.4.5.5 Depression

Though the link associating depression with intake of isotretinoin remains to be unclear if not controversial [10, 82, 195], it will be prudent for the dermatologists to check the patients for depression symptoms or medications prior to and during treatment with isotretinoin. It is best to know the tendencies of your adult female patients, since emotional and psychiatric disorders, stress, and insomnia are common in this population [3]. On the doctor's end, it is best that patients be made aware of the possibility of depression or suicidal behavior while on isotretinoin [10, 195, 211].

5.4.5.6 Inflammatory Bowel Disease [IBD]

Currently, there is no associated increased risk of IBD developing after exposure to isotretinoin [82, 203].

5.4.6 Isotretinoin May Not be for Acne Management Alone

Nickle et al. listed several other dermatological conditions with off-label indications for isotretinoin [212]. Among the studies they cited, the following had a notable response with the use of isotretinoin, alone or in combination with other modalities: rosacea (most effective for papulopustular type), extrafacial rosacea and rosacea fulminans, psoriasis (best together with NBUVB), condyloma accuminata (best together with INFa-2a), lupus erythematosus (best with SCLE), and leukoplakia.

de Souza Leao Kamamoto et al. reported that isotretinoin 10 mg given alternate days produced a significant decrease in sebum secretion rate and opined that it can be used for severe seborrhea and seborrheic dermatitis [213].

As to its benefit for photoaging, given thrice weekly at 20 mg twice per day for 12 weeks among perimenopausal women aged 45–50 years, Bravo et al. have confirmed its capacity to remodel the extracellular matrix by positively altering the distribution and thickness of the elastic fibers and increasing the density of collagen fibers [214].

5.4.7 Life with Isotretinoin Intake

For us dermatologists who have prescribed and are continuing to give isotretinoin to their patients, the responsibility is heavy. Controversies and consensus are ever-changing. We may have our preferences on how to administer the drug, monitor the patient, advise on adverse effects, and prevent pregnancy. Guidelines are evolving and as the word suggests, they serve as a guide for us to arrive at a wise decision for

the patient suffering from acne. Being aware of everything about this drug makes us prepared in facing the complaints and complications that may arise in the course of treatment of our patients.

For the patients who plan to, are into, and are done with isotretinoin, a seesaw of emotions may or have played. Being internet savvy has its pros and cons, making both fear and excitement build up. The ultimate decision to take part in the world of isotretinoin is unto them, with us serving as their final guide and mentor.

References

1. Philippine Dermatological Society Health Information Systems. Philippine Dermatological Society. c2011 [updated (April 15 2022); cited (August 2022)]. Available by request from: pdshis@outlook.
2. Collier CN, Harper JC, Cafardi JA, Cantrell WC, Wang W, Foster KW, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58(1):56–9.
3. Albuquerque RG, Rocha MA, Bagatin E, Tufik S, Andersen ML. Could adult female acne be associated with modern life? Arch Dermatol Res. 2014;306:683–8.
4. Yentzer BA, Hick J, Reese EL, Uhas A, Feldman SR, Balkrishnan R. Acne vulgaris in the United States: a descriptive epidemiology. Cutis. 2010;86(2):94–9.
5. Bagatin E, de Freitas THP, Rivitti-Machado MC, Ribeiro BM, Nunes S, da Rocha MAD. Adult female acne: a guide to clinical practice. An Bras Dermatol. 2019;24(1):62–75.
6. Zeichner JA, Baldwin HE, Cook-Bolden FE, Eichenfield LF, Fallon-Friedlander S, Rodriguez DA. Emerging issues in adult female acne. J Clin Aesthet Dermatol. 2017;10:37–46.
7. Preneau S, Dreno B. Female acne - a different subtype of teenager acne? J Eur Acad Dermatol Venereol. 2012;26:277–82.
8. Addor FA, Schalka S. Acne in adult women: epidemiological, diagnostic and therapeutic aspects. An Bras Dermatol. 2010;85:789–95.
9. Silpa-Archa N, Kohli I, Chaowattanapanit S, Lim HW, Hamzavi I. Postinflammatory hyperpigmentation: A comprehensive overview: epidemiology, pathogenesis, clinical presentation, and noninvasive assessment technique. J Am Acad Dermatol. 2017;77:591–605.
10. Oon HH, Wong SN, Aw DCW, Cheong WK, Goh CL, Tan HH. Acne management guidelines by the Dermatological Society of Singapore. J Clin Aesthet Dermatol. 2019;12(7):34–50.
11. Dréno B, Thiboutot D, Layton AM, Berson D, Perez M, Kang S. Global Alliance to improve outcomes in acne. Large-scale international study enhances understanding of an emerging acne population: adult females. J Eur Acad Dermatol Venereol. 2015;29:1096–106.
12. Danby FW, editor. Acne: causes and practical management. Hoboken, New Jersey: John Wiley & Sons Inc (US); 2015.
13. Goulden V, McGeown CH, Cunliffe WJ. The familial risk of adult acne: a comparison between first-degree relatives of affected and unaffected individuals. Br J Dermatol. 1999;141:297–300.
14. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol. 1998;134:454–8.
15. Clarke SB, Nelson AM, George RE, Thiboutot DM. Pharmacologic modulation of sebaceous gland activity: mechanisms and clinical applications. Dermatol Clin. 2007;25(2):137–46.
16. Del Rosso JQ, Harper JC, Graber EM, Thiboutot D, Silverberg NB, Eichenfield LF. Status report from the American Acne & Rosacea Society on medical management of acne in adult women, part 2: topical therapies. Cutis. 2015;96:321–5.
17. Rocha MA, Bagatin E. Skin barrier and microbiome in acne. Arch Dermatol Res. 2018;310:181–5.

18. Pontes Tde C, Fernandes Filho GM, Trindade Ade S, Sobral Filho JF. Incidence of acne vulgaris in young adult users of protein-calorie supplements in the city of João Pessoa – PB. An Bras Dermatol. 2013;88:907–12.
19. Melnik BC, Zouboulis CC. Potential role of FoxO1 and mTORC1 in the pathogenesis of Western diet-induced acne. Exp Dermatol. 2013;22:311–5.
20. Shibata M, Katsuyama M, Onodera T, Ehama R, Hosoi J, Tagami H. Glucocorticoids enhance toll-like receptor 2 expression in human keratinocytes stimulated with Propionibacterium acnes or proinflammatory cytokines. J Invest Dermatol. 2009;129(2):375–82.
21. Kazandjieva J, Tsankov N. Drug-induced acne. Clin Dermatol. 2017;35:156–62.
22. Dréno B. General antibiotic therapy in acne. Rev Prat. 2002;52:841–3.
23. Kang D, Shi B, Erfe MC, Craft N, Li H. Vitamin B12 modulates the transcriptome of the skin microbiota in acne pathogenesis. Sci Transl Med. 2015;7:293ra103.
24. Lortscher D, Admani S, Satur N, Eichenfield LF. Hormonal contraceptives and acne: A retrospective analysis of 2147 patients. J Drugs Dermatol. 2016;15:670–4.
25. Gezginc K, Balci O, Karatayli R, Colakoglu MC. Contraceptive efficacy and side effects of Implanon. Eur J Contracept Reprod Health Care. 2007;12:362–5.
26. Bahamondes L, Brache V, Meirik O, Ali M, Habib N, Landoulsi S. WHO study group on contraceptive implants for women. A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls. Hum Reprod. 2015;30:2527–38.
27. Dumont-Wallon G, Dreno B. Specificity of acne in women older than 25 years. Presse Med. 2008;37:585–91.
28. Tanghetti EA, Kawata AK, Daniels SR, Yeomans K, Burk CT, Callender VD. Understanding the burden of adult female acne. J Clin Aesthet Dermatol. 2014;7:22–30.
29. Williams C, Layton AM. Persistent acne in women: implications for the patient and for therapy. Am J Clin Dermatol. 2006;7:281–90.
30. Bhatia N, Pillai R. Randomized, observer-blind, Split-face compatibility study with clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel and facial foundation makeup. J Clin Aesthet Dermatol. 2015;8(9):25–32.
31. Zeichner JA, Patel RV, Haddican M, Wong V. Efficacy and safety of a ceramide containing moisturizer followed by fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel in the morning in combination with a ceramide containing moisturizer followed by tretinoin 0.05% gel in the evening for the treatment of facial acne vulgaris. J Drugs Dermatol. 2012;11(6):748–52.
32. Schäfer T, Nienhaus A, Vieluf D, Berger J, Ring J. Epidemiology of acne in the general population: the risk of smoking. Br J Dermatol. 2001;145:100–4.
33. Capitanio B, Sinagra JL, Ottaviani M, Bordignon V, Amantea A, Picardo M. 'Smoker's acne': a new clinical entity? Br J Dermatol. 2007;157:1070–1.
34. Yang YS, Lim HK, Hong KK, Shin MK, Lee JW, Lee SW, et al. Cigarette smoke-induced interleukin-1 alpha may be involved in the pathogenesis of adult acne. Ann Dermatol. 2014;26:11–6.
35. Yarak S, Bagatin E, Hassun KM, Parada MOAB, Talarico FS. Hyperandrogenism and skin: polycystic ovary syndrome and peripheral insulin resistance. An Bras Dermatol. 2005;80:395–410.
36. Carmina E, Godwin AJ, Stanczyk FZ, Lippman JS, Lobo RA. The association of serum androsterone glucuronide with inflammatory lesions in women with adult acne. J Endocrinol Investig. 2002;25:765–8.
37. National Institutes of Health Department of Health and Human Services. Beyond Infertility: Polycystic Ovary Syndrome (PCOS) NIH Pub. No. 08-5863, April 2008. Available at: www.nichd.nih.gov/publications/pubs/upload/PCOS_booklet.pdf. Accessed January 10 2021.
38. Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. J Obstet Gynaecol Can. 2008;30(8):671–9.

39. Jalilian A, Kiani F, Sayehmiri F, Sayehmiri K, Khodaee Z, Akbari M. Prevalence of polycystic ovary syndrome and its associated complications in Iranian women: A meta-analysis. Iran J Reprod Med. 2015;13(10):591–604.
40. Lee AT, Zane LT. Dermatological manifestations of polycystic ovary syndrome. Am J Clin Dermatol. 2007;8:201–19.
41. Koivunen R, Laatikainen T, Tomas C, Huhtaniemi I, Tapanainen J, Martikainen H. The prevalence of polycystic ovaries in healthy women. Acta Obstet Gynecol Scand. 1999;78(2):137–41.
42. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BCJM. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG. 2006;113(10):1210–7.
43. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer E, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endrocrinol Metab. 2004;89(6):2745–9.
44. Wijeyaratne CN, Balen AH, Barth JH, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among south Asians and Caucasians: is there a difference? Clin Endocrinol. 2002;57(3):343–50.
45. Nardo LG, Patchava S, Laing I. Polycystic ovary syndrome: pathophysiology, molecular aspects and clinical implications. Panminerva Med. 2008;50(4):267–78.
46. Harper JC. Evaluating hyperandrogenism: a challenge in acne management. J Drugs Dermatol. 2008;7(6):527–30.
47. Lolis MS, Bowe WP, Shalita AR. Acne and systemic disease. Med Clin North Am. 2009;93(6):1161–81.
48. Arora MK, Yadav A, Saini V. Role of hormones in acne vulgaris. Clin Biochem. 2011;44(13):1035–40.
49. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The androgen excess and PCOS society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88.
50. Housman E, Reynolds RV. Polycystic ovary syndrome: A review for dermatologists, part I. diagnosis and manifestations. J Am Acad Dermatol. 2014;71(5):847.e7–10.
51. Rostamtabar M, Esmaeilzadeh S, Tourani M, Rahmani A, Baee M, Shirafkan F, et al. Pathophysiological roles of chronic low-grade inflammation mediators in polycystic ovary syndrome. J Cell Physiol. 2021;236(2):824–38.
52. Velija-Ašimi Z. Evaluation of endocrine changes in women with the polycystic ovary syndrome during metformin treatment. Bosn J Basic Med Sci. 2013;13(3):180–5.
53. Deligeoroglou E, Vrachnis N, Athanasopoulos N, Iliodromiti Z, Sifakis S, Iliodromiti S, Creatsas G. Mediators of chronic inflammation in polycystic ovarian syndrome. Gynecol Endocrinol. 2012;28(12):974–8.
54. Tsvetanova DD, Yordanova IA, Strateva DD, Torodova KN, Yordanova-Laleva PD, Hristova PA, Gospodinov DK. Frequency of polycystic ovary syndrome and disturbances in thyroid gland function in women with acne vulgaris: hormone profiles and clinical findings. Int Invent Sci J. 2018;2(9):296–302.
55. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203(3):201.e1–5.
56. Kamangar F, Shinkai K. Acne in the adult female patient: a practical approach. Int J Dermatol. 2012;51(10):1162–74.
57. Marcondes JA, Barcellos CR, Rocha MP. Difficulties and pitfalls in the diagnosis of polycystic ovary syndrome. Arq Bras Endocrinol Metabol. 2011;55:6–15.
58. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;18(6):1–13.
59. Lucky AW. Endocrine aspects of acne. Pediatr Clin N Am. 1983;30(3):495–9.
60. Franik G, Bizoń A, Włoch S, Kowalczyk K, Biernacka-Bartnik A, Madej P. Hormonal and metabolic aspects of acne vulgaris in women with polycystic ovary syndrome. Eur Rev Med Pharmacol Sci. 2018;22(14):4411–8.

61. Ramanand SJ, Ghongane BB, Ramanand JB, Patwardhan MH, Ghanghas RR, Jain SS. Clinical characteristics of polycystic ovary syndrome in Indian women. Indian J Endocrinol Metab. 2013;17:138–45.
62. Asdaq SMB, Jomah S, Hasan R, Al-Baroudi D, Alharbi M, Alsubaie S, et al. Impact of polycystic ovary syndrome on eating behavior, depression and health related quality of life: A cross-sectional study in Riyadh. Saudi J Biol Sci. 2020;27(12):3342–7.
63. Buzney E, Sheu J, Buzney C, Reynolds RV. Polycystic ovary syndrome: A review for dermatologists part II. Treatment. J Am Acad Dermatol. 2014;71(5):859.e1–859.e15.
64. Frost RJ, Olson EN. Control of glucose homeostasis and insulin sensitivity by the Let-7 family of microRNAs. Proc Natl Acad Sci U S A. 2011;108(52):21075–80.
65. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med. 1996;335(9):617–23.
66. Li SN, Wang X, Zeng QT, Feng YB, Cheng X, Mao XB, et al. Metformin inhibits nuclear factor κB activation and decreases serum high-sensitivity C-reactive protein level in experimental atherogenesis of rabbits. Heart Vessel. 2009;24(6):446–53.
67. De Leo V, Musacchio MC, Morgante G, Piomboni P, Petraglia F. Metformin treatment is effective in obese teenage girls with PCOS. Hum Reprod. 2006;21(9):2252–6.
68. Lashen H. Role of metformin in the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2010;1(3):117–28.
69. Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc. 2019;3(8):1545–73.
70. Daniilidis A, Dinas K. Long term health consequences of polycystic ovarian syndrome: a review analysis. Hippokratia. 2009;13(2):90–2.
71. Balachandrudu B, Niveditadevi V, Rani TP. Hormonal pathogenesis of acne – simplified. Int J Sci Study. 2015;3:183–5.
72. Lakshmi C. Hormone therapy in acne. Indian J Dermatol Venereol Leprol. 2013;79(3):322–37.
73. Gollnick HP. From new findings in acne pathogenesis to new approaches in treatment. J Eur Acad Dermatol Venereol. 2015;29(suppl 5):1–7.
74. Thiboutot D. Acne: hormonal concepts and therapy. Clin Dermatol. 2004;22(5):419–28.
75. Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. J Eur Acad Dermatol Venereol. 2014;28(5):527–32.
76. Smith TM, Gilliland K, Clawson GA, Thiboutot D. IGF-1 induces SREBP-1 expression and lipogenesis in SEB-1 sebocytes via activation of the phosphoinositide 3-kinase/Akt pathway. J Invest Dermatol. 2008;128:1286–93.
77. Arlt W, Stewart PM. Adrenal corticosteroid biosynthesis, metabolism, and action. Endocrinol Metab Clin N Am. 2005;34(2):293–313.
78. Böhm M, Ehrchen J, Luger TA. Beneficial effects of the melanocortin analogue Nle4-D-Phe7-α-MSH in acne vulgaris. J Eur Acad Dermatol Venereol. 2014;28(1):108–11.
79. Chen W, Thibout D, Zouboulis CC. Cutaneous androgen metabolism: basic research and clinical perspective. J Invest Dermatol. 2002;119:992–1007.
80. Elsaie ML. Hormonal treatment of acne vulgaris: an update. Clin Cosmet Investig Dermatol. 2016;9:241–8.
81. Bettoli V, Zauli S, Virgili A. Is hormonal treatment still an option in acne today? Br J Dermatol. 2015;172(suppl 1):37–46.
82. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74(5):945–73.e33.
83. Sato T, Kurihara H, Akimoto N, Noguchi N, Sasatsu M, Ito A. Augmentation of gene expression and production of promatrix metalloproteinase 2 by *Propionibacterium acnes*-derived factors in hamster sebocytes and dermal fibroblasts: a possible mechanism for acne scarring. Biol Pharm Bull. 2011;34(2):295–9.
84. Lucidi RS. Polycystic Ovarian Syndrome Workup. Available at: https://emedicine.medscape.com/article/256806-workup#c8. Accessed Jan 10 2021.

85. Lin-Su K, Nimkarn S, New MI. Congenital adrenal hyperplasia in adolescents: diagnosis and management. Ann N Y Acad Sci. 2008;1135:95–8.
86. DHES1—Clinical: Dehydroepiandrosterone Sulfate, Serum. Mayo Clinic laboratories. Available from https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/113595. Accessed Jan 15 2021.
87. Eric K, Ricardo A. Ovarian hormones and adrenal androgens during a women's life span. J Am Acad Dermatol. 2001;45:105–15.
88. Prolactin Levels Test: High vs Low, Normal Range – WebMD. What is Prolactin test? Available from: https://www.webmd.com/a-to-z-guides/prolactin-test#1. Accessed Jan 20 2021.
89. Tyler KH, Zirwas MJ. Pregnancy and dermatologic therapy. J Am Acad Dermatol. 2013;68(4):663–71.
90. Harper JC. Use of oral contraceptives for management of acne vulgaris: practical considerations in real world practice. Dermatol Clin. 2016;34(2):159–65.
91. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2012;6:CD004425.
92. Harper JC. Should dermatologists prescribe hormonal contraceptives for acne? Dermatol Ther. 2009;22:452–7.
93. Rabe T, Kowald A, Ortmann J, Rehberger-Schneider S. Inhibition of skin 5 alpha-reductase by oral contraceptive progestins in vitro. Gynecol Endocrinol. 2000;14:223–30.
94. Palli MB, Reyes-Habito CM, Lima XT, Kimball AB. A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3 mg drospirenone/0.02 mg ethinyl estradiol compared with placebo in the treatment of moderate truncal acne vulgaris. J Drugs Dermatol. 2013;12:633–7.
95. Arrington EA, Patel NS, Geranker K, Feldman SR. Combined oral contraceptives for the treatment of acne: a practical guide. Cutis. 2012;90(2):83–90.
96. Katsambas AD, Dessinioti C. Hormonal therapy for acne: why not as first line therapy? Facts and controversies. Clin Dermatol. 2010;28:17–23.
97. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomark Prev. 2013;22:1931–43.
98. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, Berrington de González A, Colin D, Franceschi S, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007;370(9599):1609–21.
99. Cromer BA, Bonny AE, Stager M, Lazebnik R, Rome E, Ziegler J, et al. Bone mineral density in adolescent females using injectable or oral contraceptives: a 24-month prospective study. Fertil Steril. 2008;90(6):2060–7.
100. Maguire K, Westhoff C. The state of hormonal contraception today: established and emerging noncontraceptive health benefits. Am J Obstet Gynecol. 2011;205(4 suppl):S4–8.
101. ACOG Committee On practice bulletins-gynecology. ACOG practice bulletin. No. 73: use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. 2006;107:1453–72.
102. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. J Am Acad Dermatol. 1997;36:705–10.
103. London BM, Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives. Arch Dermatol. 1994;130:392–3.
104. Boisselle A, Dionne FT, Tremblay RR. Interaction of spironolactone with rat skin androgen receptor. Can J Biochem. 1979;57:1042–6.
105. Rifka SM, Pita JC, Vigersky RA, Wilson YA, Loriaux DL. Interaction of digitalis and spironolactone with human sex steroid receptors. J Clin Endocrinol Metab. 1978;46:338–44.

106. Sato K, Matsumoto D, Iizuka F, Aiba-Kojima E, Watanabe-Ono A, Suga H, et al. Anti-androgenic therapy using oral spironolactone for acne vulgaris in Asians. Aesthet Plast Surg. 2006;30(6):689–94.
107. Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Cochrane Database Syst Rev. 2009;15(2):CD000194.
108. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. J Am Acad Dermatol. 2000;43:498–502.
109. Shaw JC, White LE. Long-term safety of spironolactone in acne: results of an 8-year followup study. J Cutan Med Surg. 2002;6:541–5.
110. Layton AM, Eady EA, Whitehouse H, Del Rosso JQ, Fedorowicz Z, van Zuuren EJ. Oral spironolactone for acne vulgaris in adult females: a hybrid systematic review. Am J Clin Dermatol. 2017;18:169–91.
111. George R, Clarke S, Thiboutot D. Hormonal therapy for acne. Semin Cutan Med Surg. 2008;27:188–96.
112. Yemisci A, Gorgulu A, Piskin S. Effects and side-effects of spironolactone therapy in women with acne. J Eur Acad Dermatol Venereol. 2005;19:163–6.
113. Layton AM. Top ten list of clinical pearls in the treatment of acne vulgaris. Dermatol Clin. 2016;34(2):147–57.
114. Adalatkhah H, Pourfarzi F, Sadeghi-Bazargani H. Flutamide versus a cyproterone acetate-ethinyl estradiol combination in moderate acne: a pilot randomized clinical trial. Clin Cosmet Investig Dermatol. 2011;4:117–21.
115. Wang HS, Wang TH, Soong YK. Low dose flutamide in the treatment of acne vulgaris in women with or without oligomenorrhea or amenorrhea. Changgeng Yi Xue Za Zhi. 1999;22(3):423–32.
116. Cusan L, Dupont A, Gomez JL, Tremblay RR, Labrie F. Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. Fertil Steril. 1994;61:281–7.
117. Lowenstein EJ. Diagnosis and management of the dermatologic manifestations of the polycystic ovary syndrome. Dermatol Ther. 2006;19(4):210–23.
118. Garcia Cortes M, Andrade RJ, Lucena MI, Sánchez Martínez H, Fernández MC, Ferrer T, et al. Flutamide induced hepatotoxicity: report of a case series. Rev Esp Enferm Dig. 2001;93:423–32.
119. Jansen T, Plewig G. Acne fulminans. Int J Dermatol. 1998;37:254–7.
120. Nast A, Ernst H, Rosumeck S, Erdmann R, Jacobs A, Sporbeck B. Risk of complications due to anticoagulation during dermatosurgical procedures: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2014;28(12):1603–9.
121. Van Wayjen R, van den Ende A. Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic, and endocrine effects. Exp Clin Endocrinol Diabetes. 1995;103(4):241–51.
122. Thiboutot D, Archer DF, Lemay A, Ballagh SA, Nichols M, Weber ME. A randomized, controlled trial of a low-dose contraceptive containing 20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel for acne treatment. Fertil Steril. 2001;76:461–8.
123. Faloia E, Filipponi S, Mancini V, Morosini P, De Pirro R. Treatment with a gonadotropin-releasing hormone agonist in acne or idiopathic hirsutism. J Endocrinol Investig. 1993;16(9):675–7.
124. Ghosh S, Chauduri S, Jain VK, Aggarwal K. Profiling and hormonal therapy for acne in women. Indian J Dermatol. 2014;59(2):107–15.
125. Trifu V, Tiplica GS, Naumescu E, Zalupca L, Moro L, Celasco G. Cortexolone 17α-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study vs. placebo and tretinoin 0·05% cream. Br J Dermatol. 2011;165(1):177–83.

126. Kumari R, Jaisankar TJ, Thappa dM. A clinical study of skin changes in pregnancy. Indian J Dermatol Venereol Leprol. 2007;73:141.
127. Hassan I, Bashir S, Taing S. A clinical study of the skin changes in pregnancy in Kashmir Valley of North India: a hospital based study. Indian J Dermatol. 2015;60(1):28–32.
128. Kannambal K, Tharini GK. A screening study on dermatoses in pregnancy. J Clin Diag Res. 2017;11(5):WC01–5.
129. Panicker VV, Riyaz N, Balachandran PK. A clinical study of cutaneous changes in pregnancy. J Epidemiol Glob Health. 2017;7(1):63–70.
130. Dreno B, Blouin E, Moyse D, Bodokh I, Knol AC, Khammari A. Acne in pregnant women: a French survey. Acta Derm Venereol. 2014;94:82–3.
131. Yang CC, Huang YT, Yu CH, Wu MC, Hsu CC, Chen W. Inflammatory facial acne during uncomplicated pregnancy and post-partum in adult women: a preliminary hospital-based prospective observational study of 35 cases from Taiwan. J Eur Acad Dermatol Venereol. 2016;30:1787–9.
132. Kutlu O, Karadag AS, Unal E, Kelekci KH, Iyidal AY, Demir FT, et al. Acne in pregnancy: a prospective multicenter, cross-sectional study of 295 patients in Turkey. Int J Dermatol. 2020;59:1098–105.
133. Yu YS, Cheng YW, Chen W. Lifetime course of acne: a retrospective questionnaire study in school teachers. Dermatol Sinica. 2008;26:10–4.
134. Di Landro A, Cazzaniga S, Cusano F, Bonci A, Carla C, Musumeci ML, et al. Adult female acne and associated risk factors: results of a multicenter case-control study in Italy. J Am Acad Dermatol. 2016;75:1134–41.
135. Geraghty LN, Pomeranz MK. Physiologic changes and dermatoses of pregnancy. Int J Dermatol. 2011;50:771–82.
136. Akhavan A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. Am J Clin Dermatol. 2003;4:473–92.
137. Burge S, Matin R, Wallis D. Skin and pregnancy. In: Oxford handbook of clinical dermatology. 2nd ed. UK: Oxford University Press; 2016. p. 582–8.
138. Huddleston H (2021). Gestational hyperandrogenism. In Crowley WF, Barbieri RL (Eds). UpToDate. Retrieved December 10, 2020, from https://www.uptodate.com/contents/gestationalhyperandrogenism.
139. Kuijper EA, Ket JC, Caanen MR, Lambalk CB. Reproductive hormone concentrations in pregnancy and neonates: a systematic review. Reprod Biomed Online. 2013;27:33–63.
140. Guay A, Munarriz R, Jacobson J, Talakoub L, Traish A, Quirk F, et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: part A. serum androgen levels in women aged 20–49 years with no complaints of sexual dysfunction. Int J Impot Res. 2004;16(2):112–20.
141. Burger HG. Androgen production in women. Fertil Steril. 2002;77:3–5.
142. Caanen MR, Kuijper EA, Hompes PG, Kushnir MM, Rockwood AL, Meikle WA, et al. Mass spectrometry methods measured androgen and estrogen concentrations during pregnancy and in newborns of mothers with polycystic ovary syndrome. Eur J Endocrinol. 2016;174:25–32.
143. Mesiano S. Role of estrogen and progesterone in human parturition. Front Horm Res. 2001;27:86–104.
144. Jones SV, Ambros-Rudolph C, Nelson-Piercy C. Skin disease in pregnancy. BMJ. 2014;348:g3489.
145. Theofanakis C, Drakakis P, Besharat A, Loutradis D. Human chorionic gonadotropin: the pregnancy hormone and more. Int J Mol Sci. 2017;18:1059.
146. Chien L, Qi J, Rainer BM, Sachs D, Helfrich YR. Treatment of acne in pregnancy. J Am Board Fam Med. 2016;29:254–62.
147. Shaw JC, White LE. Persistent acne in adult women. Arch Dermatol. 2001;137:1252–3.
148. Kanda N, Watanabe S. Regulatory roles of sex hormones in cutaneous biology and immunology. J Dermatol Sci. 2005;38:1–7.

149. Danesh MJ, Murase JE. The new US Food and Drug Administration pregnancy and lactation labeling rules: their impact on clinical practice. J Am Acad Dermatol. 2015;73(2):310–1.
150. Koh YP, Tian EA, Oon HH. New changes in pregnancy and lactation labelling: review of dermatologic drugs. Int J Women's Dermatol. 2019;5:216–26.
151. Graber E (2022). Acne vulgaris: overview of management. In Dellavalle RP, Levy ML, Owen C (Eds). Uptodate. Retrieved December 10, 2020, from https://www.uptodate.com/contents/acnevulgaris-management.
152. Awan SZ, Lu J. Management of severe acne during pregnancy: a case report and review of literature. Int J Women's Dermatol. 2017;3:145–50.
153. Bio LL, Cies JJ. Lack of pregnancy warnings on over-the-counter dermatologic products containing potentially harmful hydroquinone. J Perinatol. 2017;37(7):778–81.
154. Mataparthi K, Hsu S. Topical antibacterial agents. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Philadelphia: Saunders; 2013. p. 452–8.
155. Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: part II. Lactation. J Am Acad Dermatol. 2014;70(3):417.e1–10.
156. Purdy S, de Berker D. Acne vulgaris. BMJ Clin Evid. 2011;2011:1714.
157. Dreno B, Layton A, Zouboulis CC, Lopez-Estebaranz JL, Zalewska-Janowska A, Bagatin E, et al. Adult female acne: a new paradigm. J Eur Acad Dermatol Venereol. 2013;27:1063–70.
158. Jeon C, Agbai O, Butler D, Murase J. Dermatologic conditions in patients of color who are pregnant. Int J Womens Dermatol. 2017;3(1):30–6.
159. Kong YL, Tey HL. Treatment of acne vulgaris during pregnancy and lactation. Drugs. 2013;73(8):779–87.
160. Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: part I. Pregnancy. J Am Acad Dermatol. 2014;70(401):e1–e14.
161. Pugashetti R, Shinkai K. Treatment of acne vulgaris in pregnant patients. Dermatol Ther. 2013;26:302–11.
162. Hessel AB, Cruz-Ramon JC, Klinger DM, Lin AN. Agents used for treatment of hyperkeratosis. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Saunders (Philadelphia); 2013. p. 595–8.
163. Patel M, Bowe WP, Heughebaert C, Shalita AR. The development of antimicrobial resistance due to the antibiotic treatment of acne vulgaris: a review. J Drugs Dermatol. 2010;9:655–64.
164. Kinney MA, Yentzer BA, Fleischer AB, Feldman SR. Trends in the treatment of acne vulgaris: are measures being taken to avoid antimicrobial resistance? J Drugs Dermatol. 2010;9:519–24.
165. Lucky AW, Maloney JM, Roberts J, Taylor S, Jones T, Ling M, et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long term (1 year) treatment. J Drugs Dermatol. 2007;6:981–7.
166. Thiboutot DM, Willmer J, Sharata H, Halder R, Garrett S. Pharmacokinetics of dapsone gel 5% for the treatment of acne vulgaris. Clin Pharmacokinet. 2007;46:697–712.
167. Panchaud A, Csajka C, Merlob P. Pregnancy outcome following exposure to topical retinoids: prospective study. J Clin Pharmacol. 2012;52:1844–51.
168. Kaplan YC, Ozsarfati J, Etwel F, Nickel C, Nulman I, Koren G. Pregnancy outcomes following first trimester exposure to topical retinoids: a systematic review and meta-analysis. Br J Dermatol. 2015;173:1132–41.
169. Sami N. Topical retinoids. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Philadelphia: Saunders; 2013. p. 505–17.
170. Briggs GG, Freeman RK, editors. Drugs in pregnancy and lactation. 10th ed. Philadelphia: Wolters Kluwer Health; 2015.
171. Hebert A, Thiboutot D, Gold LS, Cartwright M, Gerloni M, Fragasso E, Mazzetti A. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. JAMA Dermatol. 2020;156(6):621–30.

172. Eichenfield L, Hebert A, Gold LS, Cartwright M, Fragasso E, Moro L, Mazzetti A. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. J Am Acad Dermatol. 2020;83(2):477–85.
173. Singh O, Agrawal P, Garg R, Agarwal A. Drugs in pregnancy: an update. J South Asian Feder Obs Gynae. 2014;6(3):7–11.
174. Lin KJ, Mitchell AA, Yau WP, Louik C, Hernandez-Diaz S. Maternal exposure to amoxicillin and the risk of oral clefts. Epidemiology. 2012;23:699–705.
175. Sheehy O, Santos F, Ferreira E, Berard A. The use of metronidazole during pregnancy: a review of evidence. Curr Drug Saf. 2015;10(2):170–9.
176. Kim S, Michaels BD, Kim GK, Del Rosso JQ. Systemic antibacterial agents. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Philadelphia: Saunders; 2013. p. 92–3.
177. Makol A, Wright K, Amin S. Rheumatoid arthritis and pregnancy: safety considerations in pharmacological management. Drugs. 2011;71:1973–87.
178. Brandt S. The clinical effects of zinc as a topical or oral agent on the clinical response and pathophysiologic mechanisms of acne: a systematic review of the literature. J Drugs Dermatol. 2013;12:542–5.
179. Dreno B, Blouin E. Acne, pregnant women and zinc salts: a literature review. Ann Dermatol Venereol. 2008;135:27–33.
180. Patton TJ, Ferris LK. Systemic retinoids. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Philadelphia: Saunders; 2013. p. 252–68.
181. Lee KC, Korgavkar K, Dufresne RG, Higgins HW. Safety of cosmetic dermatologic procedures during pregnancy. Dermatol Surg. 2013;39:1573–86.
182. Trivedi MK, Kroumpouzos G, Murase JE. A review of the safety of cosmetic procedures during pregnancy and lactation. Int J Women's Dermatol. 2017;3:6–10.
183. Zhou WS, Xu L, Xie SH, Li YL, Li L, Zeng Q, et al. Decreased birth weight in relation to maternal urinary trichloroacetic acid levels. Sci Total Environ. 2012;416:105–10.
184. Drugs and Lactation Database (LactMed). Trichloroacetic Acid. https://www.ncbi.nlm.nih.gov/books/NBK500913/. Accessed Feb 2 2021.
185. Rao J, Bissonnette R. Photodynamic therapy. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. Philadelphia: Saunders; 2013. p. 299–305.
186. Zeichner JA. Narrowband UV-B phototherapy for the treatment of acne vulgaris during pregnancy. Arch Dermatol. 2011;147(5):537–9.
187. Habeshian KA, Cohen BA. Current issues in the treatment of acne vulgaris. Pediatrics. 2020;145(s2):S221–30.
188. Tan J, Boyal S, Desai K, Knezevic S. Oral isotretinoin: new developments relevant to clinical practice. Dermatol Clin. 2016;34(2):175–84.
189. Chernyshov PV, Tomas-Aragones L, Manolache L, Svensson A, Marron SE, Evers AWM, et al. Which acne treatment has the best influence on health-related quality of life? Literature review by the European academy of dermatology and venereology task force on quality of life and patient oriented outcomes. J Eur Acad Dermatol Venereol. 2018;32(9):1410–9.
190. Espinosa NI, Cohen PR. Acne vulgaris: a patient and physician's experience. Dermatol Ther (Heidelb). 2020;10:1–14.
191. Hayran Y, Uysal PI, Öktem A, Aksoy GG, Akdogan N, Yalcin B. Factors affecting adherence and patient satisfaction with treatment: a cross- sectional study of 500 patients with acne vulgaris. J Dermatolog Treat. 2021;32(1):64–9.
192. Nast A, Dreno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol. 2012;26(Suppl 1):1–29.
193. Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden JJ, et al. New insights into the management of acne: an update from the global Alliance to improve outcomes in acne group. J Am Acad Dermatol. 2009;60(5 Suppl):S1–S50.

194. Dreno B, Bettoli V, Ochsendorf F, Perez-Lopez M, Mobacken H, Degreef H, Layton A. An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. Eur J Dermatol. 2006;16:565–71.
195. Ju Q, Fan WX, Gu J, Hao F, He L, Li HJ, et al. Chinese guidelines for the management of acne vulgaris: 2019 update. Int J Dermatol Venereol. 2019;2(3):129–37.
196. Fallah H, Rademaker M. Isotretinoin in the management of acne vulgaris: practical prescribing. Int J Dermatol. 2021;60(4):451–60.
197. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. Int J Dermatol. 2016;55(5):518–23.
198. Gollnick HP, Bettoli V, Lambert J, Araviiskaia E, Binic I, Dessinioti C, et al. A consensus-based practical and daily guide for the treatment of acne patients. J Eur Acad Dermatol Venereol. 2016;30(9):1480–90.
199. Thiboutot DM, Dreno B, Abanmi A, Alexis AF, Araviiskaia E, Cabal MIB, et al. Practical management of acne for clinicians: an international consensus from the global Alliance to improve outcomes in acne. J Am Acad Dermatol. 2018;78:S1–S23.
200. Torzecka JD, Dziankowska-Bartkowiak B, Gerlicz-Kowalczuk Z, Wozniacka A. The use of isotretinoin in low doses and unconventional treatment regimens in different types of acne: a literature review. Postepy Dermatol Alergol. 2017;34(1):1–5.
201. Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. Br J Dermatol. 1997;137(1):106–8.
202. Agarwal US, Besarwal RK, Bhola K. Oral isotretinoin in different dose regimens for acne vulgaris: a randomized comparative trial. Indian J Dermatol Venereol Leprol. 2011;77:688–94.
203. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory monitoring during isotretinoin therapy for acne: a systematic review and meta-analysis. JAMA Dermatol. 2016;152:35–44.
204. Sharma P, Tkachenko E, Mostaghimi A. A retrospective evaluation of routine isotretinoin laboratory monitoring in patients older than 35 years. J Am Acad Dermatol. 2021;84(1):201–2.
205. Schmitt JV, Tavares M, Cerci FB. Adult women with acne have a higher risk of elevated triglyceride levels with the use of oral isotretinoin. An Bras Dermatol. 2011;86:807–10.
206. Kovitwanichkanont T, Driscoll T. A comparative review of isotretinoin pregnancy risk management programs across four continents. Int J Dermatol. 2018;57:1035–46.
207. Barbieri JS, Roe AH, Mostaghimi A. Simplifying contraception requirements for iPLEDGE: a decision analysis. J Am Acad Dermatol. 2020;83:4–8.
208. Tkachenko E, Singer S, Sharma P, Barbieri J, Mostaghimi A. US Food and Drug Administration reports of pregnancy and pregnancy-related adverse events associated with isotretinoin. JAMA Dermatol. 2019;155(10):1175–9.
209. Borghi A, Mantovani L, Minghetti S, Virgili A, Bettoli V. Acute acne flare following isotretinoin administration: potential protective role of low starting dose. Dermatol. 2009;218:178–80.
210. Waldman A, Bolotin D, Arndt KA, Dover JS, Gerenemus RG, Chapas A, et al. ASDS guidelines task force: consensus recommendations regarding the safety of lasers, dermabrasion, chemical peels, energy devices, and skin surgery during and after isotretinoin use. Dermatol Surg. 2017;43(10):1249–62.
211. Oliveira JM, Sobreira G, Velosa J, Correia DT, Filipe P. Association of isotretinoin with depression and suicide: a review of current literature. J Cutan Med Surg. 2018;22(1):58–64.
212. Nickle SB, Peterson N, Peterson M. Updated physician's guide to the off-label uses of oral isotretinoin. J Clin Aesthet Dermatol. 2014;7(4):22–34.
213. de Souza Leao Kamamoto C, Sanudo A, Hassun KM, Bagatin E. Low-dose oral isotretinoin for moderate to severe seborrhea and seborrheic dermatitis: a randomized comparative trial. Int J Dermatol. 2017;56(1):80–5.
214. Bravo BSF, Azulay DR, Luiz RR, Mandarim-De-Lacerda CA, Cuzzi T, Azulay MM. Oral isotretinoin in photoaging: objective histological evidence of efficacy and durability. An Bras Dermatol. 2015;90(4):479–86.

Chapter 6
Topical Steroid Damaged Face in Females with Skin of Colour

Yasmeen Jabeen Bhat and Safia Bashir

6.1 Introduction

Topical corticosteroids are among the most commonly used drugs in dermatology. The advent of topical corticosteroids is believed to have revolutionized dermatological therapy. Since the introduction of topical corticosteroids by Sulzberger and Witten in 1952 as Compound F (hydrocortisone), they have been utilized in a wide range of dermatological disorders owing to their anti-inflammatory, antiproliferative and immunosuppressive properties.

The introduction of hydrocortisone also opened up the avenue for the search of more potent molecules with more desirable properties. However shortly after topical corticosteroids were introduced, reports of adverse effects due to their usage started pouring in, the earliest of which were reported in 1955 [1]. Topical corticosteroids were substantially misused over the years which led to a plethora of adverse effects, both cutaneous and systemic, cutaneous or local side effects being more common than the systemic ones [2–4]. Earliest reports of the cutaneous side effects of topical corticosteroids emerged nearly a decade after they were first introduced [5]. The addictive potential of topical corticosteroids was however recognized later in 1970s and the term "steroid addiction" was used by Kligman and Frosh to describe the psychological and physical dependence on these drugs [6]. Face was a common site of adverse effects resulting from this addiction and abuse of topical corticosteroids. Owing to their anti-inflammatory and melanopenic properties, the use of topical corticosteroids on the face as cosmetic and particularly as bleaching

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agents or 'fairness' creams among the population with skin of colour became quite rampant [7]. Multiple studies from different parts of the world report skin lightening and acne as being the major reasons for indiscriminate and unsupervised use of topical corticosteroids on the face [8–12]. Over the years several terms like "red skin syndrome" [13], dermatitis rosaciformis steroidica [14] and steroid-induced rosacea like dermatitis (SIRD) [15] have been used to describe the condition that affects the facial skin due to topical corticosteroid abuse. The entity was labelled as "Topical steroid damaged/dependent face (TSDF)" by Kaushik Lahiri (India) in March 2008 and may be defined as follows: "Semipermanent or permanent damage to the skin of the face precipitated by the irrational, indiscriminate, unsupervised or prolonged use of topical corticosteroids resulting in a plethora of cutaneous signs and symptoms and psychological dependence on the drug." [7].

6.2 Epidemiology

While the exact incidence of TSDF is not known, it has been reported from several parts of the world [8–11, 16, 17]. While in developed countries, TSDF is usually seen consequent to prolonged or injudicious use of prescribed treatment for a steroid responsive dermatosis, the unregulated and non-prescription sale of topical corticosteroids in developing nations leads to misuse of these drugs for cosmetic reasons or steroid non responsive dermatoses [8, 9].

Females have been seen to be much more commonly affected than males in most of the studies, owing to greater cosmetic concerns in females with subsequent misuse of topical corticosteroids on face [8]. In skin of colour, the fairness obsession may be a major factor for misuse of topical steroids. Although any age group may be affected, TSDF has been seen most commonly in the age group of 20–30 years [8, 18, 19]. The misuse of topical corticosteroids in developing countries can be attributed to a number of factors which include

- Self-treatment.
- Prescription by non-dermatologists or even non medicos.
- Reuse of an old prescription for a recurrent or similar rash.
- Ease of availability of topical corticosteroids without prescription.
- Sharing of prescriptions among family and friends.

The lack of awareness among the general public regarding the hazards of self-medication with topical corticosteroids also perpetuates the problem.

6.3 Pathogenesis

Several theories have been put forward to explain the plethora of symptoms that occur in topical steroid damaged face.

1. **Role of nitric oxide**

   Prolonged and repeated application of topical corticosteroids to the face leads to inhibition of endothelial nitric oxide (NO) thus suppressing its vasodilatory effect. This results in a state of chronic vasoconstriction. Upon withdrawal of topical corticosteroids, endothelial nitric oxide is released causing vasodilation and erythema accompanied by itching and burning sensation. Reapplication of corticosteroids for alleviation of these symptoms further leads to vasoconstriction. This repeated cycle of vasoconstriction/vasodilation known as the 'trampoline effect' or 'neon sign' leads to the accumulation of nitric oxide. Release of this accumulated endothelial nitric oxide eventually leads to dilatation of cutaneous vasculature even beyond the original diameter with resultant erythema and flushing [13].
2. **Topical corticosteroid-induced immunosuppression**

   This results in the overgrowth of microorganisms which act as superantigens once the topical corticosteroids are withdrawn and induce an inflammatory reaction, causing the release of proinflammatory cytokines in the skin [20]. The role of *Demodex folliculorum* in the pathogenesis of TSDF is controversial. Bonnar et al. reported a significantly increased density of *Demodex folliculorum* in patients with steroid induced rosacea like dermatitis [21]. It may either cause an inflammatory or allergic reaction by blocking the hair follicles or act as vectors for other microorganisms [15].
3. **Direct effects on follicular epithelium**

   Degradation of follicular epithelium by topical corticosteroids with resultant extrusion of follicular contents is also postulated as a pathogenetic mechanism for occurrence of acneiform lesions in topical steroid damaged face [18].
4. Inhibitory effect of topical corticosteroids on keratinocyte proliferation, collagen synthesis as well as fibroblast and hyaluronic acid synthesis in the extracellular matrix leads to cutaneous atrophy. The lack of support to the vasculature due to dermal atrophy also aggravates the erythema in TSDF [22, 23].

   The pathogenesis of TSDF is summarized in Fig. 6.1.

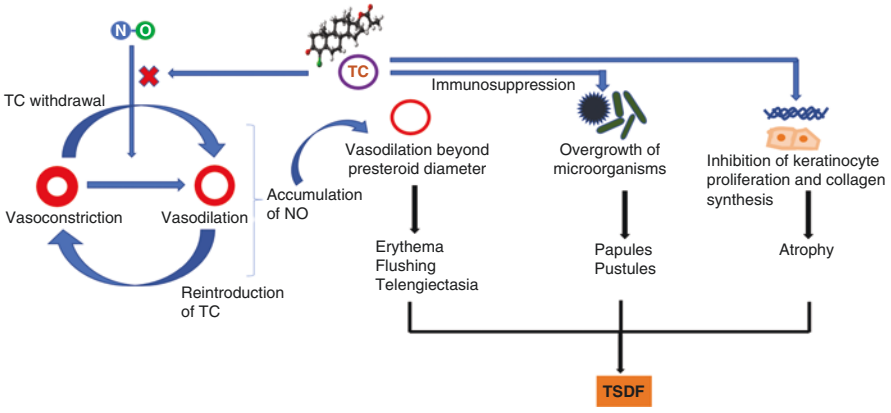

Fig. 6.1 Pathogenesis of Topical Steroid Damaged Face (TSDF), (*TC* Topical corticosteroid; *NO* Nitric oxide)

6.4 Clinical Presentation

Topical steroid damaged face presents as a symptom complex resulting from the numerous adverse effects of topical corticosteroid usage over face. Chronic abuse of topical steroids leads to psychological and physical dependence on the drug. Any attempt to withdraw the drug is faced with exacerbation of the symptoms which compels the patient to restart corticosteroid application to alleviate the symptoms [7]. While most patients develop symptoms after short term usage of potent topical corticosteroids, long term usage of less potent or mild steroids can lead to similar symptoms. Most patients with topical steroid damaged face give a history of topical corticosteroid usage for a prolonged period of time and symptoms may occur either after long-term continued usage or as a withdrawal/rebound phenomenon once the incriminating topical corticosteroid is discontinued.

Various presentations of topical steroid damaged/dependent face seen either alone or in combination include:

1. **Erythema**

   Erythema is a hallmark manifestation of TSDF which becomes more evident upon topical corticosteroid withdrawal. A diffuse erythema accompanied by a burning sensation (which may range from mild to severe) is noted in most patients with topical steroid damaged face. Following topical corticosteroid withdrawal, the erythema usually resolves in about 2 weeks followed by desquamation. Erythema however reappears within the next 2 weeks. These intermittent flares of erythema may also spread beyond the area of corticosteroid application or even to distant sites. The "headlight sign" is often present where nose and the perioral area is spared from erythema which otherwise is present over whole of the face. Erythema may be accompanied by oedema or vesiculation in severe cases. A cycle of flare ups and resolution sets in but the intensity of flares goes on decreasing and the phases of resolution are progressively prolonged till complete resolution occurs [13]. The length of time for which the steroids have been initially used determines the duration of the withdrawal phase.

   While erythema is the principal clinical feature in TSDF, it may be less pronounced in dark skinned individuals where other associated features like dryness, scaling and itching may indicate withdrawal phase or subsequent flare-ups in TSDF. (Fig. 6.2)
2. **Telangiectasia**

   Dermal atrophy in topical steroid damaged face leads to a diminished connective tissue support allowing passive dilatation and easier visualization of dermal capillaries which manifests as prominent telangiectasias [24]. (Figs. 6.3 and 6.4)
3. **Papulopustular lesions**

   Papulopustular and acneiform eruptions are frequently associated with the vascular changes in topical steroid damaged face. This has been attributed to the focal degeneration caused by direct effect of topical corticosteroids on the fol-

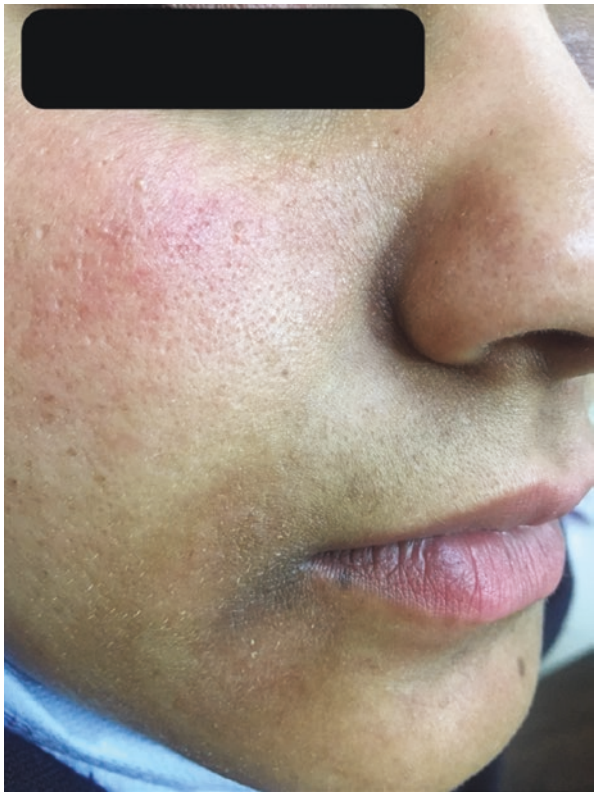

Fig. 6.2 Erythema and hyperpigmentation

licular epithelium leading to localized intrafollicular and perifollicular neutrophilic inflammatory reaction [22]. Topical steroids may also induce comedone formation by rendering the follicular epithelium more responsive to comedogenesis [25, 26]. This however is more common with systemic steroids.

The papulopustular lesions are usually monomorphic in appearance and have an unusual distribution. A rosacea-like dermatitis is commonly seen. Initial lesions may be small, pinpoint erythematous or skin coloured papules, pustules or papulovesicles. On further application of topical steroids, patients may develop diffusely erythematous and oedematous skin with deep follicular papules, pustules and nodules. The lesions may be distributed diffusely or may be localized mainly to the perioral region (resembling perioral dermatitis) and centrofacial area including the cheeks, nose, forehead and glabella [24]. (Figs. 6.5, 6.6, and 6.7)

4. **Atrophy**

A variable degree of skin atrophy is usually associated with other manifestations of topical steroid damaged face. Atrophy of the skin is reflected in the form of increased transparency and shininess of the skin (Fig. 6.8).

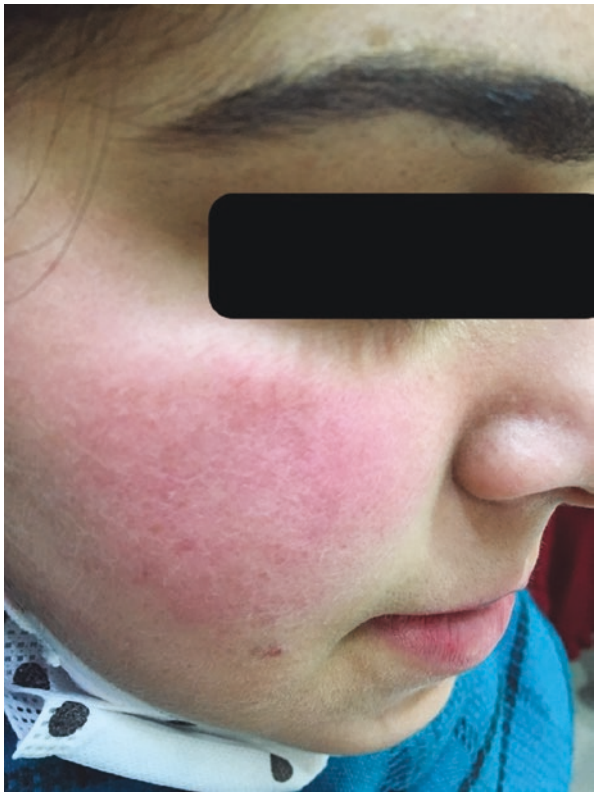

Fig. 6.3 Topical steroid induced telangiectasia

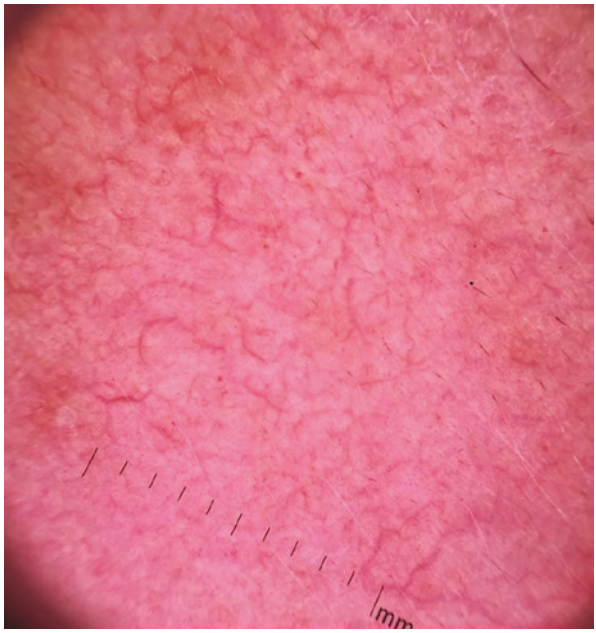

Fig. 6.4 Dermoscopy of Fig. 6.3 showing short, linear, irregular vessels

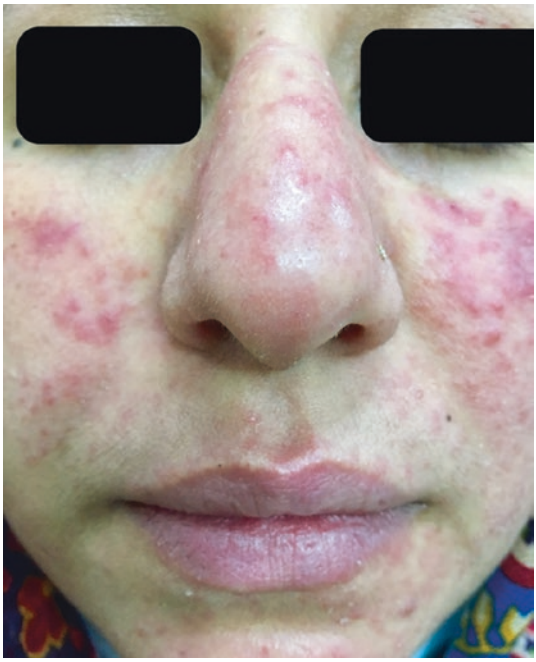

Fig. 6.5 Topical steroid induced papulopustular lesions

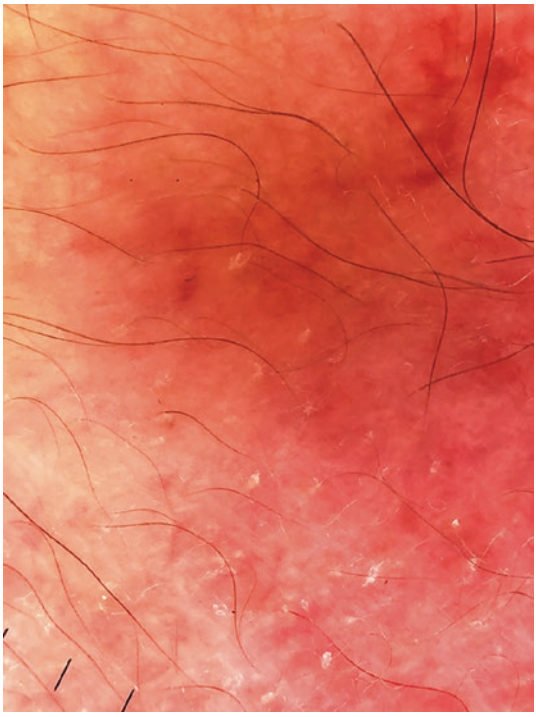

Fig. 6.6 Dermoscopy of Fig. 6.5 showing demodex tails, perifollicular erythema and hypertrichosis

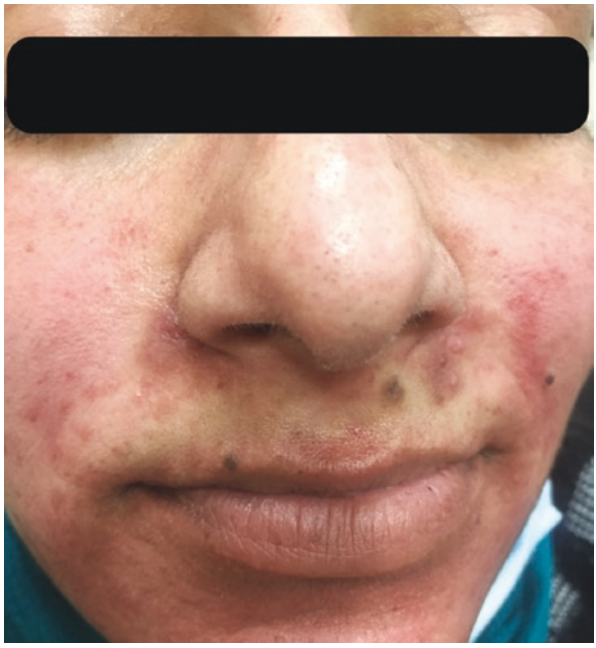

Fig. 6.7 Perioral dermatitis

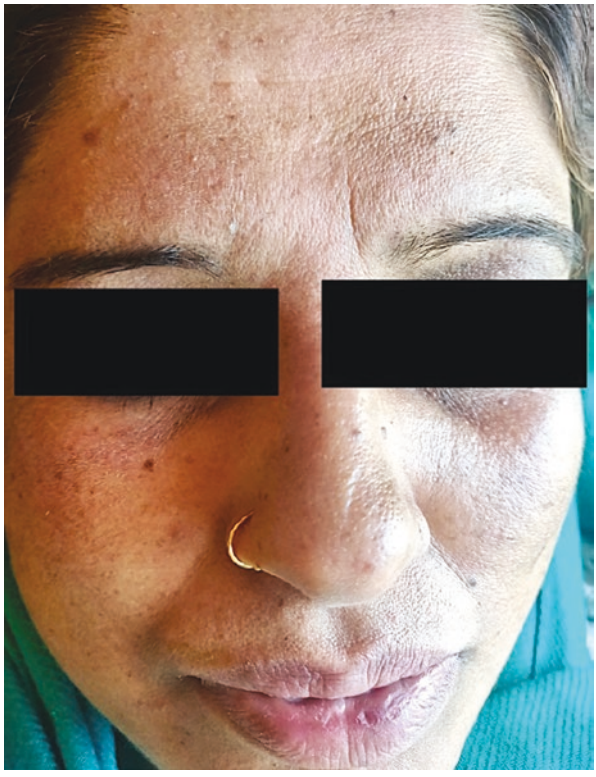

Fig. 6.8 Topical steroid induced atrophy and dyspigmentation

5. **Pigmentary changes**

   Topical corticosteroids are known to cause both hyperpigmentation and hypopigmentation. In people with skin type IV to VI, pigmentary changes especially in the form of hypopigmentation may be a prominent feature of topical steroid damaged face [12, 27]. Topical steroid–induced hypopigmentation is brought about by inhibition of prostaglandin or cytokine production in the epidermal cells which in turn leads to suppression of secretory metabolic products from melanocytes resulting in altered melanocyte function [28]. The mechanism of topical steroid induced hyperpigmentation is not well elucidated but hyperpigmentation has been reported in several cases of topical corticosteroid abuse [29, 30].

6. **Hypertrichosis**

   Hypertrichosis is a common side effect of systemic steroid use but many patients with topical corticosteroid abuse have abnormal facial hair growth.

7. **Other features**

   In addition to the aforementioned ones, topical steroid damaged face can present with several other features like photosensitivity, striae, allergic contact dermatitis and tinea incognito [31] (Figs. 6.9 and 6.10).

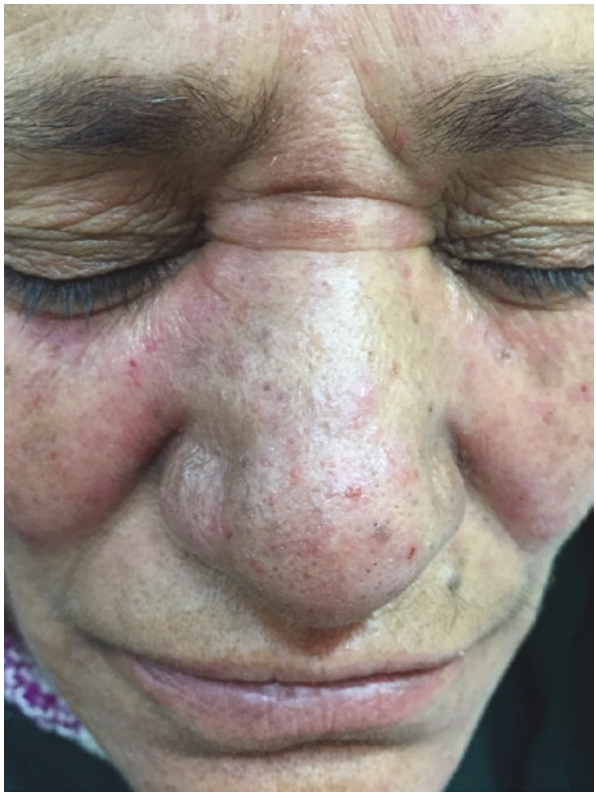

Fig. 6.9 Topical steroid induced dermatitis-rebound phenomenon

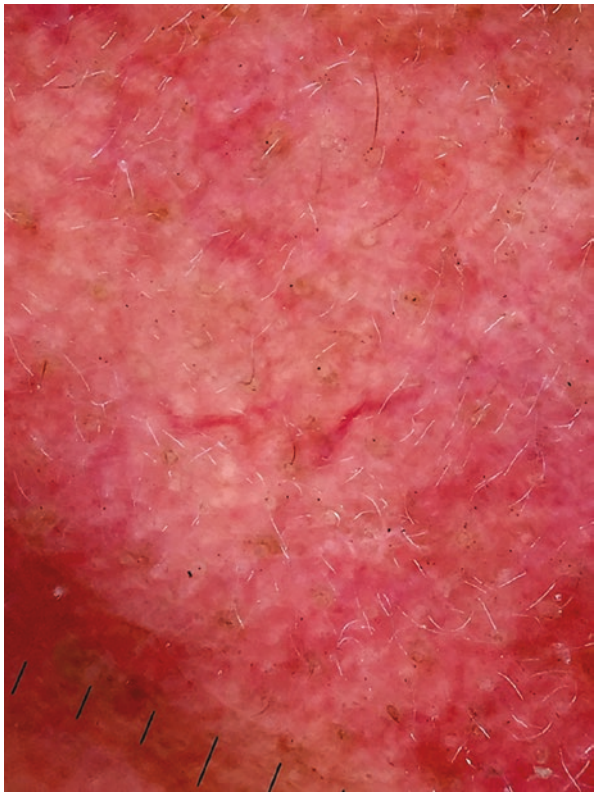

Fig. 6.10 Dermoscopy of Fig. 6.9 showing background erythema, yellow clods and short branching vessels

8. **Status cosmeticus**

   The term was first used by Fisher to describe an extreme form of cosmetic intolerance in which the patient gradually becomes completely intolerant to application of any form of makeup or cosmetic product [32]. Status cosmeticus was originally described in relation to facial dermatoses like atopic dermatitis, seborrheic dermatitis, rosacea and perioral dermatitis. Some patients with TSDF may exhibit symptoms similar to status cosmeticus where application of any cosmetic product to the face leads to severe irritation, erythema and burning sensation.

9. **Dermoscopic features of topical steroid damaged/dependent face**

   Various dermoscopic features suggestive of TSDF include the following [33].

   - Diffuse red areas with multiple, tortuous, polygonal and interconnecting blood vessels.
   - Ivory white, structureless areas to strawberry coloured patches suggestive of dermal atrophy.
   - Yellowish areas suggestive of epidermal atrophy with increased skin transparency.
   - Lesional hypertrichosis.

6.5 Management

Management of TSDF is quite difficult and requires patience on part of the patient as well as the treating physician. Treatment involves use of medication as well as patient counselling. Once the steroids are discontinued, a flare of symptoms is expected in all patients. Patients may develop severe erythema and burning sensation. Thus reluctance on part of the patients to stop corticosteroid application is expected. While some authorities advocate gradual withdrawal of corticosteroids,[15, 34, 35] others are in favour of complete cessation of topical corticosteroid usage on first contact with the patient [36, 37]. Although replacement of the potent topical steroid by a low potency one may alleviate the concerns of severe flares upon topical steroid withdrawal and make the patient more comfortable, some authorities believe that this just perpetuates the problem and hinders a full recovery [36].

Once the topical steroids are withdrawn, a total cure is expected in 6–24 months (with intermittent flares and remissions) without the use of any medication.

Various treatment modalities employed in the treatment of TSDF include:

1. **General measures**

   Repeated cold compresses help alleviate symptoms of topical corticosteroid withdrawal and those of acute flares. Soap free cleansers, bland emollients and calamine may help improve therapeutic outcome in patients with TSDF [29]. Burrow's solution may be used for weepy lesions [13].
2. **Antibiotics**

   In patients with papulopustular lesions, perioral dermatitis and rosacea like features, oral antibiotics with anti-inflammatory properties play a prominent role in the treatment. The preferred antibiotics include lipophilic tetracyclines like doxycycline and minocycline in a dose of 100–200 mg daily and oral azithromycin in a dose of 500 mg given on 3 days a week for 3–4 months. Longer duration of treatment is usually not needed. In patients who are unable to tolerate tetracyclines, oral metronidazole has also been used [38].

   In addition to the oral antibiotics, topical clindamycin, topical metronidazole, topical erythromycin and topical 5% sulphur have also been used in topical steroid induced rosacea and perioral dermatitis like lesions [38–40]. In mild cases of TSDF, topical antibiotics alone may be helpful.
3. **Oral isotretinoin**

   In patients not responding to antibiotics, a very low dose of isotretinoin (2–5 mg daily) for 3 months may be effective [38].
4. **Topical calcineurin inhibitors**

   Topical calcineurin inhibitors like tacrolimus and pimecrolimus have been found to be safe, effective and well tolerated in patients with TSDF. They may be used alone or in combination with oral antibiotics and have been found to offer a quicker initial improvement during the withdrawal phase in TSDF and the eventual resolution of symptoms may also be more rapid [41–43].

5. **Alpha adrenergic agonists**

   α adrenergic agonists like brimonidine, oxymetazoline and xylometazoline act as topical vasoconstrictors and help by reducing flushing and erythema associated with TSDF. Brimonidine tartrate in addition to being vasoconstrictive may also possess anti-inflammatory properties to some extent. Brimonidine 0.33% cream, xylometazoline 0.05% solution or oxymetazoline 0.05% solution applied once daily for variable durations have been shown to significantly improve erythema and flushing in sporadic cases [44, 45].

6. **Other treatments**

   (i) Oral and topical vitamin C and E.

   These have been used in patients with TSDF showing some improvement in vascular symptoms [29].

   (ii) Topical vitamin K. Application of 1% topical vitamin K has been found to be effective in an isolated study where rapid improvement in flushing, erythema and dryness was observed after 4 weeks of treatment [46].

   (iii) Ivermectin 1% cream.

   Ivermectin is a broad-spectrum antiparasitic agent which has been shown to significantly improve papulopustular lesions in rosacea as well as rosacea like dermatitis induced by topical steroids. It is known to act as an anti-inflammatory agent and also has antiparasitic properties against *Demodex folliculorum* [47].

   (iv) Platelet-rich plasma (PRP).

   PRP mesotherapy in the form of intradermal injections was found to be effective in the treatment of TSDF in an isolated study [48].

   (v) Lasers: Intense pulse light and pulsed dye laser have also been used in recalcitrant cases of TSDF and have been found to improve erythema and telangiectasias significantly [49, 50].

6.6 Conclusion

Topical corticosteroids are the cornerstone of treatment for a number of dermatological disorders owing to their anti-inflammatory, antiproliferative and immunosuppressive properties. However, indiscriminate and unsupervised use of topical corticosteroids can lead to a plethora of local side effects especially on the face where the skin is thin and corticosteroid absorption is enhanced. The problem is amplified manifold in females with skin of colour who in an attempt to meet the culturally sanctioned ideals of beauty, tend to misuse topical corticosteroids for skin lightening. The resulting condition in the form of topical steroid damaged/dependent face is very difficult to treat and can lead to irreversible damage to the skin. Considering the magnitude of the problem and owing to the physical, psychological and financial burden of the condition, it is immensely important to raise sufficient

public awareness regarding the ill effects of steroid abuse on face and at the same time limit the unregulated public access to potent topical corticosteroids.

References

1. Fitzpatrick TB, Griswold HC, Hicks JH. Sodium retention and edema from percutaneous absorption of fludrocortisones acetate. J Am Med Assoc. 1955;158:1149–52.
2. Ulrich R, Thomas R, Robert A, Michael J. Adverse effects of topical glucocorticoids. J Am Acad Dermatol. 2006;54(1):1–15.
3. Robertson DB, Maibach HI. Topical corticosteroids. Int J Dermatol. 1982;21:59–67.
4. Lagos BR, Maibach HI. Frequency of application of topical corticosteroids: an overview. Br J Dermatol. 1998;139:763–6.
5. Epstein NN, Epstein WL, Epstein JH. Atrophic striae in patients with inguinal intertrigo. Arch Dermatol. 1963;87:450–7.
6. Kligman AM, Frosch PJ. Steroid addiction. Int J Dermatol. 1979;18:23–31.
7. Lahiri K, Coondoo A. Topical steroid damaged/dependent face (TSDF): An entity of cutaneous pharmacodependence. Indian J Dermatol. 2016;61:265–72.
8. Saraswat A, Lahiri K, Chatterjee M, Barua S, Coondoo A, Mittal A, et al. Topical corticosteroid abuse on the face: a prospective, multicenter study of dermatology outpatients. Indian J Dermatol Venereol Leprol. 2011;77:160–6.
9. Mahe A, Ly F, Aymard G, Dangou JM. Skin diseases associated with the cosmetic use of bleaching products in women from Dakar, Senegal. BRJ Dermatol. 2003;148:493–500.
10. Dhalimi AI, MA, Aljawahiri M. Misuse of topical corticosteroids: a clinical study from an Iraqi hospital. East Mediterr Health J. 2006;12:847–52.
11. Lu H, Xiao T, Lu B, Dong D, Yu D, Wei H, et al. Facial corticosteroids addictive dermatitis in Guiyang city. China Clin Exp Dermatol. 2009;35:618–2.
12. Sendrasoa FA, Ranaivo IM, Andrianarison M, Raharolahy O, Razanakoto NH, Ramarozatovo LS, et al. Misuse of topical corticosteroids for cosmetic purpose in Antananarivo. Madagascar Biomed Res Int. 2017;2017:9637083.
13. Rapaport MJ, Rapaport V. The red skin syndromes: corticosteroid addiction and withdrawal. Expert Rev Dermatol. 2006;1:547–61.
14. Basta Juzbasic A, Subic JS, Ljubojevic S. Demodex folliculorum in development of dermatitis rosaceiformis steroidica and rosacea-related diseases. Clin Dermatol. 2002;20:135–40.
15. Rathi SK, Kumrah L. Topical corticosteroid-induced rosacea-like dermatitis: a clinical study of 110 cases. Indian J Dermatol Venereol Leprol. 2011;77:42–6.
16. Hajar T, Leshem YA, Hanifin JM, Nedorost ST, Lio PA, Paller AS, Block J, Simpson EL. (the National Eczema Association task force). A systematic review of topical corticosteroid withdrawal ("steroid addiction") in patients with atopic dermatitis and other dermatoses. J Am Acad Dermatol. 2015;72(3):541–9.
17. Sheary B. Steroid withdrawal effects following long-term topical corticosteroid use. Dermatitis. 2018;29(4):213–8.
18. Jain S, Mohapatra L, Mohanty P, Jena S, Behera B. Study of clinical profile of patients presenting with topical steroid-induced facial dermatosis to a tertiary care hospital. Indian Dermatol Online J. 2020;11:208–11.
19. Pal D, Biswas P, Das S, De A, Sharma N, Ansari A. Topical steroid damaged/dependent face (TSDF): a study from a tertiary care hospital in eastern India. Indian J Dermatol. 2018;63:375–9.
20. Ghosh A, Sengupta S, Coondoo A, Jana AK. Topical corticosteroid addiction and phobia. Indian J Dermatol. 2014;59:465–8.
21. Bonnar E, Eustace P, Powell FC. The Demodex mite population in rosacea. J Am Acad Dermatol. 1993;28(3):443–8.

22. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of glucocorticosteroids. J Am Acad Dermatol. 2006;54(1):1–15.
23. Schoepe S, Schacke H, May E, Asadullah K. Glucocorticoid therapy induced skin atrophy. Exp Dermatol. 2006;15:406–20.
24. Chen AY, Zirwas MJ. Steroid-induced rosacea like dermatitis: case report and review of the literature. Cutis. 2009;83(4):198–204.
25. Kuflik JH, Schwartz RA. Acneiform eruptions. Cutis. 2000;66:97–100.
26. Momin S, Peterson A, Del Rosso JQ. Drug-induced acneform eruptions: Definitions and causes. Cosmet Dermatol. 2009;22:28–37.
27. Lartey M, Krampa FD, Abdul-Rahman M, Quarcoo NL, Yamson P, Hagan PG, et al. Use of skin-lightening products among selected urban communities in Accra. Ghana Int J Dermatol. 2017;56:32–9.
28. Friedman SJ, Butler DF, Pittelkow MR. Perilesional linear atrophy and hypopigmentation after intralesional corticosteroid therapy. Report of two cases and review of the literature. J Am Acad Dermatol. 1988;19:537–41.
29. Bhat YJ, Manzoor S, Qayoom S. Steroid-induced rosacea: a clinical study of 200 patients. Indian J Dermatol. 2011;56(1):30–2.
30. Jha AK, Sinha R, Prasad S. Misuse of topical corticosteroids on the face: a cross-sectional study among dermatology outpatients. Indian Dermatol Online J. 2016;7:259–63.
31. Bhat YJ, Bashir S. Topical steroid damaged/dependent face. In: Sarkar R, Sinha S, editors. The sensitive skin: treatment modalities and cosmeceuticals. New Delhi: Jaypee; 2019. p. 39–48.
32. Fisher AA. "status cosmeticus": a cosmetic intolerance syndrome. Cutis. 1990;46(2):109–10.
33. Jakhar D, Kaur I. Dermoscopy of topical steroid damaged/dependent face. Indian Dermatol Online J. 2018;9:286–7.
34. Uehara M, Mitsuyoshi O, Sugiura H. Diagnosis and management of the red face syndrome. Dermatol Ther. 1996;1:19–23.
35. Sneddon IB. The treatment of steroid-induced rosacea and perioral dermatitis. Dermatologica. 1976;152:231–7.
36. Rapaport MJ, Rapaport V. Eyelid dermatitis to red face syndrome to cure: clinical experience in 100 cases. J Am Acad Dermatol. 1999;41:435–42.
37. Liu ZH, Du XH. Quality of life in patients with facial steroid dermatitis before and after treatment. J Eur Acad Dermatol Venereol. 2008;22(6):663–9.
38. Ljubojeviae S, Basta-Juzbasiae A, Lipozenèiae J. Steroid dermatitis resembling rosacea: aetiopathogenesis and treatment. J Eur Acad Dermatol Venereol. 2002;16:121–6.
39. Bikowski JB. Topical therapy for perioral dermatitis. Cutis. 1983;31:678–82.
40. Schmadel LK, McEvoy GK. Topical metronidazole: a new therapy for rosacea. Clin Pharm. 1990;9:94–101.
41. Chu CY. An open-label pilot study to evaluate the safety and efficacy of topically applied pimecrolimus cream for the treatment of steroid-induced rosacea-like eruption. J Eur Acad Dermatol Venereol. 2007;21(4):484–90.
42. Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: a preliminary report. J Am Acad Dermatol. 2001;44:995–8.
43. Pabby A, An KP, Laws RA. Combination therapy of tetracycline and tacrolimus resulting in rapid resolution of steroid-induced periocular rosacea. Cutis. 2003;72:141–2.
44. Kakkar S, Sharma PK. Topical steroid-dependent face: response to xylometazoline topical. Indian J Drugs Dermatol. 2017;3:87–9.
45. Generali JA, Cada DJ. Oxymetazoline (topical): rosacea. Hosp Pharm. 2013;48(7):558–9.
46. Abdullah GA. The effectiveness of topical vitamin K cream 1% in the treatment of steroid-induced rosacea. Research J Pharm and Tech. 2020;13(8):3883–6.
47. Anzengruber F, Czernielewski J, Conrad C, Feldmeyer L, Yawalkar N, Hausermann P, Cozzio A, Mainetti C, Goldblum D, Goldblum D, et al. Swiss S1 guideline for the treatment of rosacea. J Eur Acad Dermatol Venereol. 2017;31:1775–91.

48. Fan X, Yin Y, Dou W, Li T, Xue P, Yang Q, Ma Q. Successful treatment of corticosteroid-induced rosacea-like dermatitis with platelet-rich plasma Mesotherapy: report of seven cases. Dermatol Ther (Heidelb). 2021;11(2):615–23.
49. Maria P, Mishra N, Rastogi M, Gahalaut P. Effect of intense pulsed light on topical steroid-dependent facial dermatitis. J Pakistan Assoc Dermatologist. 2018;28:139–45.
50. Seok J, Choi SY, Li K, Kim BJ, Kim MN, Hong CK. Recalcitrant steroid-induced rosacea successfully treated with 0.03% tacrolimus and 595-nm pulsed dye laser. Eur J Dermatol. 2016;26(3):312–4.

Chapter 7
Rosacea

Johannes F. Dayrit

7.1 Introduction

Rosacea is a common chronic skin condition presenting with a combination of signs and symptoms which include flushing, persistent erythema of the central face, telangiectasia, papules, pustules, phymatous changes and ocular involvement. The cheeks, chin, nose and central forehead are the usual sites of predilection. The clinical manifestations vary from person to person and may change over time. The diagnosis is based on patient's self-reported history, observations, triggers and overlapping symptoms. Remissions and exacerbations are common [1, 2].

7.2 Epidemiology

Rosacea affects more than 20 million people worldwide, and diagnosed more often among women than in men. It may occur at any age and the onset typically occurs at any time after the age of 30. Rosacea was previously reported as a disease of fair-skinned individuals with Celtic and North European heritage (Fitzpatrick skin phototypes I and II) [1]. It has been reported less frequently in individuals with skin of colour with an estimated prevalence of 2% to 10%. A European study by Abram et al. [3] revealed a prevalence of 20% among 348 workers in Estonia, in which 55% of cases occurred in Fitzpatrick skin phototypes I and II. However, the study also showed a prevalence of 38% and 7% in Fitzpatrick skin phototypes III and IV, respectively. [3] In another study involving 168 patients, 40% had Fitzpatrick skin

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phototypes IV or V [4]. The low prevalence of rosacea in pigmented skin may be attributed to underreporting or misdiagnosis. The difficulty in detecting its characteristics in darker skin such as erythema and presence of telangiectasias might be the reasons for underdiagnosis. A delay in the diagnosis may result to advanced disease, inadequate treatment, greater morbidity, worsening of eyesight in ocular rosacea and progression of disease with disfiguring manifestations (e.g. rhinophyma and otophyma) [4].

7.3 Clinical Presentation

Rosacea usually affects the midface/centrofacial area affecting the forehead, nose, chin and cheeks. In rare cases, the neck and the scalp may be involved (extrafacial rosacea). The main symptoms include flushing, persistent erythema (Fig. 7.1a), telangiectasia, papules with/without pustules, phymatous changes (Fig. 7.1b) and ocular involvement. Apart from the other symptoms, centrofacial erythema exacerbated by heat, temperature change or intense emotion and phymatous changes are considered to be sufficient for a definite diagnosis [5].

The original standard classification of rosacea identified the most common patterns observed and were designated as follows: (1) erythematotelangiectatic, (2) papulopustular, (3) phymatous and (4) ocular. The classification by subtypes is well

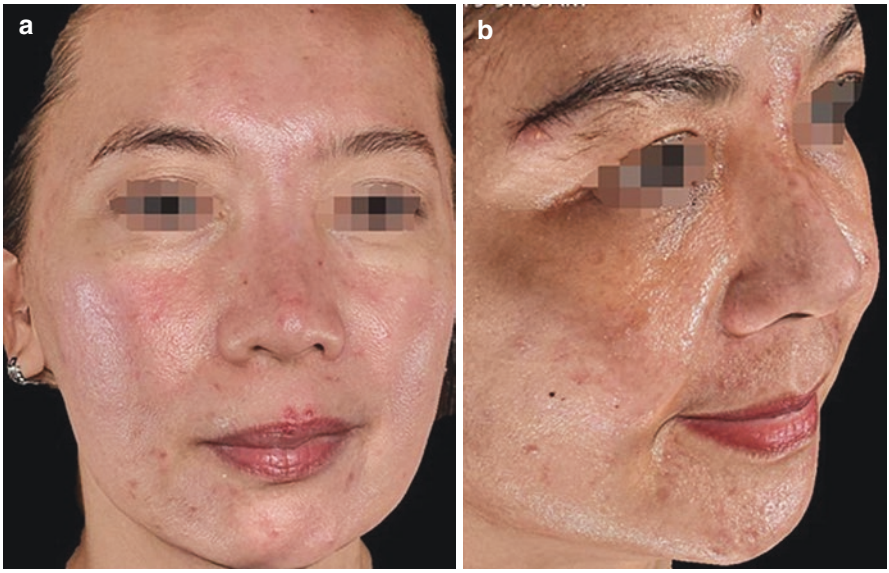

Fig. 7.1 Centrofacial redness (**a**), rhinophyma and gnatophyma (chin enlargement) (**b**) in Filipino females

known among dermatologists, but offers limited consideration for the full spectrum of signs and symptoms, and may confound the assessment of severity [1].

Erythematotelangiectatic rosacea is characterized by persistent erythema of varying severity, aggravated by the trigger factors and visible telangiectasia. Most patients also complain of burning, stinging, pain, less frequent itching as well as dryness without scaling of affected skin areas [5].

Papulopustular rosacea presents with persistent erythema of the midface with isolated or grouped, inflamed red papules and pustules which are mostly arranged symmetrically. These may persist for weeks and lymphedema can occur. It may eventually involve the whole face. Rarely extrafacial involvement affecting the chest, neck, décolletage and scalp are observed. Papulopustular rosacea may resemble acne, yet comedonal lesions typical for acne are lacking [5].

Glandular rosacea is characterized by hyperplasia of sebaceous glands and connective tissue and can be associated with circumscribed nodular changes (phymas) or diffuse thickening of the skin. It is predominantly seen in men. However, thickening of the skin may occur with the other symptoms of rosacea. The thickening and enlargement can involve the nose (rhinophyma), chin/jaw (gnatophyma), forehead (metophyma), ear (otophyma) or eyelid (blepharophyma) [6].

Current guidelines from the 2018 classification by the National Rosacea Society [1] recommends a phenotype driven approach in the diagnosis and treatment. The following features represent independent diagnostic criteria of rosacea: (1) fixed centrofacial erythema that may periodically intensify; or (2) phymatous changes. In their absence, diagnosis can also be established by two or more major features: (1) papules/pustules (Fig. 7.2a, b), (2) flushing and (3) facial telangiectasia [1]. Ocular manifestations such as lid margin telangiectasia, interpalpebral conjunctival injection (Fig. 7.2c), spade-shaped infiltrates in the cornea, scleritis and sclerokeratitis can be also considered as major features of rosacea [1]. While secondary features may occur, burning or stinging, oedema and dry appearance are not generally considered diagnostic, either alone or in combination. The revised classification aims to provide a more accurate and flexible way to diagnose, evaluate and treat rosacea within the context of current scientific understanding and clinical experience [1].

In skin of colour, important considerations for the diagnosis of rosacea include facial flushing, burning/stinging sensation, long-standing symptoms, failed acne therapies, family history and mixed heritage as reported by the patient [2].

On clinical examination the redness, papules and pustules, and phymas are usually observed on the central face. Erythema is usually noticeable by blanching using a magnifying glass or with medical photography using a blue background. In the absence of noticeable erythema and telangiectasias, dry appearance, oedema and hyperpigmentation are also important clues to the diagnosis [2].

The differential diagnoses for rosacea in skin of colour includes acne vulgaris, steroid acne, contact dermatitis, seborrheic dermatitis, periorificial dermatitis, lupus and dermatomyositis. Rare diseases which should also be ruled out include sarcoidosis and facial Afro-Caribbean childhood eruption [2].

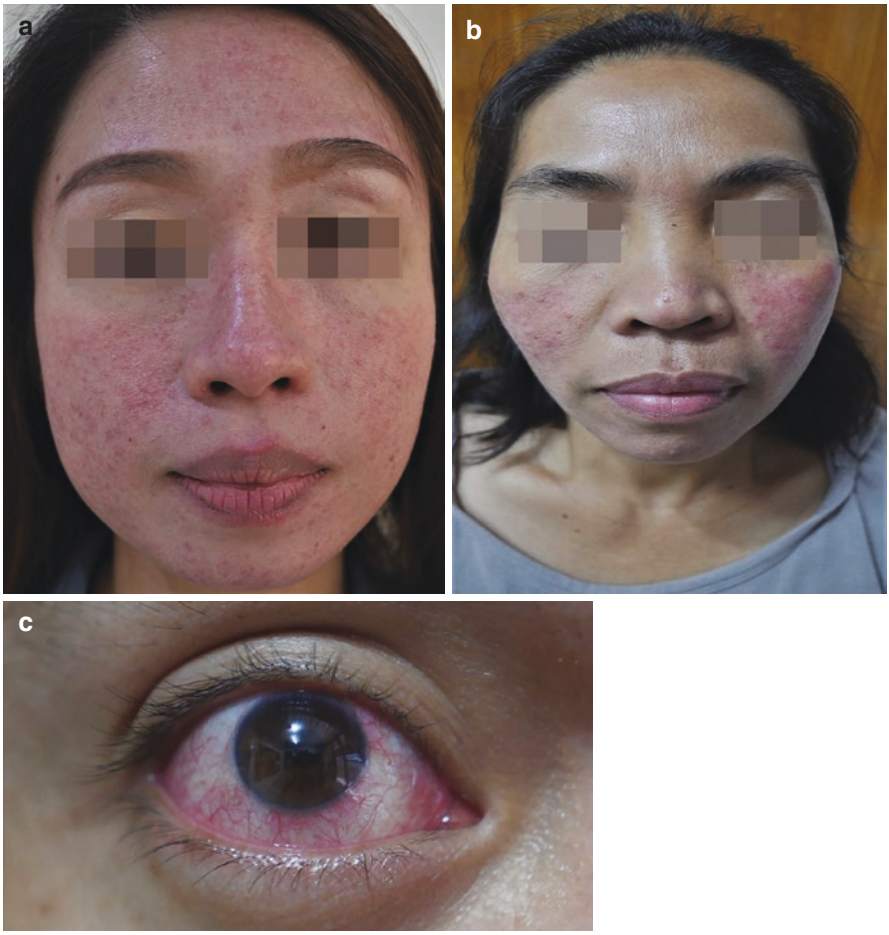

Fig. 7.2 Facial erythema and papules (**a**) papules and pustules (**b**) and conjunctival hyperemia in ocular rosacea (**c**)

7.4 Trigger Factors

An extensive discussion on the pathophysiology of rosacea is beyond the scope of this chapter. The pathogenesis has not been fully elucidated, but various factors have been implicated which include alterations of the innate immune response, vascular instability and neurogenic inflammation [7]. Sunlight exposure and temperature change are significant environmental triggers by contributing to vascular changes in predisposed individuals. Blood vessel dilatation with increased capillary permeability and oedema favours colonization of *Demodex folliculorum* which further upregulates pro-inflammatory mediators and results to dermal and blood vessel

damage [8]. Transient erythema may be triggered by a variety of endogenous and exogenous factors. Exogenous stimuli include chemical irritants, for example, components of cosmetic products such as formalin, specific soaps and exposure to heat and cold. Endogenous stimuli encompass spicy food, hot beverages and psychosocial stress. In general, the skin is very sensitive. The acute and uncontrolled flushing is often a source of great insecurity for affected patients [8].

7.5 Dermoscopy and Histopathology

Dermoscopic features of rosacea include a background of erythema and red dilated, reticular, linear, tortuous or polygonal vessels. The most important and consistent dermoscopic sign in rosacea are polygonal vessels. These vessels correspond to facial telangiectasias which are observed clinically. Some features seen on higher magnification videodermoscopy of rosacea included dilated vessels, prominent telangiectasia and large polygonal vascular reticular networks [9].

A biopsy is rarely performed for rosacea in routine clinical practice because the diagnosis can be made usually on clinical grounds. Sometimes a biopsy may be required to rule out collagen vascular diseases like lupus erythematosus, facial granulomatous skin diseases or to test for demodicosis, which is a common comorbidity. The major histopathologic features include extensive telangiectasias (Fig. 7.3a–c) throughout the superficial and middle dermis which correspond to arborizing vessels with network-like pattern in dermoscopy [8].

Different subtypes of rosacea can be differentiated with characteristic histologic features.

Erythematotelangiectatic rosacea typically shows enlarged dilated capillaries and venules in the upper dermis, frequently in bizarre shapes. The presence of *Demodex* within the follicular infundibulum can be noted even in the absence of pustules [8].

In papulo-pustular rosacea, a mixed inflammatory infiltrate with numerous plasma cells, neutrophils and few eosinophils can be seen. Marked perivascular and periadnexal inflammatory infiltrate is present in the superficial and deep layers. Pustules can be seen inside or outside the follicle. *Demodex* are almost always present in histologic samples that have been examined [6].

Granulomatous rosacea would often show infiltrates of histiocytes and lymphocytes in the superficial and mid-dermis. Large central empty spaces surrounded by a layer of neutrophils and numerous peripheral histiocytes admixed with lymphocytes may be seen. *Demodex* mites or its eosinophilic remnants may also be observed [8].

Phymatous rosacea is characterized histologically by increased number of sebaceous glands and dermal fibrosis. There is enlargement of infundibula, surrounded by infiltrates mainly composed of lymphocytes and neutrophils [8].

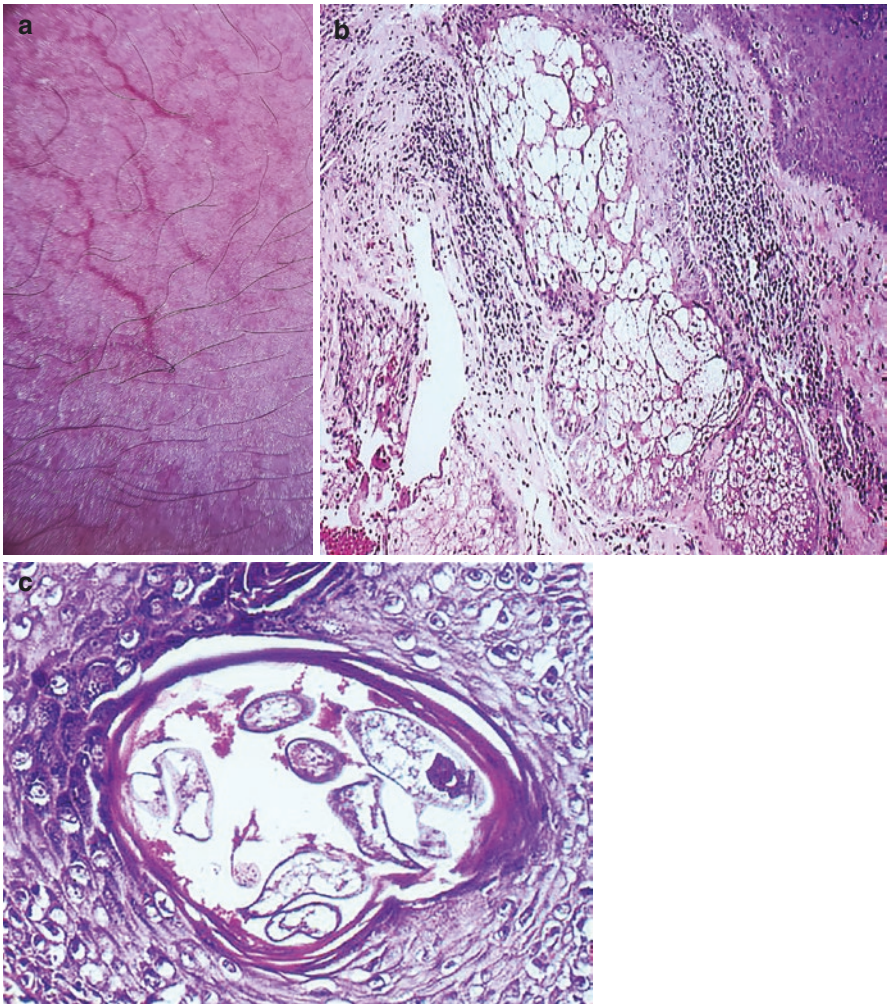

Fig. 7.3 Dermoscopy of rosacea shows background erythema and network of thickened vessel (**a**) histopathology shows dilated blood vessels, perivascular and peri-adnexal infiltrates (**b**) and *Demodex* mites (**c**)

7.6 Rosacea Fulminans

Rosacea fulminans, also known as pyoderma faciale, is a rare, acute or subacute, severe variant of rosacea with acne-conglobata like progression and predilection for post adolescent (20–30 years) women, particularly pregnant women [10]. Men are

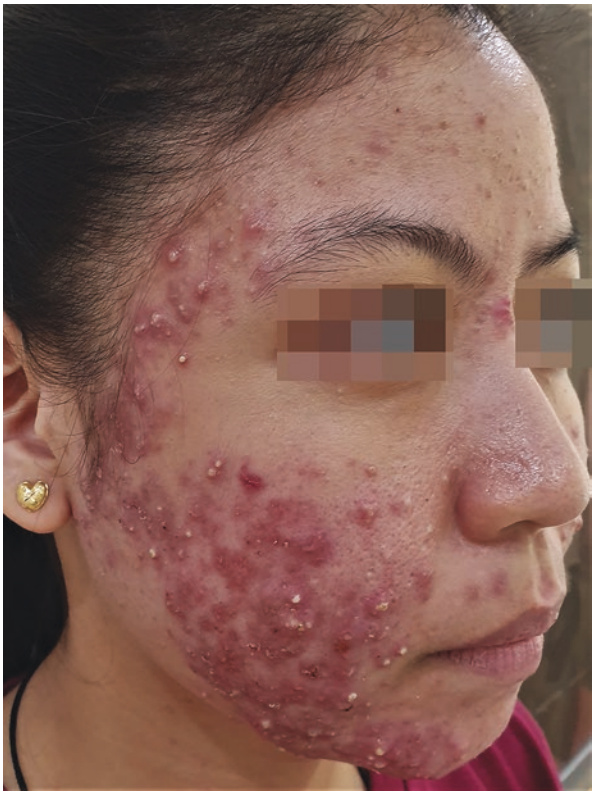

Fig. 7.4 Rosacea fulminans in a 23-year-old Filipino who presented with sudden appearance of papules, pustules and nodules. She has reported centrofacial redness and flushing since age 17

affected only rarely. The clinical manifestations develop within days to weeks and can affect the complete face-particularly the chin, cheeks, forehead and nose. The lesions may remain localized, especially when present on the neck and trunk. The lesions present with papules and pustules and coalescent purplish nodules as well as associated abscesses, which often form confluent fistulae that drain a serious seropurulent or mucoid discharge (Fig. 7.4). Reddish to violaceous firm swelling of the face is commonly noted. Patients often report a history of "flushing and blushing" and oiliness of the skin before the outbreak of rosacea fulminans [11, 12]. Despite the horrendous clinical picture, systemic symptoms (fatigue, fever, arthralgia and anaemia) are usually absent. When the disease is controlled it does not tend to recur after resolution. In contradistinction, severe nodular acne vulgaris presents with more comedones and a more gradual evolution of lesions. Plewig, Jansen and Kligman suggested pyoderma faciale be best considered in the rosacea spectrum and suggested the designation to be changed to rosacea fulminans. Pyoderma faciale or rosacea fulminans resolves reliably with a combination therapy of oral prednisone and isotretinoin [10].

7.7 Acquired Forms of Rosacea

Steroid rosacea occurs from prolonged treatment with topical corticosteroids [13]. The atrophic side effects of the medication sometimes lead to an aggravation of the condition. The complexion changes to a deep flaming red or copper-red covered by a network of telangiectasias. The atrophic skin develops patches of scales, follicular papules and pustules, nodules and secondary comedones. The area of involvement is restricted to the area of corticosteroid application. Patient reports a severe discomfort and nagging pain sensation. A pathognomonic finding is the development of small pustules on a pre-existing or newly formed erythema background. The clinical picture is difficult to distinguish from papulopustular rosacea. However, because of the difference in therapy, discriminating from papulopustular rosacea is essential. Halogen rosacea results from the ingestion of iodides or bromides which provokes a rosacea-like reaction or aggravate a pre-existing rosacea [13]. The clinical findings resemble acne and acne conglobata. The condition is rare and typically improves in 4 to 6 weeks after elimination of the exposure. Scarring and post-inflammatory pigmentation might occur as residuals [13].

7.8 Treatment

Rosacea is characterized by multifactorial, inflammatory events and often requires a multidisciplinary approach including adequate skin care, topical and/or systemic therapy as well as physical modalities to treat the various symptoms in an appropriate and targeted manner [1, 2].

The goal of treatments is the following: reducing papules and pustules, promoting clearance of lesions and avoidance of concomitant post-inflammatory hyperpigmentation. Long-term suppression of erythema and inflammation are usually desired by both clinicians and patients (Fig. 7.5a, b). However, it is essential to set realistic expectations for the timeline of improvement during the course of disease. It is important to educate patients about the chronicity of the disease and its long-term treatment [2]. The treatment approach in patients with darker and lighter skin is similar, involving the same topical, oral, laser, light-based or surgical treatment targeted to the patients' individual signs of rosacea [1].

For a skin-care regimen in skin of colour, Alexis et al. [2] recommend gentle, non-alkaline, fragrance-free, emollient cleanser once a day in the evening. Silicone-based moisturizers, light water-based cosmetics and physical sunscreens are also recommended. Alcohol-based cleansers, astringents or abrasive exfoliating cleansers should be avoided. The use of non-silicone–based moisturizers, cosmetics with iridescent effects and chemical sunscreens is not recommended especially when sensitivity is reported [2].

The management of erythema, telangiectasia, papules, pustules and phymatous changes is the main concern of patients and dermatologists. Because of the

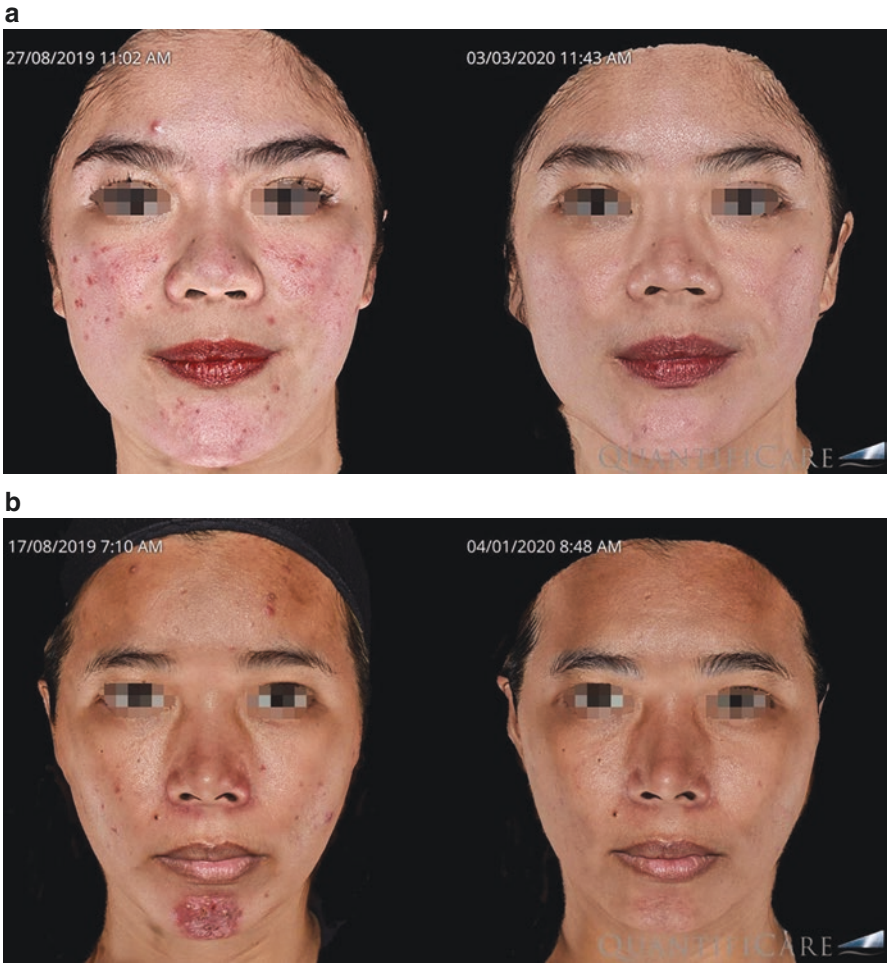

Fig. 7.5 (**a**) Papulopustular rosacea in a Filipino woman treated with low dose isotretinoin and topical metronidazole cream (**b**) Papulopustular rosacea localized on the chin in a Filipino with Fitzpatrick skin phototype V, treated with oral azithromycin thrice weekly for 6 weeks and low dose isotretinoin for 6 months and topical metronidazole cream

chronicity and relapsing character of the disease, patients are often dissatisfied with traditional treatments. Engin and colleagues published an article which recommended treatments for rosacea based on the updated and revised consensus classification. The treatments were discussed based on their established roles on erythema, telangiectasia, papules and pustules, and phymas. Since the pathogenesis of rosacea is complex and patients usually present with a combination of phenotypes, the treatment has always been challenging to the dermatologist [14].

7.8.1 Erythema

Whether transient or persistent, facial erythema is usually longstanding and may persist for years. Topical steroids may help reduce erythema by vasoconstriction but its use should be avoided because of the potential side effect of atrophy [14, 15]. Topical calcineurin inhibitors may also be used on short term basis but there is potential for irritation [14, 16].

Topical metronidazole, azelaic acid and systemic tetracyclines are believed to control erythema in molecular studies but most often the effect is suboptimal in cases of persistent erythema [14, 17, 18]. Brimonidine tartrate 0.5% in gel preparation is a potent vasoconstrictor and has been approved for the treatment of transient and persistent erythema in patients aged 18 years old and above. It reduces erythema by 60–70% and the effect is recognized 30 min after application. However, the effect is only transient and erythema may reappear 9–12 h after [14, 19].

Oxymetazoline hydrochloride 1% cream is an alpha 1a-adrenergic receptor agonist used for moderate to severe persistent facial erythema in adults. Bauman et al. [20] observed 29 patients who used oxymetazoline cream for 29 days and concluded that once daily application is effective and safe for patients with rosacea. Reduction of facial erythema usually starts 1 h after application of the cream [14, 20, 21].

Intradermal botulinum toxin type A injection is a promising treatment modality for facial flushing and erythema. Park et al. [22] demonstrated significant improvement in 2 patients treated with 50 and 65 units with two treatment sessions. Symptomatic relief was observed for 4 months after treatment and both patients requested for a repeat dose [22].

In patients with diffuse facial erythema, pulsed dye laser (PDL) and intense pulse light (IPL) may be used for cosmetic improvement. Two treatment sessions of PDL usually results to a significant cosmetic improvement. It also decreases symptoms of burning, stinging, sensitivity, itching and dryness [23]. Side effects such as facial bruising may be encountered if very high fluences are used. Intense pulsed light, when filtered at 560 nm demonstrate similar efficacy with the PDL, but lesser side effects are encountered [14, 24].

7.8.2 Telangiectasia

Topical and systemic agents are ineffective in the treatment of telangiectasias. Lasers and light devices that specifically target the cutaneous vasculature are effective in treating telangiectasias. Commonly used devices include PDL, long pulsed Nd:YAG lasers and IPL [14]. All these devices show significant reduction in telangiectasias. Pulsed dye laser was more effective than Nd:YAG laser based on one study, and it appeared to be as effective as IPL with a low quality of evidence.

Lesser side effects have been observed with the long-pulsed Nd:YAG and IPL. Laser and lights treatment of telangiectasias may also be combined with topical retinoids, brimonidine, and oral minocycline with better results [14, 25–30].

7.8.3 Papules and Pustules

Papules and pustules are the more problematic lesions in rosacea and are considered as major phenotypes in the most recently updated consensus classification. Topical treatment may be sufficient to treat mild lesions. However, a combination of systemic and topical medications is usually recommended for moderate or severe flares. The most common topical treatments used include metronidazole, azelaic acid, and ivermectin. The most commonly prescribed systemic medications are oral antibiotics and retinoids [14].

Metronidazole 0.75–1% cream [31, 32] is effective in the treatment of PPR when applied twice daily. A study by Nielsen [32] revealed that topical metronidazole has a clearance rate of 90%. Azelaic acid 15% gel [33] on the other hand, applied twice daily for 15 weeks also produced a significantly better treatment outcome compared to Metronidazole cream. Ivermectin 1% cream is a safe and tolerable treatment for PPR, especially when Demodex coinfection is present. The study by Dall'Oglio demonstrated a 32% complete resolution within 8 weeks use of topical ivermectin [34]. A significant reduction of erythema was also observed. Topical ivermectin appeared to be slightly more effective than topical metronidazole for papulopustular rosacea, based on one study, for improving quality of life and participant and physician assessed outcomes (high quality evidence for these outcomes) [35].

Low dose oral Tetracyclines (40 mg/day) are effective in the treatment of PPR. The daily use of Doxycycline 40 mg/day was not associated with any form of antibiotic resistance even with prolonged use. Oral tetracycline was compared with topical metronidazole in four studies and showed no statistically significant difference between the two treatments for any outcome (low-to-moderate quality evidence) [35–38].

In published studies, Azithromycin has been shown to be equally effective with doxycycline [25, 38]. In a Korean study of 67 patients, azithromycin 500 mg were given thrice weekly on the first month, 250 mg thrice weekly on the second month and 250 mg twice weekly on the third month and the efficacy was comparable to doxycycline 100 mg once daily for 3 months [38]. In a case report on intractable rosacea in a 67-year-old lady who was previously treated with oral isotretinoin, doxycycline and metronidazole, azithromycin 500 mg once daily for 2 weeks resulted to a dramatic improvement [39].

Isotretinoin one to five times a week and equivalent to 5 mg/day is an effective treatment in mild-to-moderate papulopustular rosacea in a retrospective study done in 59 patients, mostly women. The clinical response of 91% of patients was

complete clearance and was excellent. Cheilitis was reported in 50% of patients, but majority of the subjects tolerated the medication well [40].

Isotretinoin at 0.3 mg/kg has been demonstrated by Gollnick et al. to be efficacious and safe for the treatment of rosacea subtypes II (PPR) and III (phymatous). In 573 patients, it demonstrated significant superiority over placebo and significant non-inferiority versus doxycycline in the double blind, randomized, placebo-controlled trial in the clinical trial by Gollnick [40]. The study lasted for 12 weeks in 35 German centres [41]. In the updated Cochrane systematic review of rosacea treatments, the authors highlighted that isotretinoin was slightly more effective versus doxycycline 50 to 100 mg [35].

Isotretinoin is also an effective treatment for difficult to treat papulopustular rosacea. In a multicentre double-blind placebo-controlled trial, 57.4% of 108 patients demonstrated 90% clearance of papules and pustules. However, relapse was observed in 58.3% of 57 responders who followed up after 4 months of treatment with a median of 15 weeks to recurrence [42].

7.8.4 Phymas

Systemic treatment modalities for phyma which demonstrate a high level of evidence in systematic reviews are doxycycline 40 mg/day and low dose isotretinoin (0.3 mg/day) [43]. In several studies, isotretinoin significantly decreased nasal volume and diminished size and number of sebaceous glands in rhinophyma [43]. Lasers used to treat phymas include carbon dioxide (CO_2) and Erbium:YAG lasers. A combination of both lasers shows optimal cosmetic results and minimal scarring with the combination of CO_2 laser and Erbium:YAG resurfacing [44, 45].

7.9 Associated Conditions

Rosacea was once believed to be a disorder which is limited to the skin, but recent studies suggest a relationship with other systemic disease such as cardiovascular diseases, allergies, psychiatric problems, gastrointestinal disorders, malignancies, and autoimmune conditions. The study by Egeberg et al. in European patients have reported an increased odds ratio (OR) for type 1 diabetes mellitus, celiac disease, multiple sclerosis, and rheumatoid arthritis [44, 45].

A recent study by Woo [46] and colleagues attempted to investigate the odds of systemic comorbidities in Korean patients with rosacea. The effects of age and sex on the associations between rosacea and various systemic disorders were evaluated, as well.

The study revealed a significant association between rosacea and Sjogren syndrome, systemic sclerosis, rheumatoid arthritis, ankylosing spondylitis, autoimmune thyroiditis, alopecia reata, vitiligo, lung cancer, hepatobiliary cancer, alcohol

abuse, diabetes mellitus, obesity, allergic rhinitis, allergic conjunctivitis, chronic rhinosinusitis, herpes infection and human papillomavirus infection. Higher odds for Sjogren syndrome, systemic sclerosis, ankylosing spondylitis, thyroiditis, vitiligo, hepatobiliary cancer and obesity were exclusive in female subjects with rosacea. Only those 50 years and older exhibited higher odds for vitiligo, lung cancer and gastroesophageal reflux disease while individuals younger than 50 were exclusively associated with hepatobiliary cancer, allergic conjunctivitis and irritable bowel syndrome. The study suggests that Koreans with rosacea are most likely to experience systemic comorbidities. It is important to highlight that the study also validated the strong association between rosacea and metabolic syndrome (i.e. diabetes mellitus and obesity). It is postulated that systemic inflammation underlying rosacea induces structural changes of the lipoprotein, which adversely affects the lipid profile. In populations where obesity is prominent extra attention should be given in patients with coexisting rosacea, obesity and diabetes mellites [46].

A meta-analysis done by Von Eynatten and colleagues also confirmed an association between migraine and rosacea. And follow up studies should research for the common pathophysiology between these two conditions [47].

7.10 Conclusion

The complex condition of rosacea implies that there is a need for a tailored multimodal approach for treatment success. Most especially now that we are encouraged to use the phenotype-driven approach in the diagnosis and treatment of rosacea. Patient education, skin care and a usual combination of therapeutic options are necessary for the control of rosacea but must be reiterated that none of these are definitely curative. Standardization of treatment algorithm is still needed to help guide physicians, dermatologists and patients. Further researches on pathophysiology and disease associations are further encouraged.

References

1. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, Thiboutot D. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society expert committee. J Am Acad Dermatol. 2018;78(1):148–55.
2. Alexis AF, Callender VD, Baldwin HE, Desai SR, Rendon MI, Taylor SC. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: review and clinical practice experience. J Am Acad Dermatol. 2019;80(6):1722–9.
3. Abram K, Silm H, Maaroos HI, Oona M. Risk factors associated with rosacea. J Eur Acad Dermatol Venereol. 2010;24(5):565–71.
4. Bae YI, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Clinical evaluation of 168 Korean patients with rosacea: the sun exposure correlates with the erythematotelangiectatic subtype. Ann Dermatol. 2009;21(3):243–9.

5. Reinholz M, Ruzicka T, Steinhoff M, Schaller M, Gieler U, Shofer H, Homey B, Lehmann P, Luger TA. Pathogenesis and clinical presentation of rosacea as a key for a symptom-oriented therapy. J Dtsch Dermatol Ges. 2016;14(Suppl. 6):4–15.
6. Aloi F, Tomasini C, Soro E. The clinicopathological spectrum of rhinophyma. J Am Acad Dermatol. 2000;42(3):468–72.
7. Kellen R, Silverberg NB. Pediatric rosacea. Cutis. 2016;98(1):49–53.
8. Cribier B. Rosacea under the microscope: characteristic histological findings. J Eur Acad Dermatol Venereol. 2013;27:1336–43.
9. Micali G, Lacarrubba F, Massimino D, Schwartz RA. Dermatoscopy: alternative uses in daily clinical practice. J Am Acad Dermatol. 2011;64(6):1135–46.
10. Plewig G, Jansen T, Kligman AM. Pyoderma faciale. A review and report of 20 additional cases: is it rosacea? Arch Dermatol. 1992;128(12):1611–7.
11. Crawford GH, Pelle MT, James WD. Reply to the letter to the editor. J Am Acad Dermatol. 2005;53(6):1105–6.
12. Crawford GH, Pelle MT, James WD, Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol. 2004;51(3):327–41.
13. Steinhoff M, Buddenkotte J. Rosacea. In: Sewon K, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS, editors. Fitzpatrick's dermatology in general medicine. 9th. ed. New York: McGraw-Hill Companies Inc; 2019. p. 1426.
14. Engin B, Özkoca D, Kutlubay Z, Serdaroğlu S. Conventional and novel treatment modalities in Rosacea. Clin Cosmet Investig Dermatol. 2020;20(13):79–86.
15. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol. 2006;54(1):1–15.
16. Teraki Y, Hitomi K, Sato Y, Izaki S. Tacrolimus-induced rosacea-like dermatitis: a clinical analysis of 16 cases associated with tacrolimus ointment application. Dermatology. 2012;224(4):309–14.
17. Layton AM. Pharmacologic treatments for rosacea. Clin Dermatol. 2017;35(2):207–12.
18. Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea. F1000Res. 1885;2018:7.
19. Fowler J Jr, Jackson M, Moore A, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. J Drugs Dermatol. 2013;12:650–6.
20. Baumann L, Goldberg DJ, Stein GL, et al. Pivotal trial of the efficacy and safety of Oxymetazoline cream 1.0% for the treatment of persistent facial erythema associated with Rosacea: findings from the second REVEAL trial. J Drugs Dermatol. 2018;17(3):290–8.
21. Tanghetti E, Dover J, Goldberg D, et al. Clinically relevant reduction in persistent facial erythema of rosacea on the first day of treatment with oxymetazoline cream 1.0%. J Drugs Dermatol. 2018;17:621–6.
22. Park KY, Hyun MY, Jeong SY, Kim BJ, Kim MN, Hong CK. Botulinum toxin for the treatment of refractory erythema and flushing of rosacea. Dermatology. 2015;230(4):299–301.
23. Tan SR, Tope WD. Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. J Am Acad Dermatol. 2004;51(4):592–9.
24. Handler MZ, Bloom BS, Goldberg DJ. IPL vs PDL in treatment of facial erythema: a split-face study. J Cosmet Dermatol. 2017;16(4):450–3.
25. Anzengruber F, Czernielewski J, Conrad C, et al. Swiss S1 guideline for the treatment of rosacea. J Eur Acad Dermatol Venereol. 2017;31(11):1775–91.
26. Feaster B, Cline A, Feldman SR, Taylor S. Clinical effectiveness of novel rosacea therapies. Curr Opin Pharmacol. 2019;46:14–8.
27. Maxwell EL, Ellis DA, Manis H. Acne rosacea: effectiveness of 532 nm laser on the cosmetic appearance of the skin. J Otolaryngol Head Neck Surg. 2010;39(3):292–6.
28. Kim SJ, Lee Y, Seo YJ, Lee JH, Im M. Comparative efficacy of radiofrequency and pulsed dye laser in the treatment of Rosacea. Dermatol Surg. 2017;43(2):204–9.

29. Ko HS, Suh YJ, Byun JW, Choi GS, Shin J. Pulsed dye laser treatment combined with oral minocycline reduces recurrence rate of Rosacea. Ann Dermatol. 2017;29(5):543–7.
30. Dall'Oglio F, Verzì AE, Luppino I, Bhatt K, Lacarrubba F. Treatment of erythemato-telangiectatic rosacea with brimonidine alone or combined with vascular laser based on preliminary instrumental evaluation of the vascular component. Lasers Med Sci. 2018;33(6):1397–400.
31. Dahl MV, Jarratt M, Kaplan D, Tuley MR, Baker MD. Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. J Am Acad Dermatol. 2001;45:723–30.
32. Nielsen PG. A double-blind study of 1% metronidazole cream versus systemic oxytetracycline therapy for rosacea. Br J Dermatol. 1983;109:63–6.
33. Draelos ZD, Elewski B, Staedtler G, Havlickova B. Azelaic acid foam 15% in the treatment of papulopustular rosacea: a randomized, double-blind, vehicle-controlled study. Cutis. 2013;92(6):306–17.
34. Dall'Oglio F, Lacarrubba F, Luca M, et al. Clinical and erythema-directed imaging evaluation of papulo-pustular rosacea with topical ivermectin: a 32 weeks duration study. J Dermatolog Treat. 2019;20:1–5.
35. van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MM, Charland L. Interventions for rosacea. Cochrane Database Syst Rev. 2015;2015(4):CD003262. https://doi.org/10.1002/14651858.CD003262.pub5.
36. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. J Am Acad Dermatol. 2007;56:791–802.
37. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. J Drugs Dermatol. 2008;7:573–6.
38. Akhyani M, Ehsani AH, Ghiasi M, Jafari AK. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. Int J Dermatol. 2008;47(3):284–8.
39. Kim JH, Oh YS, Choi EH. Oral azithromycin for treatment of intractable rosacea. J Korean Med Sci. 2011;26(5):694–6.
40. Rademaker M. Very low-dose isotretinoin in mild to moderate papulopustular rosacea; a retrospective review of 52 patients. Australas J Dermatol. 2018;59(1):26–30.
41. Gollnick H, Blume-Peytavi U, Szabó EL, Meyer KG, Hauptmann P, Popp G, Sebastian M, Zwingers T, Willers C, von der Weth R. Systemic isotretinoin in the treatment of rosacea - doxycycline- and placebo-controlled, randomized clinical study. J Dtsch Dermatol Ges. 2010;8(7):505–15.
42. Sbidian E, Vicaut É, Chidiack H, Anselin E, Cribier B, Dréno B, Chosidow O. A randomized-controlled trial of Oral low-dose isotretinoin for difficult-to-treat Papulopustular Rosacea. J Invest Dermatol. 2016;136(6):1124–9.
43. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. J Am Acad Dermatol. 2004;51(4):499–512.
44. Goon PK, Dalal M, Peart FC. The gold standard for decortication of rhinophyma: combined erbium-YAG/CO_2 laser. Aesthet Plast Surg. 2004;28(6):456–60.
45. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Assessment of the risk of cardiovascular disease in patients with rosacea. J Am Acad Dermatol. 2016;75(2):336–9.
46. Woo YR, Kim HS, Lee SH, Ju HJ, Bae JM, Cho SH, Lee JD. Systemic comorbidities in Korean patients with Rosacea: results from a multi-institutional case-control study. J Clin Med. 2020;9(10):3336.
47. von Eynatten M, Schneider JG, Humpert PM, Rudofsky G, Schmidt N, Barosch P, Hamann A, Morcos M, Kreuzer J, Bierhaus A, Nawroth PP, Dugi KA. Decreased plasma lipoprotein lipase in hypoadiponectinemia: an association independent of systemic inflammation and insulin resistance. Diabetes Care. 2004;27(12):2925–9.

Chapter 8
Hidradenitis Suppurativa

Dhanashree Bhide

8.1 Introduction

Hidradenitis suppurativa is a chronic condition affecting pilosebaceous apocrine units. Initially, it was considered as an infective condition. However, with the better understanding of aetiopathogenesis in the past few years, different cytokines responsible for initiation and perpetuation of inflammation have been identified. Follicular occlusion is main event and apocrinitis is secondary. Clinically, patients suffer from painful nodules with discharging sinuses. The chronic nature and the presenting symptoms have lot of psychological impact leading to depression and social isolation. The negative psychological impact is due to occurrence of lesions in sensitive areas, pain, foul smell, scarring and chronicity of the disease [1–4].

There is genetic predisposition in familial cases. There are various exogenous and endogenous factors responsible for inflammation. The aetiology is multifactorial, but the end result is follicular occlusion. The treating physician should target the therapy against different arms in the pathogenesis and should also address the psychological factors. Satisfactory and sustainable response can be achieved with a multidisciplinary approach.

8.2 Aetiopathogenesis [5–11]

The main target in the pathogenesis is pilosebaceous apocrine unit. The initiating factor is over response of toll like receptors. This over response of TLR is to the commensal organisms. In familial HS, there are mutations observed in gamma secretase subunits. This leads to defect in notch signalling pathway.

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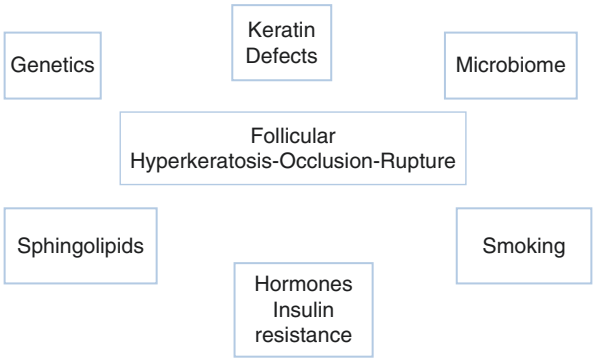
The inflammatory process results in different stages like subclinical disease, actual clinical manifestations and perpetuation of the clinical signs and symptoms in response to ongoing inflammation leading to chronicity. The immune dysfunction leads to alteration in pilosebaceous apocrine unit causing occlusion of the duct.

The changes observed in the follicular unit are the following.

1. Impaired maturation of follicular cells leading to epithelial fragility.
2. Infundibular hyperkeratosis and follicular obstruction.
3. Biofilm production and microbial dysbiosis leading to enhancement of follicular obstruction and infundibular hyperkeratosis.
4. Stimulation of dendritic cells creating a proinflammatory environment leading to epithelial fragility.

8.3 Factors Involved in Immune Pathogenesis of HS

Various exogenous and endogenous factors are involved in the process of secretion and alteration of inflammatory cytokines. Various hormones, genetic factors, high insulin levels and smoking contribute to creating a proinflammatory environment. Due to constant feedback from cytokine-driven pathway the inflammation becomes chronic. There is follicular occlusion leading to development of painful nodules, discharging sinuses and scarring.



8.3.1 Genetics [12]

Positive family history is found in one-third of cases.

Reported inheritance is autosomal dominant.

The genetic defect

1. Affects gamma secretase subunit. Loss-of-function mutations in 3 of the 4 subunits of gamma-secretase. Gamma-secretase cleaves the intracellular domain of Notch, leading to defective Notch signaling.
2. As a result of defective notch signalling there is inhibition of the hair growth cycle, the conversion of hair follicles into keratin enriched epidermal cysts, and poor sebaceous gland differentiation.
3. Notch signalling suppresses TLR-4-induced proinflammatory cytokine responses by macrophages.
4. Notch deficiency helps in development of a proinflammatory environment.
5. Notch Deficiency Causes Deficiency of IL-22 which Is Dependent on the Notch Pathway

8.3.2 Microbiome: Role of Antimicrobial Peptides (AMP), Pathogen Recognition Receptors (PRR) and Biofilm [13]

The microbiome is different in lesional and non-lesional skin of patients with H.S. Lesional skin mainly consists of Corynebacterium, Porphyromonas, and Peptoniphilus species, while non-lesional skin has predominantly. Acinetobacter and Moraxella.

8.3.2.1 AMP—Antimicrobial Peptide [14]

Antimicrobial peptides are secreted by keratinocytes in response to invasive pathogens. They have the following functions.

(a) Antimicrobial.
(b) Immune modulation.

In HS there is altered function as well as altered levels of AMP. There is deficiency of AMP in HS.

8.3.2.2 PRR—Pathogen Recognition Receptors

There are two recognised PRR—TLR Toll-Like Receptor and NOD.

They have the following functions.

(a) Proinflammatory signalling.
(b) Complement activation.
(c) Opsonisation.
(d) Phagocytosis.
(e) Regulation of opsonins.

In HS there is overexpression of TLR 2 and C type lectin in epidermis and dermis of affected skin.

The response of TLR to commensal bacteria may be overzealous. This may be the initiating event**.**

8.3.2.3 Biofilm formation [5]

Initially there is no secondary infection. As the disease becomes chronic there is colonisation by bacteria. In the sinus tracts these bacteria are found in a biofilm. The formation of biofilm poses therapeutic challenge and also leads to propagation of disease process.

8.3.3 Smoking [14–16]

There are the following effects seen in smokers.

1. Epidermal hyperplasia. Stimulation of follicular keratosis and occlusion.
2. Alteration of skin immune response (more neutrophilic).
3. Increases microbial virulence.
4. Decreases skin antimicrobial peptides.
5. Down-regulation of Notch signalling.

8.3.4 Obesity, Hormones and Insulin Resistance [17–22]

Obesity has the following effects

1. Inflammation: There is proinflammatory state in which adipocytes secrete metabolically active proinflammatory cytokines known as adipokines .
2. Increased friction and follicular microtrauma .
3. High systemic inflammatory burden leads to insulin resistance. IR is responsible for endothelial dysfunction and atherosclerosis.
4. There is an association of HS and the metabolic syndrome**.**

Hormones [18–22]

Two hormones, androgens and female hormones, have been studied in HS.

The testosterone and DHT levels in patients of HS are comparable with controls and hyperandrogenism is usually absent. Hence, it is postulated that the role of androgens is probably relevant at local sites rather than systemically.

It is observed that 43% of female patients experience worsening of symptoms around menses. Progesterone-containing OCPS worsen HS, whereas spironolactone improves clinical signs and symptoms of HS.

8.3.5 Sphingolipids [23]

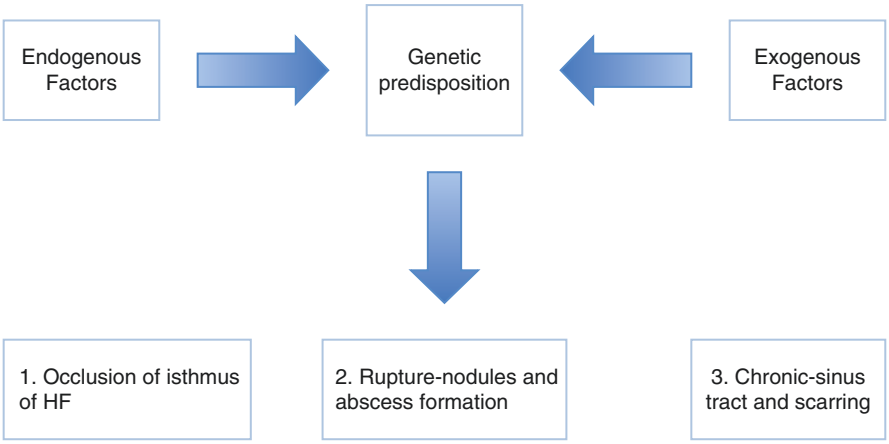
Sphingolipids are membrane lipid–signalling molecules.

In HS lesional skin there is decreased expression of enzymes that generate ceramide and sphingomyelin as well as increased expression of enzymes that catabolise ceramide. Decreasing ceramide and sphingomyelin levels disrupt the cutaneous barrier and cause immune activation.

8.3.6 Keratin Defects

There is decreased cytokeratin CK 17 and upregulated CK 5 AND CK6. This leads to hyperkeratosis of follicular infundibulum with resultant occlusion and initiates inflammatory processes.

8.4 Diagrammatic Representation



8.5 Stages in Development of HS (Figs. 8.1, 8.2, and 8.3) [24]

These tunnels are habitats for biofilm producing bacteria responsible for continuous inflammation and purulent discharge

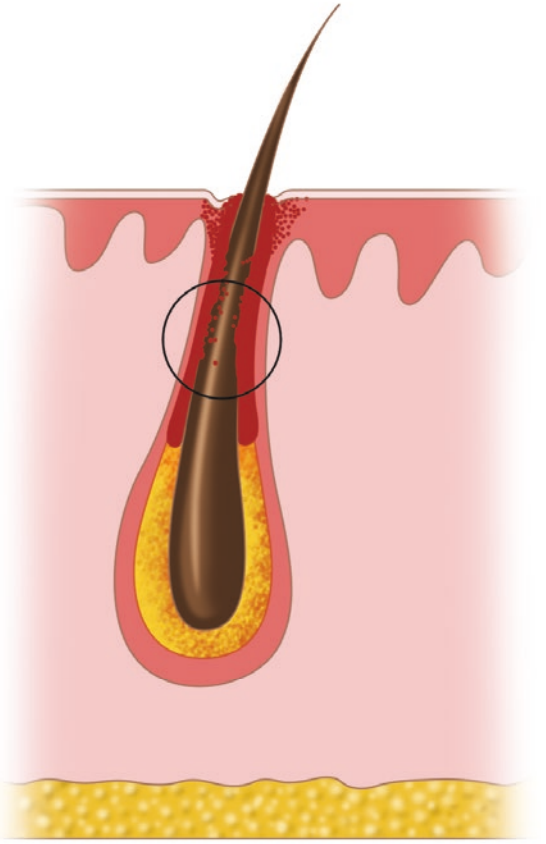


Fig. 8.1 Follicular occlusion and dilatation by various exogenous and endogenous factors

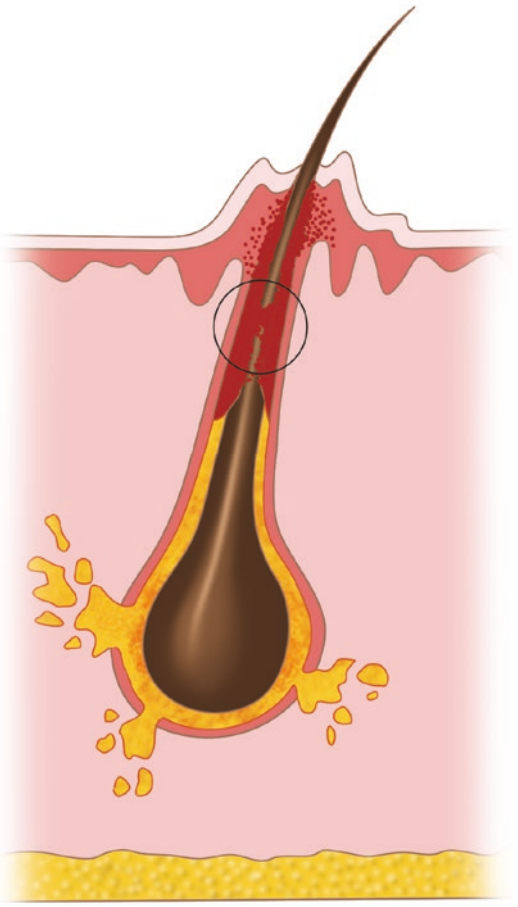


Fig. 8.2 Rupture of follicle leading to release of keratin fibres, commensal flora or pathogen in the dermis. Triggering of immune response (Activation of Th17/IL-23, NLRP inflammasome and Innate receptors TLR2). Development of nodules with diverse infiltrate in the dermis

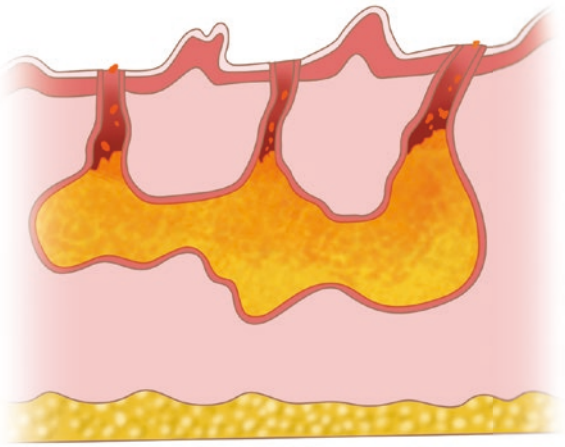


Fig. 8.3 Chronic stage develops leading to formation of sinus tracts, fistulae and rope-like scars Ki67+ strands from ruptured follicles proliferate and activate immune system continuously. There are other changes like (1) imbalance of MMP and tissue inhibitor metalloproteinases and (2) increased activity of fibrotic factors TGF beta 1,2,3. There is formation of scars, tunnels and fistulae.

8.6 Factors Playing Role in Immune Pathogenesis [25–27]

8.6.1 Receptors

TLR 2 are present on polymorphonuclear leucocytes, keratinocytes and dendritic cells.

8.6.2 Cytokines, Complement and Inflammasomes in HS

TNF alpha, IL-1 alpha, IL-1 beta, IL-6, IL-8, IL-10, IL-12, IL-17, IL-22, IL-23.
IL-36 Ra, IL-36.
MMP, Caspase 1, C5 alpha.

8.6.3 Inflammatory Cells Recruited at Site

Dendritic cells, CD4 T lymphocytes, Th17 and Th1 cells, macrophages, neutrophils.

8.6.4 Net Effect

Released cytokines lead to an environment conducive for epithelial fragility.

8.7 Immunopathogenesis of HS [28, 29]

1. **Genetic Factors—**Gamma secretase deficiency. Environment suitable for epithelial fragility.
2. **IL-36–IL-36Ra imbalance and stimulation of cholinergic receptors by nicotine in smokers**—increased infundibular hyperkeratosis and occlusion.
3. **Microbial dysbiosis and biofilm formation**—Enhances follicular obstruction and inflammation by stimulating beta defensins.
4. **Altered sphingolipids and decreased ceramides, overexpression of TLR due to altered microbiome, increased IL-36 and decreased IL-36Ra—**Activation of dendritic cells. Release of IL-23, IL-1, IL-6 and TNF from activated dendritic cells.
5. **TNF alpha released from keratinocytes and activated dendritic cells**—Induces hyperkeratosis. Decreases adiponectin secretion from adipocytes. Increases MMP expression.
6. **IL-23 released from activated dendritic cells.**
   (a) Stimulates CD4 T cells. Stimulated CD4 T cells lead to development of Th17 cells. Th17 cells produce IL-17 A (These Th17 cells are the main producers of IL-17 A). IL-17 A induces expression of IL-1 beta, IL-6, TNF alpha (through mechanisms involving NLRP3 inflammasome).
   (b) Induces overexpression of IL-17. IL-17 in turn induces expression of NLRP3 in neutrophils and macrophages. This leads to release of more cytokines, caspases and MMP in follicular unit and perilesional skin.

8.8 Comorbid Conditions Associated with HS [30–33]

Other comorbid conditions where inflammation plays an important role are seen to be associated in patients with HS. Hypertension, obesity, thyroid dysfunction, PCOS, dyslipidaemia and psychiatric disorders are some of the other comorbidities observed in patients suffering from hidradenitis suppurativa.

Follicular occlusion disorders, inflammatory bowel diseases, especially Crohn disease, spondyloarthropathy, other hyperergic diseases, genetic keratin disorders associated with follicular occlusion and squamous cell carcinoma were the most common hidradenitis suppurativa comorbid diseases.

8.9 Follicular Occlusion Triad, Tetrad and Other Syndromes Associated with HS

1. **Follicular Occlusion triad** [34, 35]
   HS, acne conglobata and dissecting cellulitis of the scalp.
2. **Follicular occlusion tetrad**
   HS, acne conglobata, dissecting cellulitis of the scalp, pilonidal sinus.

3. **SAPHO Syndrome**
   Synovitis, acne, acral pustulosis, hyperostosis, osteitis SAPHO syndrome is characterised by arthritis and/ or osteitis with preferential anterior chest wall involvement, and although most commonly associated with palmoplantar pustulosis, it has also been associated with other chronic suppurative skin disorders including HS, acne conglobata or acne fulminans and dissecting cellulitis of the scalp.
4. **PAPASH Syndrome**
   Pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa.
5. **PASH Syndrome**
   Pyoderma gangrenosum, acne and suppurative hidradenitis.
6. **PASS Syndrome**
   PG, acne conglobata, HS and axial spondyloarthropathy.

8.10 Investigations [36]

Investigations have a role in determining the extent and severity of the disease rather than for confirming the diagnosis.

Surgical planning as well as staging requires precision and hence investigations like colour Doppler ultrasound and MRI have been advocated.

Most commonly performed investigation is ultrasound. The MRI is usually restricted for deep seated lesions especially in anogenital area.

Re interpretation of clinical diagnosis is possible after imaging as it can detect the subclinical lesions as well.

Thus, imaging helps to obtain objective and precise information about the extent.

It is also possible to determine the blood flow patterns on sonography.

There are specific criteria on sonography for diagnosis and staging of HS [37].

1. Widening of the hair follicles.
2. Thickening and/or abnormal echogenicity of the dermis.
3. Dermal pseudocystic nodules (i.e. round or oval-shaped hypoechoic or anechoic nodular structures).
4. Fluid collections (i.e. anechoic or hypoechoic fluid deposits in the dermis and/or hypodermis connected to the base of widened hair follicles).
5. Fistulous tracts (i.e. anechoic or hypoechoic bandlike structures across skin layers in the dermis and/or hypodermis connected to the base of widened hair follicles).

The presence of 3 findings is the sonographic criteria for diagnosing HS.

8.11 Sonographic Staging [37]

Stage I: Single fluid collection and/or dermal changes affecting a single body segment (either one side or bilateral), without fistulous tracts.
Stage II: Two to four fluid collections and/or a single fistulous tract with dermal changes, affecting up to two body segments (either one side or bilateral).
Stage III: Five or more fluid collections and/or two or more fistulous tracts with dermal changes, and/or involvement of three or more body segments (either one side or bilateral).

8.12 Other Investigations [38]

1. **Microbiological Screening**
   It is useful when a secondary infection is suspected and the patient has fever with other constitutional symptoms.
2. **Genetic studies and Biomarkers**
   Useful for research purposes and in clinical trials. In day-to-day practice these tests do not have any role in the diagnosis of the disease.
3. **Histopathology**
   The histology is not specific and rarely performed. The studies on histopathology are limited. If performed it helps in understanding pathogenesis and helps to detect superimposed squamous cell carcinoma.
4. **Screening for comorbid conditions**
   The appropriate investigations should be performed based on the clinical suspicion of underlying diseases like metabolic syndrome, PCOS, DM and many other autoinflammatory syndromes.

8.13 Clinical Features [38]

The disease is characterised by recurrent, painful, nodules and abscesses that rupture, leading to the formation of sinus tracts and scarring. Lesions usually affect apocrine gland-bearing anatomical areas of the body and areas where terminal follicles are dependent on low androgen levels. HS typically occurs after puberty.

Other morphological lesions like painful and/or tender erythematous papules <1 cm in diameter, dermal contractures and rope-like elevation of the skin, double-ended comedones may be present.

Symptoms: pain, burning, stinging, itching, sensation of warmth and hyperhidrosis may be present.

8.14 Distribution [38]

Lesions are distributed in following areas, in order of decreasing frequency.

Axillary, inguinal, perineal and perianal, mammary and inframammary, buttocks, pubic region, chest, scalp, retroauricular, and eyelid.

Aberrant lesions may occur in the waist, abdomen, specially periumbilical region, and thorax.

The criteria suggested for diagnosis in the second international conference on HS are as follows [39].

1. Typical lesions, that is, deep-seated painful nodules: "blind boils" in early lesions; abscesses, draining sinus, bridged scars and "tombstone" double-ended pseudo-comedones in secondary lesions.
2. Typical topography, that is, axillae, groins, perineal and perianal region, buttocks, infra-and inter-mammary folds.
3. Chronicity and recurrences.

The severity can be judged by various staging systems [40–44]

Hurley's staging system is most commonly used and is still relevant. The advantage is that it is easy and fast.

The disadvantage is that it is not quantitative.

Stage I: (Fig. 8.4) Abscess formation, single or multiple, without sinus tracts and cicatrisation.

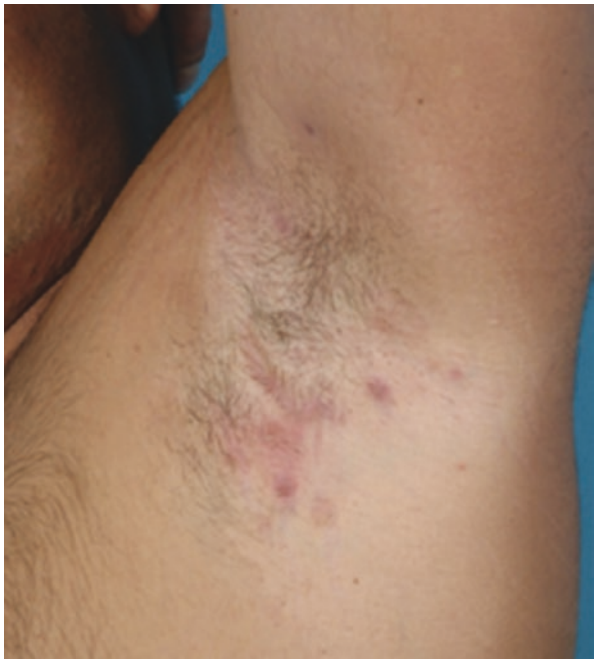


Fig. 8.4 Erythematous papules and nodules

Stage II: (Fig. 8.5) Single or multiple, widely separated, recurrent abscesses with tract formation and cicatrisation.

Stage III: (Fig. 8.6) Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

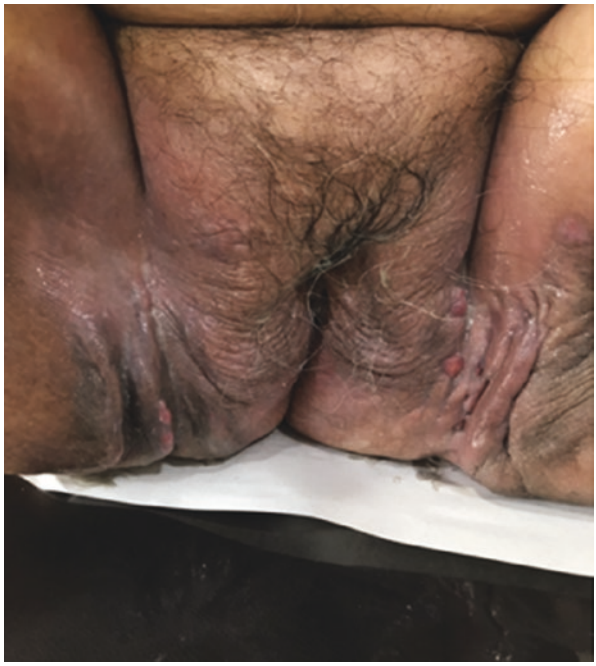


Fig. 8.5 Rope-like scars

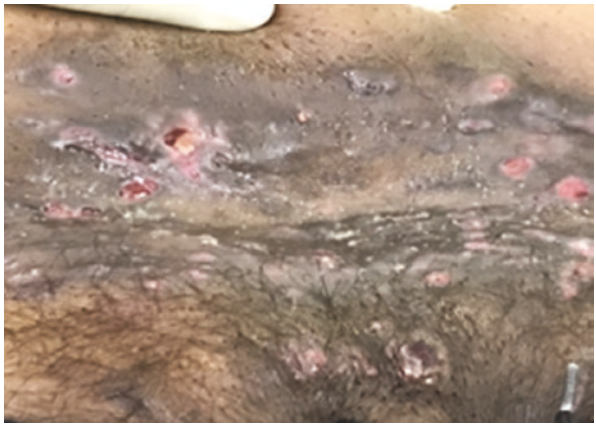


Fig. 8.6 Abscesses, nodules and sinuses

8.15 Other Staging Systems [40–44]

HS Physician's Global Assessment (PGA), the modified Sartorius score (MSS) and HS Severity Index (HSSI).

Each of these scoring systems has advantages and disadvantages, and no scoring system is a gold standard.

A. **Sartorius Score systems** have been used for assessing differences in treatment effects. The following outcome variables have been taken into account.

- Anatomic region involved (axilla, groin, genital, gluteal, or other inflammatory region left and/or right): 3 points per region involved.
- Number and scores of lesions (abscesses, nodules, fistulas, scars): 2 points for each nodule, 4 points for each fistula, 1 point for each scar, 1 point each for "other".
- Longest distance between 2 relevant lesions (i.e. nodules and fistulas, in each region, or size if only 1 lesion): Less than 5 cm, 2 points; less than 10 cm, 4 points; more than 10 cm, 8 points.
- Lesions clearly separated by normal skin in each region: If yes, 0 points; if no, 6 points.

B. **Six-stage physician global assessment (PGA)** is defined as follows.

- Clear: No inflammatory or noninflammatory nodules.
- Minimal: Only the presence of noninflammatory nodules.
- Mild: Fewer than five inflammatory nodules or one abscess or draining fistula and no inflammatory nodules.
- Moderate: Fewer than five inflammatory nodules or one abscess or draining fistula and one or more inflammatory nodules or 2–5 abscesses or draining fistulas and fewer than 10 inflammatory nodules.
- Severe: Two to five abscesses or draining fistulas and 10 or more inflammatory nodules.
- Very severe: More than five abscesses or draining fistulas.

C. **MSS**

In this system it is required to count individual nodules and fistulas within seven anatomical regions. Disadvantages of the MSS are that the system is time-consuming, difficult to interpret and not optimal for evaluating inflammatory manifestations in clinical practice or trials.

D. **HS-PGA**

HS-PGA is easy and often used to measure clinical improvement in clinical trials of medical treatments. In this system severity is assessed by counting the number of abscesses, fistulas, and inflammatory and noninflammatory nodules in all skin areas. There are 6 stages −1 is the least and 6 is the most severe form. The limitation is that clinical improvement does not correlate well with reduction in their HS-PGA score.

E. **HSSI**

HSSI is another HS-specific severity index. It includes parameters like body surface area involved, number of skin lesions, pain severity, and drainage. HSSI

scores ≥13 indicate severe disease, scores between 8 and 12, moderate disease, and scores between 0 and 7, mild disease.

HiSCR is currently the most appropriate clinical endpoint and does represent patient response and treatment evaluation more accurately. The disadvantage is that HiSCR does not take into account the size or severity of individual lesions and does not measure how treatment response affects a patient's level of pain or quality of life.

8.16 Differential Diagnosis [38]

Common abscess, carbuncles, furunculosis, infected Bartholin's gland, Inflamed epidermal cysts, pilonidal cyst, scrofuloderma, actinomycosis, lymphogranuloma venereum, Crohn's disease.

8.17 Management [45–48]

Treatment of HS is quite challenging. There are established treatments like antibiotics, anti-inflammatory medicines and various surgical modalities.

With understanding of immune pathogenesis and role of various cytokines new targeted therapies have been studied and researched and many clinical trials are ongoing to develop appropriate treatment for this debilitating disease.

Combining biological therapies with other immunosuppressive agents gives better results than either therapy alone. The optimum results can be achieved by combining various modalities of treatment and maintaining the results with appropriate molecule suitable for each patient. The treatment can be divided into the following.

1. General care.
2. Medical Management.
3. Laser and light-based therapies.
4. Surgical management.

8.18 General Care [38, 49]

1. Counselling: Cessation of smoking, strict hygiene practices, weight loss, glycaemic control, psychological support.
2. Clothing: Avoid tight and wired undergarments, avoid non-breathable fabric, disposable panties quite useful for those having discharging sinuses in anogenital region.
3. Addressing important aggravating factors like smoking and obesity.

Nicotine (smoking) induces follicular hyperkeratosis and produces follicular obstruction.

Obesity—increased intertriginous surface area, friction, increase in follicular microtrauma, increases sweat production and retention. These patients may show evidence of hormonal changes in the form of androgen excess. There are more chances of associated metabolic syndrome.

4. Diet.
   Fibre-rich and plant-based diet which increases diversity of gut microbiota is recommended.
   The patients should avoid refined carbohydrates, sweets and fatty food.
5. Exercise.
   Aerobics, interval training resistance training(weights) lead to enhanced insulin signaling, increase lean body mass and increase insulin sensitivity.
   This helps to improve features of metabolic syndrome.
6. Local area hygiene and wound care.
   Normal saline or KMNO4 or povidone iodine should be used to clean the wounds.
   Dettol or Savlon should be avoided s it can cause irritation.
   Absorbent material for dressing should be used wherever possible.

8.19 Medical Management [38, 49, 50]

This is the mainstay of therapy and should be used judiciously by weighing pros and cons of each molecule. The available options are antibiotics, anti-inflammatory medicines, immunosuppressives, hormones, retinoids, antidiabetics and others like zinc gluconate, botulinum toxin, IVIG.

8.19.1 Therapeutic Targets

1. Follicular hyperkeratinisation.
2. Inflammation.
3. TNF alpha and other immunological mediators (cytokines).
4. Hormones—anti-androgens.
5. Lifestyle modification, Wt reduction, cessation of smoking.

8.19.2 Antibiotics

The lesions in HS per se are not infective. Bacterial colonisation is a secondary phenomenon and in suspected cases of secondary bacterial infection appropriate antibiotics should be added for a short period of time. For disease control long-term antibiotics are needed depending upon the severity.

Short Term: According to pus culture and sensitivity for the episodes of secondary infection.

Long Term: For disease control and maintaining the remission the following options are available.

Doxycycline, Minocycline.

Rifampicin, Clindamycin.

Ofloxacin, Trimethoprim+Sulfamethoxazole.

8.19.3 Other Antibiotics

Triple therapy—Quinolones+Metronidazole+Rifampicin.

Dapsone—oral and topical.

Clindamycin—Topical.

Ertapenem—Beta-lactam antibiotic.

8.19.4 Antibiotic Strategies

Antibiotics have dual therapeutic benefit as they have anti-inflammatory action in addition to antibacterial effects.

Monotherapy is tried as first line.

For severe cases the following combinations can be tried.

Clindamycin+Rifampicin(s/e pseudomembranous colitis and hepatotoxicity) or moxifloxacin +metronidazole+rifampicin(s/e gastrointestinal disturbance and vaginal candidiasis).

Long-term use of clindamycin can pose the problem of drug resistance.

Usually broad-spectrum antibiotics and combinations are preferred over monotherapy.

8.19.5 Antibiotic Resistance in HS

Tetracycline and metronidazole—Low risk of resistance.

Clindamycin and rifampicin—High risk of resistance.

I/V B Lactum—Lowest risk of antibiotic resistance, but not practically feasible.

8.19.6 Anti-Inflammatory Agents

1. **Short course oral steroids**—Low dose is tried.

   Most studies have used 10 mgm/day.

   Additional benefit—neutralises anti-adalimumab antibodies and improves response to biologics.

2. **Antibiotics as they also have anti-inflammatory action.**
3. **Intralesional Triamcinolone Immunosuppressives**

Prednisolone in higher dose.
Cyclosporine.
HCQS.
Dimethyl fumarate.

8.19.7 Pros and Cons of Immunosuppressive Therapy

Augments effect of adalimumab.
Cyclosporine has shown good anti-inflammatory effects in few studies.
Can be used for long time and safer than steroids; needs monitoring.
Intralesional Steroids—Quick response; useful for solitary lesions.
HCQS trials in progress—no published data.

8.19.8 Hormonal Therapy [51]

Spironolactone.
Finasteride/dutasteride.
OCPS.
Leuprolide acetate, flutamide, degarelix gonadotropin-releasing hormone agonist.

8.19.9 Pros and Cons of Hormonal Therapy

Spironolactone: low dose as effective as high dose.
Drospirenone-containing oral contraceptive pills give best results.
Oral Contraceptive Pills prevent premenstrual flares.
Finasteride has shown results in 4 weeks.

8.19.10 Retinoids

1. Isotretinoin.
2. Acitretin—The mechanism of action is it normalises cell differentiation.
   Thins the cornified layer by directly reducing the keratinocyte's rate of proliferation.

Decreases inflammation in the dermis and epidermis by inhibiting the chemotaxis of polymorphonuclear cells and the release of proinflammatory mediators by neutrophils.

3. Alitretinoin has a similar mode of action as acitretin, but has the advantage of having a shorter half-life and hence can be a option in child bearing age group women

   Dose: 10 mg/d for 24 weeks.

8.19.11 Pros and Cons of Retinoid Therapy

Isotretinoin—Most patients have shown no response.
May be useful in younger patients with acne.
Acitretin—Shown promising results.
Requires monitoring.
Judicious use in childbearing age as it requires contraception for 3 years.

8.19.12 Antidiabetics

Mixed results and limited efficacy data.
Metformin, glucagon-like peptide-1 analogues/agonists have been tried.

8.19.13 Other Therapies

Zinc Gluconate—requires copper, cheap, not effective for severe disease.
3 times daily wash with antibacterial soap.
Sodium fusidate 2% ointment—Tested only in stage 1 axillary—reduces pain and pruritus.
Botulinum Toxin—expensive, unproven.
IVIG-expensive, unproven.

8.19.14 Biologics [45, 46]

The US FDA-approved biologic in the treatment of hidradenitis suppurativa is adalimumab (anti TNF alpha).
Amongst various biologics tried in HS strongest evidence supports use of infliximab (anti-TNF alpha) and adalimumab.

8.19.15 Adalimumab

Pre-treatment screen for adalimumab.
Viral screen (HIV, HBV, HCV).
ANA/Ds DNA, CBC, LFT, ESR, CRP, X-ray chest and TB GOLD.

8.19.16 TB Screening Guidelines [47]

Screening for latent infection by either an IFN-γ release assay (IGRA) or a tuberculin skin test (TST) with cut-off guidelines as per CDC recommendations, along with a chest radiograph before initiation of anti-TNF therapy.

Current tests for latent TB (Tuberculin skin test TST and IFN-γ release assay IGRA [QuantiferonTB-Gold and T-SPOT TB]) merely demonstrate immune sensitisation by detecting a cell-mediated immune response.

They do not indicate the presence of viable *Mtb*, and often remain positive after treatment.

ACR guidelines published in 2015 for rheumatoid arthritis (RA) treatment recommend testing and treating LTBI in patients receiving biologics. The risk is more with TNF alpha blockers. It recommends IGRA over TST only in persons with prior BCG vaccination. For the rest, either test can be used. As the TST can cause IGRA positivity, IGRA must always precede TST testing. Repeat testing is recommended in immunosuppressed, and those with high-risk conditions. Treatment for LTBI must be given to all who are either IGRA/TST positive and without active TB. After at least 1 month of treatment, biological therapy can be given. If biological therapy must be continued, then LTBI screening may be considered on an annual basis if the patient initially tested negative.

8.19.17 Interpretation of Results

TST positivity can be interpreted for different patient groups in ≥5 mm group, ≥10 mm group, and ≥15 mm group. Patients with HIV co-infection, recent TB contacts, post–organ transplant and those taking prednisolone >15 mg/day or other immunosuppressive drugs for more than a month are considered positive if TST >5 mm. Whereas children immigrants (<5 years) from high TB burden countries, intravenous drug addicts, resident/employees of high-risk congregate settings (prison, nursing home, health-care facility, etc.), mycobacterium laboratory personnel, patients with diabetes mellitus, chronic renal failure, silicosis, leukaemia, lymphoma, head and neck cancer, and gastrectomy are considered positive if TST ≥10 mm.

Those patients who are not at risk of TB on clinical history and evaluation are considered to be TST positive if it is ≥15 mm.

8.19.18 Dosing Schedule of Adalimumab

Total duration 12 weeks.
Loading 160mgm.
Day 15—80 mgm.
Day 30 onwards—40 mgm/week for 11 weeks.

8.19.19 Other Biologics and Small Molecules

TNF alpha blockers—etanercept, golimumab.
IL-17 inhibitors—secukinumab, ixkizumab.
IL12/IL23 blockers—guselkumab, ustekinumab.
Other biologics—Anakinra(targets IL-1).
MABp1 against IL-1 alpha.
Apremilast—PDE4 Inhibitor.
IFxi—monoclonal antibody against C5a.

8.19.20 Laser and Light-Based Devices in HS [48–54]

Most extensively studied laser in hidradenitis suppurativa is Nd YAG laser. Diode and Alexandrite lasers can also be used.

MNRF, fractional CO2, ablative CO2 and IPL have been tried.

These therapies work by reducing the occurrence of painful HS flare-ups by decreasing the number of hair follicles, sebaceous glands, and bacteria in affected areas, and by ablatively debulking chronic lesions.

8.19.21 Surgical Treatment In HS [55, 56]

Various surgical modalities like deroofing, incision and drainage, excision and primary closure, excision and secondary intention closure, wide excision, reconstruction with flap and STEEP technique have been recommended.

Deroofing and Incision and drainage—for pain relief in tense lesions and acute abscess. Deroofing—useful for Hurley Stage I/II. These are minimally invasive.

STEEP procedure—alternative to wide excision because it saves healthy tissue to a maximum and achieves complete removal of lesional tissue.

Split-thickness skin grafts are used typically for large wounds.

Flaps can be used in genital and inguinal areas.

SIH ensures usually good functional and cosmetic results in defects of up to 140 cm^2.

8.20 Conclusion

Hidradenitis suppurativa is a very chronic and debilitating disease. The pain, discharge and chronicity have a severe psychological impact. The approach in management should consider all the factors and the molecules should be used judiciously. The targeted therapies like biologicals can help to improve quality of life and this option should be discussed with patient. The different modalities should be combined to achieve prolonged remission and attention should be given to the lifestyle modifications. Good counselling session, a sympathetic approach and appropriate use of various treatment modalities can help the patients to lead a near-normal life (Tables 8.1 and 8.2).

Clinical Results: (Figs. 8.7 and 8.8).

Table 8.1 Treatment Algorithm for HS [57, 58]

Hurley grade	Lifestyle modification	Medical management	Surgical and laser treatment
Mild-moderate	Weight reduction, cessation of smoking, loose clothes, antiseptic wash, pain management, psychological support	Topical clindamycin 1% for 12 weeks ILS for acute and recalcitrant lesions Zinc gluconate Doxycycline 100 mg bd	For both stationary and recurrent nodules and abscesses—Excision, CO_2 evaporation, drainage
Moderate to severe	Same as above	Oral clindamycin 300 mgm bd + rifampicin 300 mgm bd for 12 weeks Adalimumab for 12 weeks and evaluate or infliximab Other oral therapies Dapsone 25–200 mgm/day Acitretin 0.2–0.5 mgm/day Prednisolone 40–60 mgm per day and taper Cyclosporine 3–5 mgm/day	Deroofing of sinus tracts Excision of sinus tracts CO_2 laser Wide local excision plus second degree closure

Table 8.2 Medical management of HS

Mild localised	Mild widespread	Moderate	Severe
First line Topical treatment Clindamycin (1%) twice daily for 12 week (GRADE B) or Resorcinol (15%) once daily; twice daily for flares as needed (GRADE C) Second line Miscellaneous treatment for individual lesions such as intralesional triamcinolone (3–5 mg) one time, then repeated monthly if necessary (GRADE C)	First line Oral treatment Tetracycline (500 mg) twice daily for 12 week (GRADE B) or Doxycycline and minocycline (50–100 mg) twice daily (GRADE D)	First line Tetracycline (500 mg) twice daily for 12 week (GRADE B) or Doxycycline and minocycline (50–100 mg) twice daily (GRADE D) Second line Clindamycin + rifampicin combination for 10 week (GRADE B) Clindamycin (300 mg) twice daily Rifampicin (300 mg) twice daily Third line TNF-α inhibitor Adalimumab for 12 week followed by assessment (GRADE A) Loading doses Week 0 (160 mg subcutaneous) Week 2 (80 mg subcutaneous) Maintenance (40 mg subcutaneous) weekly or Infliximab (5 mg/kg intravenous) on weeks 0, 2 and 6, and then every 8 weeks thereafter (GRADE B) or Dapsone (25–200 mg) daily (GRADE C) or Acitretin (0.5 mg/kg) daily (GRADE C)	First line Clindamycin+rifampicin combination for 10 week (GRADE B) Clindamycin (300 mg) twice daily Rifampicin (300 mg) twice daily TNF-α inhibitor Adalimumab for 12 week followed by assessment (GRADE A) Loading doses Week 0 (160 mg subcutaneous) Week 2 (80 mg subcutaneous) Maintenance (40 mg subcutaneous) Weekly or Infliximab (5 mg/kg intravenous) on weeks 0, 2 and 6, and then every 8 weeks thereafter (GRADE B) Second line Immunosuppression for short treatment course Prednisone (40-60 mg) daily For 3–4 days then taper (GRADE C) or Cyclosporine (3-5 mg/kg) daily (GRADE C)

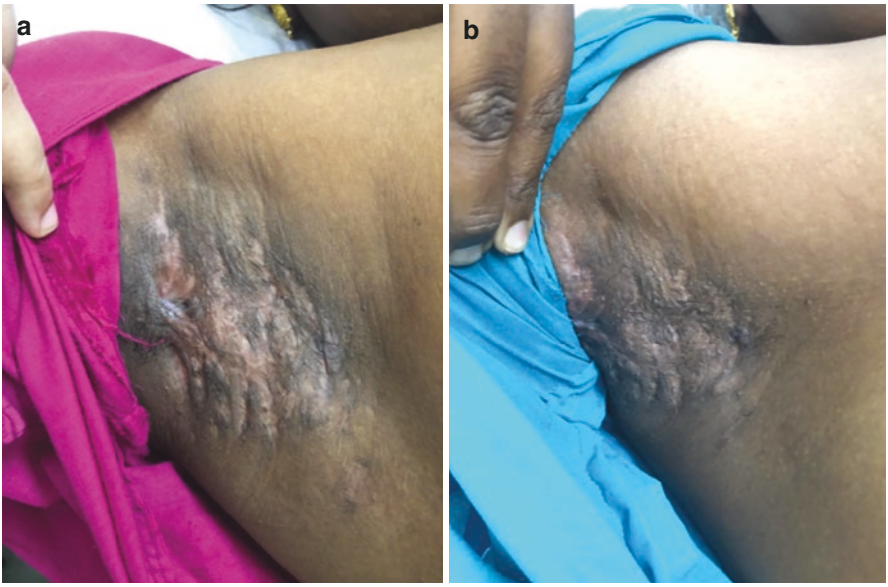


Fig. 8.7 (**a**) Pre-treatment. (**b**) Post-treatment

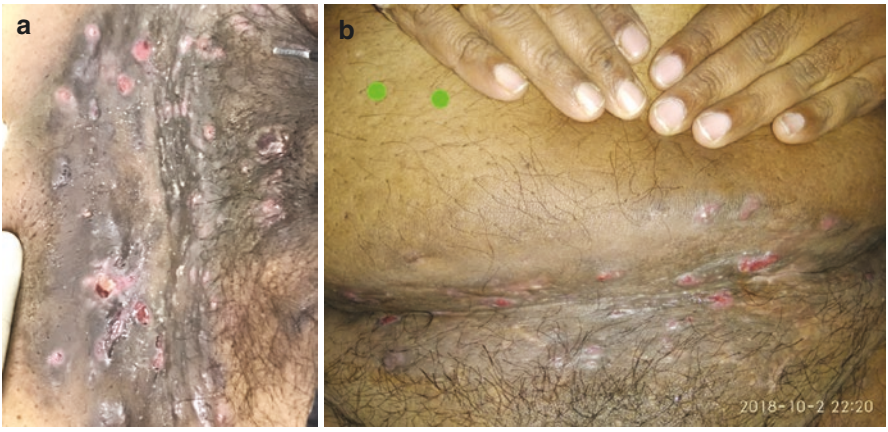


Fig. 8.8 (**a**) Pre-treatment. (**b**) Post-treatment

References

1. Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. J Invest Dermatol. 2013;133:97–103.
2. Tiri H, Jokelainen J, Timonen M, Tasanen K, Huilaja L. Somatic and psychiatric comorbidities of hidradenitis suppurativa in children and adolescents. J Am Acad Dermatol. 2018;79:514–9.

3. Shavit E, Dreiher J, Freud T, Halevy S, Vinker S, Cohen AD. Psychiatric comorbidities in 3207 patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2015;29:371–6.
4. Kouris A, Platsidaki E, Christodoulou C, et al. Quality of life and psychosocial implications in patients with hidradenitis suppurativa. Dermatology. 2016;232:687–91.
5. Kelly G, Prens EP. Inflammatory mechanisms in hidradenitis suppurativa. Dermatol Clin. 2016;34:51–8.
6. Goldberg SR, Strober BE, Payette MJ. Hidradenitis suppurativa epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol. 2020;82(5):1045–58.
7. Napolitano M, Megna M, Timoshchuk EA, Patruno C, Balato N, Fabbrocini G, et al. Hidradenitis suppurativa: from pathogenesis to diagnosis and treatment. Clin Cosmet Investig Dermatol. 2017;10:105–15.
8. Prens E, Deckers I. Pathophysiology of hidradenitis suppurativa: An update. J Am Acad Dermatol. 2015;73:S8–11.
9. Wang B, Yang W, Wen W, et al. Gamma-secretase gene mutations in familial acne inversa. Science. 2010;330:1065.
10. Gentle ME, Rose A, Bugeon L, Dallman MJ. Noncanonical notch signaling modulates cytokine responses of dendritic cells to inflammatory stimuli. J Immunol. 2012;189:1274–84.
11. Melnik BC, Plewig G. Impaired notch signalling: the unifying mechanism explaining the pathogenesis of hidradenitis suppurativa (acne inversa). Br J Dermatol. 2013;168:876–8.
12. Ingram JR. The genetics of hidradenitis suppurativa. Dermatol Clin. 2016;34:23–8.
13. Ring HC, Thorsen J, Saunte DM, et al. The follicular skin microbiome in patients with hidradenitis suppurativa and healthy controls. JAMA Dermatol. 2017;153:897–905.
14. Miller IM, McAndrew RJ. Iltefat Hamzavi Prevalence, risk factors, and comorbidities of hidradenitis suppurativa. Dermatol Clin. 2016;34:7–16.
15. Garg A, Papagermanos V, Midura M, Strunk A. Incidence of hidradenitis suppurativa among tobacco smokers: a population-based retrospective analysis in the USA. Br J Dermatol. 2018;178:709–14.
16. Micheletti R. Tobacco smoking and hidradenitis suppurativa: associated disease and an important modifiable risk factor. Br J Dermatol. 2018;178:587–8.
17. Kromann CB, Ibler KS, Kristiansen VB, Jemec GBE. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. Acta Derm Venereol. 2014;94(5):553–7.
18. Khandalavala BN, Do MV. Finasteride in hidradenitis suppurativa: a “male” therapy for a predominantly “female” disease. J Clin Aesthet Dermatol. 2016;9:44–50.
19. Clark AK, Quinonez RL, Saric S, Sivamani RK. Hormonal therapies for hidradenitis suppurativa: review. Dermatol Online J. 2017;23(10):13030/qt6383k0n4.
20. Karagiannidis I, Nikolakis G, Sabat R, Zouboulis CC. Hidradenitis suppurativa/acne inversa: an endocrine skin disorder? Rev Endocr Metab Disord. 2016;17:335–41.
21. Riis PT, Ring HC, Themstrup L, Jemec GB. The role of androgens and estrogens in hidradenitis suppurativa—a systematic review. Acta Dermatovenerol Croat. 2016;24:239–49.
22. Vossen AR, van Straalen KR, Prens EP, van der Zee HH. Menses and pregnancy affect symptoms in hidradenitis suppurativa:A cross-sectional study. J Am Acad Dermatol. 2017;76(1):155–6.
23. Dany M, Elston D. Gene expression of sphingolipid metabolism pathways is altered in hidradenitis suppurativa. J Am Acad Dermatol. 2017;77:268–273.e6.
24. Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model. Front Immunol. 2018;9:2965.
25. Vilanova I, Hernandez JL, Mata C, et al. Insulin resistance in hidradenitis suppurativa: a case-control study. J Eur Acad Dermatol Venereol. 2018;32:820–4.
26. Malara A, Hughes R, Jennings L, et al. Adipokines are dysregulated in patients with hidradenitis suppurativa. Br J Dermatol. 2018;178:792–3.

27. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116:1784–92.
28. Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol. 2020;82:1045–58.
29. Cubilla JAG, Abdalla BMZ, Criado PR, Oyafuso LK. Immunological pathways in hidradenitis suppurativa: current concepts and innovative therapies. Clin Res Dermatol. 2018;5:1–7.
30. Shlyankevich J, Chen AJ, Kim GE, Kimball AB. Hidradenitis suppurativa is a systemic disease with substantial comorbidity burden: a chart-verified case-control analysis. J Am Acad Dermatol. 2014;71:1144–50.
31. Dauden E, Lazaro P, Aguilar MD, et al. Recommendations for the management of comorbidity in hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2018;32:129–44.
32. Zouboulis CC, Bechara FG, Dickinson-Blok JL, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. J Eur Acad Dermatol Venereol. 2019;33:19–31.
33. Menter A. Recognizing and managing comorbidities and complications in hidradenitis suppurativa. Semin Cutan Med Surg. 2014;33:S54–6.
34. Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol. 2012;66(3):409–15.
35. Saraceno R, Babino G, Chiricozzi A, Zangrilli A, Chimenti S. PsAPASH: A new syndrome associated with hidradenitis suppurativa with response to tumor necrosis factor inhibition. J Am Acad Dermatol. 2015;72:e42–3.
36. Alikhan A, Sayed C, Alavi A, Alhusayen R. North American clinical management guidelines for hidradenitis suppurativa:A publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Part I: Diagnosis, evaluation, and the use of complementary and procedural management. J Am Acad Dermatol. 2019;81(1):91–101.
37. Wortsman X. Imaging of hidradenitis suppurativa. Dermatol Clin. 2016;34:59–68.
38. Napolitano M, Megna M, Timoshchuk EA, Patruno C, Balato N, Fabbrocini G, Monfrecola G. Hidradenitis suppurativa: from pathogenesis to diagnosis and treatment. Clin Cosmet Investig Dermatol. 2017;10:105–15.
39. Fimmel S, Zouboulis CC. Comorbidities of hidradenitis suppurativa (acne inversa). Dermatoendocrinol. 2010;2(1):9–16.
40. Hurley HJ. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pemphigus: surgical approach. In: Roenigk RK, Roenigk Jr HH, editors. Dermatologic surgery: principles and practice. 2nd ed. New York: Marcel Dekker; 1996.
41. Thorlacius L, Garg A, Riis PT, et al. Inter-rater agreement and reliability of outcome measurement instruments and staging systems used in hidradenitis suppurativa. Br J Dermatol. 2019;181(3):483–91.
42. Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol. 2003;149:211–3.
43. Rondags A, van Straalen KR, van Hasselt JR, et al. Correlation of the refined Hurley classification for hidradenitis suppurativa with patient-reported quality of life and objective disease severity assessment. Br J Dermatol. 2019;180:1214–20.
44. Senthilnathan A, Kolli SS, Cardwell LA, Richardson I, Feldman SR, Pichardo RO. Validation of a hidradenitis suppurativa self-assessment tool. J Cutan Med Surg. 2019;23:388–90.
45. Lee RA, Eisen DB. Treatment of hidradenitis suppurativa with biologic medications. J Am Acad Dermatol. 2015;73:S82–8.
46. Ghias MH, Johnston AD, Kutner AJ. High-dose, high-frequency infliximab: a novel treatment paradigm for hidradenitis suppurativa. J Am Acad Dermatol. 2020;82:1094–101.
47. Saha S, Kumar A, Saurabh K, Shankar SH, Kashyap A, Nischal N, et al. Current status of treatment of latent tuberculosis infection in India. Indian J Med Sci. 2019;71(2):54–9.

48. Saunt DM, Lapins J. Lasers and intense pulsed light hidradenitis suppurativa. Dermatol Clin. 2016;34:111–9.
49. Alikhan A, Sayed C, Alavi A, Alhusayen R, Brassard A, Burkhart C, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations Part II: Topical, intralesional, and systemic medical management. J Am Acad Dermatol. 2019;81(1):91–101.
50. Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa current and emerging treatments. J Am Acad Dermatol. 2020;82:1061–82.
51. Golbari NM, Porter ML, Kimball AB. Antiandrogen therapy with spironolactone for the treatment of hidradenitis suppurativa. J Am Acad Dermatol. 2019;80:114–9.
52. Hamzavi IH, Griffith JL, Riyaz F, Hessam S, Bechara FG. Laser and light-based treatment options for hidradenitis suppurativa. J Am Acad Dermatol. 2015;73:s78–81.
53. Khandalavala BN, Do MV. Finasteride in hidradenitis suppurativa: a “male” therapy for a predominantly “female”disease. J Clin Aesthet Dermatol. 2016;9:44–50.
54. Zouboulis CC, Okun MM, Prens EP, Gniadecki R, Foley PA. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. J Am Acad Dermatol. 2019 Jan;80(1):60–69.e2.
55. Danby W, Hazen PG, Boer J. New and traditional surgical approaches to hidradenitis suppurativa. J Am Acad Dermatol. 2015;73(5):S62–5.
56. van der Zee HH, Prens EP, Boer J. The deroofing: a tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. J Am Acad Dermatol. 2010;63(3):475–80.
57. Jafari SMS, Hunger RE, Schlapbach C. Hidradenitis suppurativa: current understanding of pathogenic mechanisms and suggestion for treatment algorithm. Front Med. 2020;7:68.
58. Saunte DML, Jemec GBE. Hidradenitis suppurativa advances in diagnosis and treatment. JAMA. 2017;318:2019–32.

Chapter 9
Pigmentary Disorders in Women

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9.1 Vitiligo

Vitiligo is a common cutaneous disease with depigmented skin as its hallmark feature. Certain gene polymorphisms in association with environmental factors have been shown to trigger autoimmunity resulting in melanocyte death. The affliction is usually asymptomatic. However, in races with coloured skin, the colour loss is easily discernible and amounts to considerable stigma which impacts the quality of life of affected people.

9.1.1 Epidemiology

Global prevalence ranges from 0.1 to 3%. One-fourth of these cases begin before 10 years of age. The onset peaks around second and third decade of life. Of late, an epidemiological study of vitiligo in European patients noted a significant delay in age of onset from 14 years to 30 years over a period spanning from 1973 to 2000 [1]. All races and ethnic groups are equally affected with vitiligo. No sex predisposition is seen [2].

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9.1.2 Clinical Features

Clinically, asymptomatic depigmented macules or patches are seen on the skin. Based upon the distribution of skin lesions, vitiligo can be classified as segmental or non-segmental. The non-segmental variants include generalized/vulgaris, acral/acrofacial (Fig. 9.1) and localized. A subtype of acrofacial vitiligo is the "lip-tip" variety which is seen more frequently in males [3]. Some of the documented triggering or exacerbating factors include emotional stress, physical illness, sunburn and pregnancy.

The affliction of the genital region in females may mimic genital lichen sclerosus (LS). However, genital vitiligo lacks the itch, atrophy, induration and loss of normal anatomy associated with typical genital LS. LS lesions are usually depigmented areas with or without erythema, often associated with itch and burning sensation. These lesions may also be associated with bleeding, constipation, dysuria, urinary obstruction, sexual dysfunction and dyspareunia. Any disorganization of genital anatomy (missing clitoris, buried clitoral hood, etc.) always point towards LS. A bimodal pattern of onset is seen with peaks in prepubertal girls and post-menopausal women. Histopathologically LS can be differentiated from vitiligo as LS lesions reveal lichenoid infiltrate at the dermoepidermal junction and dense homogenous fibrosis in the papillary dermis. A subset of LS patients presents with clinically vitiligo-like lesions but histopathological features diagnostic of LS. Such patients are considered to be having a variant of LS known as vitiligoid LS. Symptoms are usually amenable to response with high potency topical steroids and/or calcineurin inhibitors. Treatment with these agents leads to improvement or resolution of symptoms (pain, pruritus, bleeding); however, mild or no improvement of the depigmentation is seen [4].

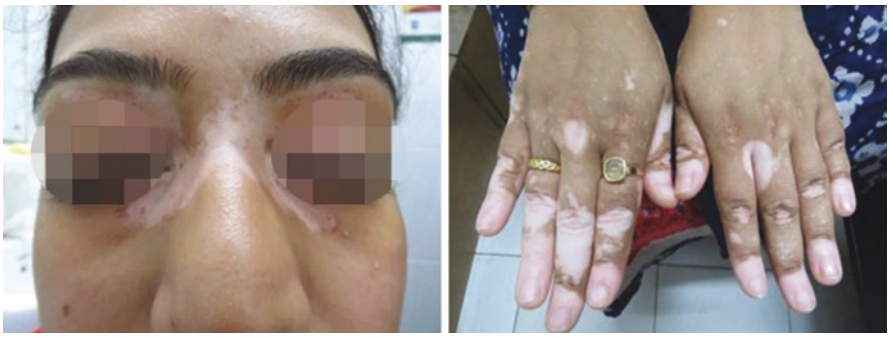

Fig. 9.1 Image of an Indian woman with acrofacial vitiligo

9.1.3 Pathogenesis

An autoimmune mechanism is currently the most accepted reason for loss of epidermal melanocytes, primarily those located in the interfollicular epidermis [5]. Follicular melanocytes are usually spared probably because of immune privilege mechanisms and limited immune surveillance at this site. Hitherto, a few linkage and genome-wide association studies (GWAS) have attempted to identify vitiligo associated loci and have successfully identified more than 50 such loci. Most of them encode for immune regulators such as components of innate immunity and adaptive immune system. Also, gene polymorphisms of HLA DR4, Dw7 and DR7 are noted to be associated with vitiligo. Maximum genetic risk is seen with HLA-A polymorphisms. Polymorphisms of FAS L4, TYR, PMEL, MC1R and IRF 4 have also been identified in vitiligo patients. Based upon these findings, expression of abnormal melanocyte antigens is implicated in induction of autoimmunity. A few autoimmune diseases such as Type 1 diabetes mellitus, autoimmune thyroiditis, pernicious anaemia, Addison's disease and Alopecia areata share the implicated gene loci of vitiligo.

The process of melanin production in melanocytes generates a high load of reactive oxygen species (ROS). The mechanisms responsible for quenching ROS in the melanocytes including catalase enzyme are found to be inherently deficient in vitiligo. When the melanocytes are overwhelmed with increased levels of H_2O_2 and other ROS, the stressed melanocytic endoplasmic reticulum's capacity to degrade unfolded or misfolded proteins is compromised. This leads to unfolded protein response which likely triggers the innate immune response. The innate response to these abnormal proteins is dysfunctional and increases the levels of heat shock protein (HSP)-70. It mediates the coupling of innate with adaptive response and sustains further immune cascade.

The predominant effector cells of adaptive response are CD8+ cytotoxic T-cells which reach the compromised melanocytes by chemo-attractants like CXCL9 and CXCL10 secreted by surrounding melanocytes. IFN-gamma secreted by the recruited CD8+ T cells stimulates melanocytes to further produce CXCL9 and CXCL 10. Thus ensues a vicious cycle where these chemokines further recruit T cells and thereby further melanocyte destruction. Their levels are persistently high in active phases of disease. A plethora of cytokines are found to have raised levels in serum of vitiligo patients such as IL-17, IL-23 and TNF-alpha, while serum TGF-β levels are seen to be significantly decreased . However, none of the serum cytokine levels have been found to correlate with gender, positive family history, course and type of vitiligo [6]. There has been considerable research on the role of drugs inhibiting cytokine effects, without much success, probably implying that cytokines are probably not central to progression of disease.

Skin damage might induce vitiligo as is suggested by the Koebner's phenomenon. In some cases, vitiligo may be triggered by a viral infection like CMV and herpesvirus. Environmental exposure to compounds containing sulfhydryl groups, phenols and catechols may also destroy melanocytes. A quarter of these cases are seen to be developing vitiligo at sites distant from the site of actual chemical contact, indicating that these chemicals cause direct toxicity as well as probably induce autoimmunity.

Relapse in vitiligo is noticed to occur at the same areas involved previously, probably brought about by long lived autoreactive resident memory T cells (Trm cells) with CD69, CD103 and CD49a as their surface markers. They themselves have limited cytotoxicity but they are very efficient in producing cytokines which further recruit effectors from the circulation. The survival of Trm cells is maintained by IL-15 [7].

Regulatory T cells (Tregs) form the backbone of the tolerance mechanism known as anergy, as they keep the self-reactive effector T cells in check by reducing their proliferation as well as activation. Treg cells are found to be deficient in vitiligo which explains the escape of melanocyte reactive CD8+ T cells into circulation.

Anti-PD1/PDL1 therapies and tyrosine kinase inhibitors have been seen to produce vitiligo lesions over sun exposed areas in patients of melanoma, lung and kidney cancer. Vitiligo-like lesions developing during treatment with these drugs are clinically characterized by well-defined borders and predilection for sun-exposed areas. Sometimes, anti-TNF agents may also trigger or worsen vitiligo. Tofacitinib, a JAK-kinase (1 and 3) inhibitor is also reported to induce de-novo vitiligo. JAK 2 mediated upregulation of IFN-gamma has been proposed to be responsible for development of vitiligo [8]. Recently, CDK4/6 inhibitors induced vitiligo lesions in a group of patients with metastatic breast cancer. The underlying pathogenic mechanism is unclear. The authors proposed that CDk4/6 inhibitors possibly caused passive melanocyte premature death by inducing apoptosis [9].

9.1.4 Vitiligo and Pregnancy

Pregnancy has a predominant Th2 profile and thus exerts an immunosuppressive effect on a few autoimmune diseases. Stable or improved vitiligo activity during pregnancy has been noted which corroborates this effect [10]. Probable reasons include an increase in the levels of serum cortisol to nearly 3× the baseline levels during the second and third trimesters. Also, raised progesterone levels may induce placental trophoblast cells to secrete increased IL-10, an anti-inflammatory regulator.

On the other hand, it is believed that active vitiligo characterised by enhanced Th1 and Th17 responses might be detrimental to maternal and foetal health [11]. However, in earlier studies, vitiligo was not found to be associated with adverse pregnancy outcome in any stage, that is, prenatal, natal and postnatal as well as birth outcome [12]. Therefore, the obstetric management hitherto has been on

conventional lines. However, a recent population-based cohort study on 4738 pregnancies of women with vitiligo and 47,380 pregnancies of age matched controls without vitiligo from Korea pointed to different observations—abortions were high and thus correspondingly live birth rate was significantly lower amongst pregnant women with vitiligo [13]. Though the authors could not point out to a cause and result relationship between vitiligo and adverse pregnancy outcomes, a cautious approach is warranted while managing pregnancies of women with vitiligo.

9.1.5 Investigations

The diagnosis of vitiligo is clinical. Laboratory investigations are usually not required. When diagnosis is confirmed, anti-TPO and antithyroglobulin antibodies should be ordered as vitiligo is significantly associated with autoimmune thyroiditis. TSH should be done to assess thyroid function and other tests like anti-TSHR antibodies are required if Graves' disease is suspected. However, if a patient's relevant clinical work up suggests an additional autoimmune disease, further autoantibodies should be evaluated. In rare circumstances when the diagnosis is not possible clinically, a skin biopsy is recommended. Also, in such a setting, other tests might be needed such as mycological assessment and tests to detect lymphoma cells through molecular biological tools [14].

9.1.6 Treatment

Management of vitiligo should ideally aim at modulating the immune response, reducing the oxidative stress and stimulating the stem cells in hair follicles and the epidermis to differentiate into melanocytes. The various management options are listed in Table 9.1. Also, counselling regarding chronic nature and unpredictable course of disease as well as long-term treatment goes a long way in achieving satisfactory results.

Table 9.1 Management of vitiligo

S. No.	Treatment modality	Recommendations for use
1.	Cosmetic camouflage	In patients of type I and II skin In patients with visible areas of depigmentation which affect confidence and self-image of an individual Level of recommendation is D and evidence is IV
2.	Topical corticosteroids	Once a day application of a potent TCS in adults and in children with recent onset of vitiligo with limited, extrafacial involvement for a period no longer than 3 months Level of recommendation is B and evidence is I+

(continued)

Table 9.1 (continued)

S. No.	Treatment modality	Recommendations for use
3.	Topical Calcineurin inhibitors	As an alternative to a topical steroid for new, actively spreading, lesions on thin skin, in particular the head and neck region Twice-daily applications for 6–12 months is recommended Level of recommendation is C and evidence is II+
4.	Depigmentation	Reserved for adults severely Affected by vitiligo
5.	Oral PUVA	In adult patients with generalized vitiligo as a second-line therapy
6.	NB-UVB	First-line therapy for generalized NSV involving more than 15–20% of the body area Also considered as treatment for active spreading vitiligo
7.	Targeted phototherapies (laser and nonlaser)	Indicated for localized vitiligo and in particular for small lesions of recent-onset childhood vitiligo
8.	Combination therapies: Topical steroids and phototherapy	The combination of TCS and UVB sources (NB-UVB and 308 nm excimer lasers or lamps) may be promising for difficult-to-treat areas, for example, over bony prominences. Potent topical steroids applied once a day (3 weeks out of 4) can be used on vitiligo lesions for the first 3 months of phototherapy
9.	TCI and phototherapy	A combination of TCI and UV radiation is effective and provides better results than the two treatments used alone
10.	Vitamin D analogues and phototherapy	Not recommended as the benefit of the combination therapy is very limited
11.	Phototherapy And oral antioxidants	Might be beneficial but the preliminary results need to be confirmed before such a combination can be recommended
12.	Phototherapy after surgery	Good level of evidence that phototherapy (NB-UVB or PUVA) should be used for 3 or 4 weeks after surgical procedures to enhance repigmentation
13.	OMP therapy	Weekend OMP starting with low doses (2.5 mg daily) of dexamethasone for fast-spreading vitiligo can be considered for a period of 3–6 months
14.	Other immunosuppressants or biologics	Not recommended based upon current data
15.	Antioxidant supplementation	Could be useful during UV therapy, and during the reactivation phase of vitiligo However, current data is limited
16.	Surgery	Should be reserved for patients with SV and other localized forms of vitiligo, after the documented failure of medical interventions For NSV, patients with the stable form of the disease and a negative history of Koebner phenomenon are eligible for surgery

Table 9.1 (continued)

S. No.	Treatment modality	Recommendations for use
17.	Psychological treatments	Assessment of the psychological and QoL effects of vitiligo on adults and children Level of recommendation is C and evidence is II+ Psychological interventions should be offered as a way of improving coping mechanisms. Besides individual psychosocial therapeutic interventions, community interventions may be necessary in certain circumstances Level of recommendation is D and evidence is IV+

9.1.6.1 Topical

Cosmetic camouflage is a complementary painless option which can be added to the standard treatment of vitiligo. It aids in improving the person's quality of life, boosts self-confidence and self-image of vitiligo patients [15]. It involves use of a pigmented cosmetic cream in the form of a water-in-oil emulsion, oil-in-water emulsion, or an oil-free facial foundation containing dimethicone or cyclomethicone to suit various skin types like oily, dry and normal skin. The colouring agents used are usually titanium dioxide, iron oxide and ultramarine blue. Another way of camouflage is semi-permanent camouflage by use of sunless or self-tanning products which contain dihydroxyacetone (DHA), usually 6%, which may or may not be combined with erythrulose, tyrosine derivatives and naphthoquinone. The combination of DHA with amino acids in the stratum corneum produces pigment known as melanoidins which are shed in a few days along with corneocyte desquamation. Of the newer camouflage methods, waterproof breathable products are available. This method of colour matching is applied using a roller or airbrush with compressor and utilizes an ethanol and natural oil-based technology that binds to the epidermis and remains effective for a minimum of 7 days. Alcohol diluent evaporates immediately after application and a thin layer very similar to skin is left at the application site. The colour of the film matches closely to that of the surrounding skin. This simulated skin is prepared using digital photography and colour matching program to match appropriately to the patient skin colour [16]. Camouflage cosmetics may be offered as the only therapy in patients with skin types I and II as the difference in skin colour is minimally apparent in these skin types [17]. Other forms of camouflage include permanent camouflage and tattoos. These modalities might have limited value for depigmented lips and nipples.

9.1.6.1.1 Topical Corticosteroids (TCS)

Mid- and high-potent steroids are indicated for limited vitiligo (<10% body surface involvement). Repigmentation may take 3 months or longer. Prolonged use may cause skin atrophy, striae and telangiectasia. They should not be used in the periocular location because of the risk of glaucoma or on the face. They are pregnancy category C drugs. Lactating mothers having vitiligo may apply topical steroids at sites other than breasts and nipples. In children and adults affected with vitiligo, potent topical steroids may be given for a period less than 2 months to avoid cutaneous adverse events associated with prolonged use of topical steroids [17]. However, if TCS need to be given for a prolonged period, they may be given discontinuously with periodic assessments.

9.1.6.1.2 Topical Immunomodulators

Topical immunomodulators exert their effect on vitiligo by multiple mechanisms. These include inhibition of TNF-alpha production, stimulation of stem cell differentiation into melanocytes and melanocyte migration to the depigmented area. They include topical calcineurin inhibitors such as tacrolimus (0.03% and 0.1%) and pimecrolimus (1%). They are safe to use on facial vitiligo lesions as well as those over neck and other thin-skinned areas. Side effects are uncommon and include redness, itching and burning sensation over application site. They are recommended for use over vitiligo lesions of head and neck region at 12-hourly intervals. The therapy is usually combined with moderate daytime sun exposure. An initial trial of 6 months is recommended which can be further prolonged based upon response [14]. They are also pregnancy category C drugs.

9.1.6.1.3 Topical Calcipotriol

It is available in a 0.005% formulation. When combined with TCS, efficacy and safety profile of steroids is improved. However, a recent Indian study aimed to evaluate the extent of repigmentation and time to initial repigmentation showed that the combination did not significantly increase the efficacy of NB-UVB therapy [18]. It is a pregnancy category C drug.

9.1.6.2 Systemic

9.1.6.2.1 Systemic Steroids

Oral steroids in a low dose (prednisolone 0.3 mg/kg/day) for a short duration or oral mini pulse with betamethasone or dexamethasone may be utilized in cases of vitiligo where progression is very rapid. The duration for administering systemic

steroids in progressive vitiligo should be limited to 3–6 months. They are a pregnancy category C drug.

9.1.6.2.2 Systemic Immunosuppressants

Immunosuppressants other than oral steroids which have been found to have efficacy in controlling progressive vitiligo include methotrexate (up to 10 mg weekly), azathioprine (up to 50 mg twice a day) and cyclosporine (3 mg/kg/day). However, they should be used to control progressive vitiligo after reviewing the risks and benefits [19].

9.1.6.3 Phototherapy

PUVA photochemotherapy: can be administered as oral, topical or bath PUVA. It comprises of use of methoxasalen (8-methoxypsoralen or 8-MOP) or trioxsalen and their interaction with UVA to selectively cause immunosuppression as well as stimulate melanocytes to produce repigmentation. Vitiligo was the first approved indication for PUVA therapy. PUVA induced repigmentation is unpredictable and variable and also adverse events like phototoxicity, risk of skin cancer, gastrointestinal upset and need for ocular protection for 12–24 h beyond the treatment session have decreased the popularity of this treatment modality. Oral PUVA therapy forms the second-line therapy in adults with generalised vitiligo [14]. Time to achieve maximal repigmentation with oral PUVA therapy ranges from 12 to 24 months. Owing to the risk of retinal toxicity, it is contraindicated in children younger than 12 years.

Phototherapy can be administered through topical route as well. 8-MOP cream is applied over affected area followed by UVA exposure half an hour later. Systemic and ocular phototoxicity are significantly minimized with topical use of PUVA therapy as plasma levels are minimal. However, blisters may form with consequent perilesional hyperpigmentation at the site of application. The main disadvantage with topical PUVA therapy is its inability to halt the progression of active vitiligo.

NB-UVB therapy: It forms the backbone of vitiligo treatment in present times. NB-UVB is the treatment of choice for generalised vitiligo, that is, affecting more than 20% body surface area. Data is inconclusive as to whether NB-UVB can check the progression of active vitiligo, although it continues to be utilized for the purpose in clinical settings [14]. It involves irradiating the patient's skin using UV lamps emitting wavelengths with peak emission around 311 nm. It achieves comparable results to PUVA therapy by inducing cutaneous immunosuppression and stimulating melanogenesis without producing systemic adverse effects. It is a safe option in pregnant patients also. It can be administered through whole body unit in case of generalized vitiligo as well as through a targeted phototherapy system in case the vitiligo is localized.

Recently, recommendations with regard to the dosing and administration of NBUVB in vitiligo have been put forward by the Vitiligo Working Group phototherapy committee [20]. Frequency of NBUVB sessions has been recommended to be thrice a week for faster onset of initial repigmentation. However, it can be administered twice in a week in case of high patient load units and where affordability is an issue. The previous protocol of measuring MED for each patient has been done away with and instead an initial 200 mJ/cm2 dose of NBUVB has been fixed by the committee regardless of skin type. No phototoxic reactions are seen to occur with this dose. Increments in subsequent doses should be 10–20%. Pink asymptomatic erythema which fades away within 24 h is the intended response with phototherapy. Having achieved this end point, the same dose should be administered until erythema disappears. Thereafter, subsequently doses are increased by 10–20%.

Based upon body sites, maximum admissible doses per session have been recommended—1500 mJ/cm2 for face and 3000 mJ/cm2 for rest of the body. Guidelines have also been issued with regards to interrupted therapy when doses are missed due to any reason. When there is an interruption in therapy for less than a week, dose need not be changed. In case the doses are missed for 1–2 weeks, the dose should be decreased by 25%. In case of treatment gap of 2–3 weeks, the dose of NBUVB should be decreased by 50%. However, if the treatment has not been taken for more than 3 weeks, NBUVB therapy should be started at the initial dose of 200 mJ/cm^2.

The committee did not fix any upper limit to the number of sessions in patients with skin phototype IV, V and VI. Keeping in mind that some patients may be slow responders, the committee recommended a minimum of 48 sessions before planning to discontinue therapy. For objective documentation, serial photography should be undertaken at first session for baseline record of severity of vitiligo and then every 3 months for sequential assessment. Response assessment can further be assessed using a few validated scoring systems such as VASI (Vitiligo Area Severity Index) or VETF (Vitiligo European Task Force assessment). Broad-spectrum sunscreens having SPF of more than 30 should always be advised in patients undergoing phototherapy. Also, the need to reapply every 2 h must be emphasised. Mineral oil can be applied prior to NBUVB phototherapy session.

Comprehensive guidelines to taper the administration of NBUVB have been given once maximal repigmentation has been achieved. A maintenance regime should be followed for a month at an administering frequency of 2 times in a week. During the second month post repigmentation, once a week administration of NBUVB should be continued. Thereafter, frequency is further decreased to once every alternate week for the next 2 months. If there is no recurrence in these 4 months, the therapy can be stopped.

It is recommended to consider children for NBUVB therapy once they are able to stand in the phototherapy chamber with proper eye shield which usually occurs around 7–10 years of age. In a case scenario where the depigmented patch is present on the eyelid, then protective goggles should be done away with and instead the patient should be advised to keep the eyes shut during NBUVB session.

Excimer laser (EL): It produces monochromatic irradiation at a wavelength of 308 nm. It is seen to produce satisfactory repigmentation in more than 3 months. It

is seen to produce synergistic effect with topical tacrolimus as well as topical methoxasalen. This modality is best suited to treat localised vitiligo. As of now some clinical evidence has begun to support the superior efficacy of EL treatment in comparison to NBUVB therapy, although it is still minimal to make the claim. Nonetheless, the novel treatment modality certainly bears advantage in management of localised vitiligo as the treatment targets only the depigmented area and in childhood vitiligo as it doesn't require a child to stand in an irradiation chamber. Recently, a modified Delphi study by Bae et al. had made recommendations for dose and administration of EL treatment. The study recommends fixed initial dose based upon the body site involved—100 mJ/cm2 for face and neck, 200 mJ/cm2 for trunk and extremities and 300 mJ/cm2 for hands and feet. A further increment of 20–50 mJ/cm^2 in dose should be made with subsequent sessions until erythema or repigmentation is achieved. The frequency of administering EL treatment should be 2 times per week. Treatment should be continued for at least 3–6 months. It should, however, be discontinued if no further improvement is noticed in the preceding 3 months [19].

9.1.6.4 Other Therapies

9.1.6.4.1 Antioxidants

A few open trials have found a few antioxidant supplements to be of use in either controlling the further activity of disease or in development of pigmentation over vitiligo lesions. These include vitamin A, vitamin C, alpha-lipoic acid, zinc, L-phenylalanine, *Ginkgo biloba* and *Polypodium leucotomos*, among others. It was noted that these supplements might act as adjuvants in increasing the efficacy of UV therapy by Taieb et al. The authors also found them to be useful in the reactivation phase of vitiligo. Further clinical evidence is, however, required to corroborate these findings and for inclusion of these supplements in the armamentarium of vitiligo therapies [14].

9.1.6.4.2 Depigmentation

Depigmentation aims to depigment the residual skin and may be offered to non-responding individuals who suffer from extensive vitiligo (>30–40% body surface area involvement). Various methods include the use of bleaching creams such as MBEH (mono benzone ether of hydroquinone) and 4-methoxyphenol; phenol; lasers and cryotherapy. MBEH 20% cream is a phenolic substance which is prescribed to be used 2–3 times a day. It takes about 1–4 moths of regular treatment to obtain the desired result. After 4 months of treatment without success, the drug should be discontinued. The depigmentation thus achieved needs to be maintained with topical application of monobenzone cream twice a day. Sometimes, resistance

to treatment is encountered which can be circumvented with the concomitant use of retinoic acid.
Q-switched ruby laser at 755 nm, alone or in combination with methoxyphenol, has also been used to achieve depigmentation. Cryotherapy has also been utilised as an inexpensive depigmentation therapy in experienced hands. However, it runs the risk of scarring, hence it falls out of favour with most dermatologists [14].

9.1.6.5 Surgical Management

Surgical modalities are a good option for patients with stable vitiligo for at least 6 months to 1 year. Various procedures are available which basically involve transplantation of healthy melanocytes to depigmented areas where they proliferate and induce repigmentation. Various surgical options include punch grafts (PG), mini punch grafts, single hair grafts, split thickness grafts, suction blister grafts, cultured epidermal suspensions and autologous melanocytes cultures and the list continues to expand. PG or skin tissue graft is technically the easiest and the most inexpensive method, the only deterrent being that it is time-consuming. Hence, it is suitable for treating small lesions only. Cobblestoning is also a common side effect. A novel innovation in the form of motorized 0.8-mm micropunch grafting has significantly reduced the time taken to perform this surgery.

Newer surgical approaches involve the use of autologous suspensions containing melanocytes and keratinocytes. Thin shave biopsies from the graft area are obtained which are then used to generate cell suspension by enzymatic separation of cells. Single-use kits are now available for this purpose which can be used in the operating room itself. They produce the desired suspension within 1 h and thus obviate the need of a laboratory support for the same. For treatment of lesions involving large areas, transplants of pure cultured melanocytes may be undertaken. A small donor skin is expanded in vitro for generation of melanocyte culture. The main limitation of the method is that it requires a state of the art laboratory set up with specialized staff. Also, the process is expensive and time consuming [19].

9.1.6.6 Newer Drugs

Interferon -γ induced CXCL 9 and CXCL10 in keratinocytes are increasingly being acknowledged for their role in the pathogenesis of vitiligo. CXCL10 has a key role in the recruitment of autoreactive T cells to the skin which maintains the progression of vitiligo. This insight has prompted the use of Janus kinase (JAK) inhibitors to target this pathway. Tofacitinib is a potent JAK1 and JAK3 inhibitor. It has been shown to produce repigmentation in vitiligo lesions when given 5 mg orally once or twice a day for 3–9 months. Oral tofacitinib treatment, otherwise well tolerated at these doses, produced a few mild adverse events such as increase in the rate of

infections of upper respiratory tract, diarrhoea, increase in body weight, arthralgia and mild elevations in lipid levels. T cell numbers and chemokines CXCL9 and CXCL10 in the skin are significantly reduced with Tofacitinib therapy. Decreased levels of serum chemokines were also observed with Tofacitinib use. However, no effect on the number of autoreactive T cells in the blood was seen with tofacitinib therapy [21]. Another first-generation JAK inhibitor, ruxolitinib, produced significant repigmentation in vitiligo at a dose of 20 mg orally 2 times in a day given for a period of 5 months [22]. Ruxolitinib, a JAK 1 and 2 inhibitor, has also been evaluated in topical cream form by Rosmarin and colleagues. They reported a large prospective randomised trial showing efficacy of ruxolitinib cream at 1·5% applied two times in a day as well as once in a day in re-pigmenting vitiligo lesions successfully [23]. Topical ruxolitinib cream was reported to be very well tolerated. The only side effect encountered was acne. It has been observed that vitiligo lesions present on the face and sun-exposed areas are more responsive to JAK inhibitor therapy. Low-level light may be required for repigmentation during treatment with JAK inhibitors. Though high doses of NBUVB are required to suppress the disease activity in the skin, it is postulated that probably low doses are sufficient to boost regeneration of melanocytes and subsequent melanogenesis [21]. Unfortunately, recent literature has observed that JAK inhibitor induced repigmentation is not maintained after their discontinuation [24]. Also, no difference in response rates in patients taking oral versus topical forms of JAK inhibitors for vitiligo has been observed as reiterated in a recent systematic review [25].

Potential vitiligo treatments being explored and which hold promise for the future include antibodies against HSP 70, NK cells and CD8 T cells, and IL-15 antibodies to target Trm cells. Other molecules under research include anti-CXC chemokine ligand receptor 3 antibodies to upregulate Treg cells and thus prevent the melanocyte apoptosis, and WNT agonists to promote melanocyte stem cell differentiation [26].

9.1.7 Vitiligo and Quality of Life

Vitiligo patients have impaired quality of life and limited social interactions and activities because they have low self-esteem and poor body image. This is attributable to easy visibility of vitiligo lesions which affects social interactions, chronic course of the disease, unpredictable outcome with the current treatment modalities and lack of definite cure in the present time. It has been found that one fourth of vitiligo patients suffer from depression and one in seven vitiligo patients have anxiety. Prevalence of depression in Asian and female vitiligo patients is noted to be significantly higher than those in Caucasians and males [27]. Moreover, it is seen that female patients suffer significantly more deterioration of general and psychological health and have less social relationships as compared to males with vitiligo

[28]. A recent systematic review identified other prevalent psychological disorders amongst vitiligo patients. These included dysthymic disorders, psychopathic personality, hysteria, ADHD, adjustment disorder, sleep disturbances, social phobia, agoraphobia, sexual dysfunction, neurotic symptoms and obsession [29].

9.2 Melasma

Melasma is a very common acquired disorder of increased pigmentation resulting in asymmetrically tan macules mainly over facial skin specially in Asian and Hispanic women. Men are less commonly affected. Predisposed genetic background, coupled with chronic UV exposure leading to photoaging and effect of female hormones produces the clinical picture. Main triggers for this clinical entity include pregnancy, hormonal therapies, contraceptive pills, cosmetics, photosensitizing drugs and ovarian tumours. A variety of treatment options are available like topical depigmenting creams, chemical peeling agents, lasers and light devices and a few systemic therapeutic options. Melasma significantly impairs quality of life because of its predisposition to affect face which makes it instantly noticeable, long course, variable response to treatment and the requirement for prolonged maintenance therapy.

9.2.1 Epidemiology

The exact prevalence of melasma is hitherto unknown. However, it is seen to be more prevalent in the range of 9 to 50% in certain populations like Hispanics and Asians which are of dark skin and receive high ultraviolet exposure in their geographical location. The average age of onset is usually in the third decade of life. Females clearly outnumber males in this affliction. They are 9 times more frequently affected as compared to males. However, a recent Indian study estimated the ratio to be 4:1 and a Brazilian study found the ratio to be 39:1. Melasma in men is also similar clinically as well as similar exacerbating factors like sun exposure related to outdoor work are implicated [30].

9.2.2 Etiology

Melasma probably has a multifactorial etiology. A few implicated factors include familial predisposition, sun-exposure (UV as well as visible light), pregnancy, cosmetics, phototoxic and photoallergic drugs, nutrition, thyroid dysfunction and hormone use. Lentigines and naevi are other cutaneous disorders that are frequently associated with melasma.

A recent Korean study identified at least 334 abnormally expressed genes in melasma lesional skin [31]. The genes found to be involved include those involved in PPAR signaling, stratum corneum barrier genes, *TYR* and *TYRP1* genes. Also *NQO1* is upregulated which suppresses tyrosine degradation and thus increases melanogenesis.

Data garnered from hormonal evaluations done so far show a predominant role of serum oestrogen in triggering and maintaining the disease by causing increased production of tyrosinase (TYR) and tyrosinase related proteins 1 and 2 (TYR 1,2) which upregulate the process of melanogenesis. Gopichandani et al. evaluated hormonal profile in female melasma patients and their findings suggested underlying ovarian as well as pituitary dysfunction in such patients [32]. Reduced serum DHEAS have also been reported [33]. Sarkar et al. reported decreased levels of testosterone and increased LH in male melasma patients, indicating an underlying testicular resistance.

9.2.3 Pathogenesis

New insights have been gained into the complex pathogenesis of melasma which is brought about by a well-orchestrated interplay of melanocytes, keratinocytes, mast cells, vascular compartment, basement membrane injury on a background of predisposed genetics as evidenced by abnormalities of gene regulation. UV light seems to act on all the effectors in the pathogenesis of melasma. Therefore, the new theory being floated is that it might be a photoaging disorder with abnormal melanogenesis.

UV light upregulates MSH/MC1R. Also, it induces 1,2 diacyl glycerols which are second messengers which further activate tyrosinase. Post UVB damage, p53 upregulates proopiomelanocortin which stimulates MC1R. Cumulative sun exposure leads to solar elastosis which is now recognized to be a histopathological feature in 83–93% of melasma biopsies. Ultraviolet and visible light exposure also stimulates melanogenesis by inducing ROS production. NBUVB induces iNOS, various growth factors, cytokines, plasmin production by keratinocytes which stimulates melanogenesis.

Mast cells secrete histamine in response to UV exposure which stimulate tyrosinase pathway and leads to hyperpigmentation. Also mast cell tryptase secretion is enhanced which degrades dermal ECM and disrupts BMZ via ProMMP. It also promotes production of elastin from dermal fibroblasts and contributes to solar elastosis. Disrupted BMZ allows the descent of melanin into the dermis where it is either free or engulfed by macrophages to produce the dermal component of melasma. Also, mast cells release VEGF, FGF 2 and TGF-beta which are important in contributing to vascular proliferation, that is, increase in number, size and density of blood vessels. Endothelin 1 (ET-1) secreted by endothelial cells targets endothelin receptor B which is present at the melanocytes' surface and stimulates melanogenesis.

Paracrine effects are also reported to be exerted by sebocytes on melanocytes through various cytokines like IL-1 alpha, IL-6, angiopoietin and adipokine. Facial skin is rich in sebocytes as well as oestrogen receptors. Moreover, melanogenesis can be stimulated by UVB, UVA as well as visible light. Thus, the pathogenesis is multifactorial and the exact sequence needs to be explored.

Melasma occurs in up to 20% cases during pregnancy. The exact process by which pregnancy affects the process of melanogenesis is unknown. Elevated levels of oestrogen, progesterone and alpha MSH may be contributory. Nulliparous women with melasma are not found to have high levels of oestrogen and MSH [34]. Melasma may occur in 10% of women after menopause. It is more often seen in women on hormone replacement therapy or progesterone. Even topical application of oestrogen cream to mitigate the effects of photoaging in a post-menopausal woman has been observed to produce melasma [35].

Recent evidence points to a dermal vascular compartment in melasma pathogenesis. An increase in the number and size of dermal blood vessels and an increased expression of vascular endothelial growth factor (VEGF) has been observed in lesional skin. It is thus speculated that the altered cutaneous vasculature and melanocytes may interact to produce hyperpigmentation of melasma. Since normal human melanocytes show functional VEGF receptors, they may respond to angiogenic factors. Moreover, elevated VEGF receptors are observed in keratinocytes in melasma lesions. Thus it is hypothesised that they play an important role in vascularisation of melasma lesions. Also, they are noted to enhance the release of arachidonic acid. The possibility that the metabolites from the arachidonic acid pathway affect melanogenesis is gaining credibility. It also seems possible that chronic UV exposure leads to increased vascularisation apart from producing solar elastosis. Solar elastosis leads to elevated level of c-kit which is a strong melanogenic cytokine, that is, it mediates increase in melanogenesis of the overlying epidermis. Furthermore, solar elastosis is associated with elevated SCF and inducible nitric oxide synthase which affect vascularization. Melasma is now considered as a unique phenotype of photodamage during the ageing process [36].

9.2.4 Clinical Features

Melasma presents as symmetrical hyperpigmented macules with irregular borders on forehead, chin, cheeks, nose, mandibular region and rarely on upper extremities. Clinically, it is of 3 types, that is, centrofacial, malar and mandibular (Fig. 9.2). Based upon the depth of pigmentation, it has been conventionally divided into epidermal, dermal and mixed melasma. However, most cases of melasma are of mixed variety. Wood's lamp examination helps in assessing the depth of pigment non-invasively. Epidermal pigment is accentuated under a Wood's lamp and dermal pigment is not.

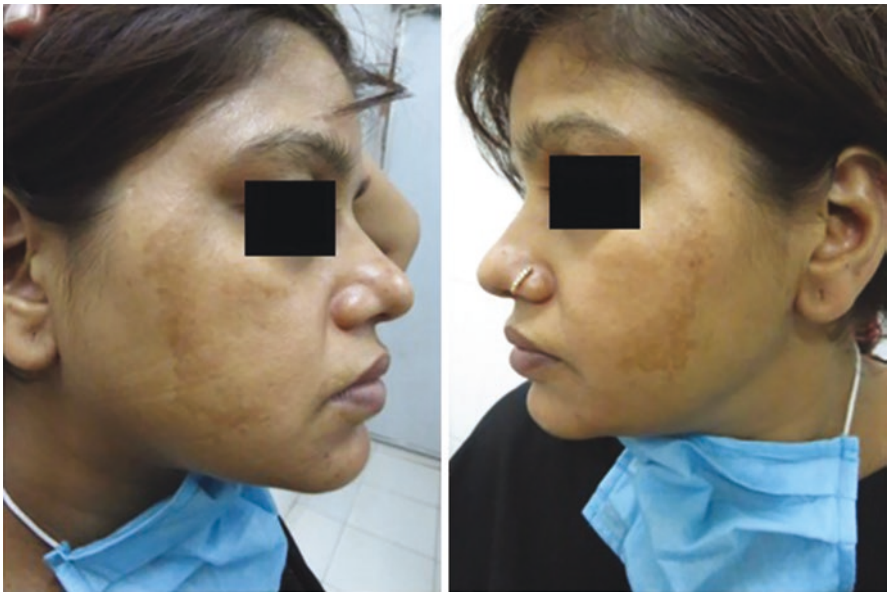

Fig. 9.2 Mandibular melasma in an Indian female patient

9.2.5 Dermatoscopy

Dermatoscopy is a non-invasive tool which helps in determining the depth of melasma and rules out other differential diagnosis/other causes of facial hyperpigmentation. It is also utilised to monitor effect of treatment and side effects like atrophy, telangiectasia and exogenous ochronosis. Dermatoscopy assesses pigmentary and vascular elements in melasma. Common dermatoscopic findings in melasma include a light-to-dark brown background and brown granules and globules with perifollicular sparing. The basic pigmentary pattern may be reticular or pseudoreticular (more common in deeper melasma). The pigment colour might give a clue of the depth of melasma. A recent study has demonstrated increased vascularization on dermatoscopy in 74.2% of melasma patients [37].

A recent Indian study assessed the various dermatoscopic features of melasma in Indian population [38]. Reticuloglobular pattern of pigmentation was most characteristic finding and was statistically significant in association with melasma ($p < 0.0001$). The other patterns which were shown to be significantly associated with melasma included an un-patterned patchy brown black pigment and a granular pigmentary pattern. Granular pigment or dots were seen in approximately one third of patients. These dots represent dermal melanophages present in the dermis and represent cases of mixed or dermal melasma. Telangiectasia was seen more frequently in patients.

9.2.6 Histopathology

The key histopathological findings are excess melanin deposition in the epidermis (epidermal type), dermal macrophages (dermal type) or both (mixed). Of late, research has focused on photoaging as well and includes features such as abnormal accumulated elastic tissue in the dermis, disrupted basement membrane, increased dermal mast cells and increase in the number, size and density of dermal blood vessels [36].

9.2.7 Treatment

Various treatment modalities have been compiled in Table 9.2 for easy reference. Photoprotection is the cornerstone of melasma management as it acts as an adjuvant to other depigmenting therapies as well as afford prevention of relapses to some

Table 9.2 Evidence-based management of melasma

S. No.	Management option	Recommendations for use
1.	Sunscreens	Broad-spectrum sunscreens containing UVA, UVB filters and iron oxide SPF of at least 30 Liberal application every 2–3 h Recommended in any melasma management strategy (Grade A recommendation)
2.	Hydroquinone	HQ alone in a concentration of 2% to 5% can be used as an effective monotherapy Grade A recommendation for HQ 4% The maximum recommended duration is 16 weeks
3.	Hydroquinone combinations—TCC: 4% HQ, 0.05% tretinoin, and 0.01% FA	It has level A quality of evidence in treating melasma and is approved by the US FDA
4.	Triple combination with glycolic peel	GA peel can be added to TC to increase the efficacy Grade of recommendation—B
5.	Mequinol	Paucity of literature Cannot make a recommendation for mequinol in melasma
6.	Corticosteroids	Their use as monotherapy is not recommended due to the plethora of AE and misuse by the patients
7.	Azelaic acid (AA)	By its efficacy and good safety profile, it is a good option for patients who cannot tolerate TCC Level and quality of evidence: IB
8.	Kojic acid	KA is less effective when used as monotherapy but shows good results in combination with HQ and GA Level and quality of evidence: B

Table 9.2 (continued)

S. No.	Management option	Recommendations for use
9.	Arbutin	Competitively inhibits tyrosinase and is cytotoxic to melanocytes Level and quality of evidence: C
10.	Vitamin C	Inhibits melanogenesis by acting as a reducing agent at various oxidative steps in melanin synthesis Level and quality of evidence IB
11.	Niacinamide	Reduces pigmentation by inhibiting the transfer of melanosomes to keratinocytes Level and quality of evidence: IB
12.	Oral tranexamic acid	Oral TA may be used alone or as an adjuvant to conventional topical drugs It can also be used when other topical treatments fail Larger RCTs are required to evaluate the efficacy as well as serious adverse events Oral TXA 500–750 mg/day in a divided dose may be used in melasma expecting a mild to moderate response for a maximum period of 6 months (Grade A recommendation) Pretreatment laboratory evaluation and monitoring during treatment is necessary Oral TXA can be used along with other topical therapies or IPL/Nd:YAG laser (Grade A recommendation)
13.	Oral Procyanidin	Only one RCT has evaluated the efficacy of oral procyanidin but not as monotherapy Further evidence needed before it can be recommended Evidence level—B
14.	Oral *Polypodium leucotomos* extract	Improvement in MASI and melasma-related quality-of-life, but not statistically significant Evidence level—B Lack of evidence to recommend this drug in melasma
15.	Oral pycnogenol	Antioxidant properties Cannot be recommended in melasma at present. Needs further evaluation
16.	Oral glutathione	Not recommended as no studies are available
17.	Chemical peels—Glycolic peel	For melasma peeling, it is used in a concentration of 30–70%. Two to three weeks apart weekly sessions are conducted for a series of 4–6 sessions Level of evidence for glycolic peel is II-I and strength of recommendation is A Its efficacy can be increased combining HQ 2% or 0.25% tretinoin. Also, it can be added to other therapies Like azelaic acid or even TC to increase the overall Efficacy or the speed of improvement, respectively (Grade B recommendation)

(continued)

Table 9.2 (continued)

S. No.	Management option	Recommendations for use
18.	Lactic acid peel	Proved beneficial when used as 92% strength at pH 3.5 with double coats, which are applied for 10 min every 3 weeks for epidermal melasma Level of evidence for lactic acid peel is II-III and strength of recommendation is B
19.	Mandelic acid	At 10–50%, can be used twice a month for 4–5 sessions Level of evidence for mandelic acid peel is III and strength of recommendation is C
20.	Beta hydroxy acid peels—Salicylic acid peel	20–30% strength Eliminates epidermal pigment Level of Evidence-II-III, Strength of recommendation-B
21.	Trichloroacetic acid peel	15% TCA is a superficial peel and 35% TCA is a medium depth peel The sessions can be conducted at the monthly interval for about four sessions TCA peel can be used in melasma as monotherapy, or combined with other peel like modified Jessner's solution Level of Evidence—II-III Strength of recommendation—B
22.	Pigment-specific Lasers- Nd:YAG laser monotherapy/ combination therapy Alexandrite laser Q-switched ruby laser	Not recommended in melasma
23.	Ablative lasers—Fractional CO2 laser, Er:YAG laser, Er:Glass laser 107	Not recommended in melasma
24.	Vascular laser—Copper bromide laser	Not recommended until further evidence is available
25.	Miscellaneous drug: Lignin peroxidase	It is a fungal derivative and has high redox potential to oxidise melanin Used in topical form Recommended in melasma (Grade B recommendation)

extent. Broad spectrum sunscreens containing UVA, UVB filters and iron oxide which block visible light are very effective. Regular use of sunscreen has been shown to prevent onset of melasma in pregnancy. A broad-spectrum sunscreen ideally a blend of inorganic and organic with SPF of at least 30 covering UVA, UVB and visible light is recommended which is effective as well as cosmetically acceptable [39].

9.2.7.1 Topical Depigmenting Agents

Hydroquinone (HQ) (Level of evidence IB) had been regarded as the gold standard depigmenting molecule so far. It is a tyrosinase inhibitor. It can also cause melanocyte destruction and melanosome degradation. It has good efficacy in reducing

pigmentation but irritant dermatitis in some individuals and ochronosis with prolonged use are major deterrents to its long-term use.

Other such molecules which target the process of melanogenesis include steroids, azelaic acid, rucinol cream, glycolic acid, kojic acid and ascorbic acid. Corticosteroids have anti-inflammatory effects and produce non-selective suppression of melanogenesis. However, they are not the agents of choice for monotherapy as long-term topical steroids might cause atrophy, striae, hypopigmentation, telangiectasia and acne. Azelaic acid has similar efficacy to hydroquinone, however, local irritation is more noted with azelaic acid as compared to hydroquinone. Stinging, burning and pruritus are common with rucinol cream. These side effects are, however, circumvented with the use of liposomal encapsulated cream. Ascorbic acid chelates copper ions which are cofactors of various enzymes involved in melanogenesis. It is also postulated to decrease reactive oxygen species and thereby decreases the inflammation. Level and quality of evidence is IB. Retinoids promote skin turnover, decrease melanosome transfer and facilitate absorption of other concomitantly used drugs. Also, they reduce tyrosinase transcription and melanin synthesis.

Kojic acid (KA) acts by inhibiting the key enzyme tyrosinase, by chelating copper at the active site of the enzyme. It is used at a concentration of 1–4%. Arbutin is a derived from D-glucopyranoside. It competitively inhibits tyrosinase and is cytotoxic to melanocytes. A synthetic derivative of arbutin known as deoxyarbutin has higher efficacy and stability. Niacinamide is the active amide of vitamin B3 that reduces pigmentation by inhibiting the transfer of melanosomes to keratinocytes.
Concomitant use of various topical agents instead of using monotherapy is a preferred clinical practice. Dual topical preparations containing tretinoin and hydroquinone have been found useful in reducing melasma. Triple combination creams which are usually one or the other modification of Kligman's formula contain a Hydroquinone, a retinoid and a fluorinated corticosteroid. A triple combination of 4% HQ, 0.05% retinoic acid and 0.01% fluocinolone acetonide has level of evidence IA. The combination of 4% HQ and 20/30% Glycolic acid has level of evidence IB [39]. Another combination topical therapy includes a solution containing glycolic acid and kojic acid. A few natural compounds have also shown improvement in melasma which includes niacinamide, *Bellis perennis* flower extract, liquorice, emblica, lignin peroxidase, arbutin and soy.

9.2.7.2 Oral Therapy

Tranexamic acid (TA), a synthetic derivative of lysine has emerged as a potential therapy in melasma. It is available in oral, topical and injectable form. It acts by decreasing VEGF and endothelin 1 and thus decreases the vascularity of affected lesions. Also, it reduces melanogenesis by decreasing arachidonic acid and MSH production through its anti-plasmin activity. Clinical improvement is noticeable after 2–6 months of oral therapy. Common side effects include headache, menstrual irregularities and abdominal bloating. Patients at risk of venous thrombosis must

not be given systemic tranexamic acid as there are rare events of DVT with this drug. Sharma et al. conducted a clinical trial and reported that oral TA 250 mg twice daily showed similar efficacy to intradermal TA 4 mg/mL microinjections weekly in 100 patients for 3 months. The main adverse effects noted were minor and included mild epigastric discomfort, hypomenorrhoea, headache and injection site pain. Although a lot of studies testify to the beneficial effect of TA there is still no consensus on the optimum route, dose and timing of the treatment with TA in melasma as reiterated in a recent review by Kaur et al. For oral TA effectiveness the duration of therapy has been suggested to be more important than the dose. Therefore, a minimum of 3 months trial is recommended. Topical TA is also recommended to be used regularly rather than intermittently for flare episodes. When used along with microneedling and intradermal injections, the frequency of the treatment vary widely and no consensus exists [40].

A systematic review to assess the efficacy and safety of TA in melasma showed that TA is beneficial for melasma, either alone or as an adjuvant to other treatment modalities [41]. Data on TA-only observational studies showed a significant in MASI ($p < 0.001$) after TA treatment. The decrease in MASI was the greatest with oral TA, followed by that with TA microinjection and topical TA. The results suggested that pigment lightening is likely to be apparent after 3 months of therapy. The meta-analysis showed that addition of TA to routine treatments, that is, topical hydroquinone, triple combination cream, Q-switched Nd: YAG laser, IPL resulted in a further decrease in MASI by 0.94 ($p = 0.03$). TA treatment needs to be maintained for an extended period of time in view of relapse on cessation of therapy. However, the optimal time of maintenance needs to be further studied. The systematic review by Kim et al. suggested that TA was well-tolerated, with a small proportion of patients experiencing transient adverse effects.

Oral Polypodium leucotomos is an antioxidant that is postulated to reduce melasma pigmentation by decreasing ROS and photo damage. However, controlled randomized trials have failed to show significant benefit [42]. No study is available to assess the use of glutathione in melasma.

9.2.7.3 Chemical Peels

Glycolic acid, salicylic acid, mandelic acid and TCA peels have been used in melasma as adjunctive therapy as they promote epidermal turnover and remodelling and also prevents melanosome transfer to keratinocytes. They are usually used along with a topical depigmenting agent. Also, combination peels are used such as salicylic acid and mandelic acid. They form the second-line of management in melasma. Level of Evidence for glycolic peel is II-I and strength of recommendation is A [43]. Level of Evidence for lactic acid peel is II-III and strength of recommendation is B. Level of Evidence for mandelic acid peel is III and strength of recommendation is C. Other peels that are used include salicylic acid peel and Gessner's peel and both have level of Evidence-II-III and strength of recommendation is B. Good practices pertaining to their use includes good priming

and strict sun protection as this minimizes the risk of postinflammatory hyperpigmentation after peels. Maintenance treatments with topical agents is mandatory to prevent recurrence.

Light and laser systems: Non ablative lasers like low fluence Q switched Nd:YAG, Q-switched Ruby laser and 1550 Erbium lasers selectively target the chromophore melanin and thus decrease pigmentation. However, addition of a sunscreen and a topical depigmenting cream promotes quicker improvement. IPL system is also used for management of melasma. Results are shown to be better if it is combined with a Q switched laser.

Emerging therapies: These are the upcoming novel therapies that may have a place in the management of melasma in future. These include topical siRNA (small interfering) agents and MITF-siRNA formulation. Topical omeprazole is also seen to decrease melanogenesis by interfering with copper acquisition by tyrosinase. Oral metformin is also a promising option. It decreases cAMP levels and thereby decreases melanogenesis.

9.3 Periocular Hyperpigmentation

It is also known as periorbital hyperpigmentation, periocular melanosis, infraorbital darkening and idiopathic cutaneous hyperchromia of the orbital region. The impression of dark circles around eyes is aesthetically unappealing and gives an aged and fatigued look to the bearer and often leads to dermatological consultation for the same. Majority of them are females in the second and third decade of life. The condition though benign causes poor self-esteem in the patient and poses a therapeutic challenge to the treating physician.

9.3.1 Epidemiology

There is scarcity of data regarding incidence and prevalence of periocular hyperpigmentation. Females are 3–4 times more commonly affected than males. However, a western study noted an equal incidence in both the sexes. Most common age group affected is 16–30 years of life.

9.3.2 Etiology and Pathogenesis

The condition may be congenital or acquired later in life and is multifactorial in etiology. Idiopathic cutaneous hyperchromia of the orbital region (ICHOR) is a primary type of pigmentation characterized by bilateral darkening of the orbital skin and eyelid, which occurs in the absence of any underlying systemic or local diseases

[44]. The pathogenesis is multifactorial in case of secondary type of periorbital hypermelanosis (POH). Genetic basis of this entity was proposed as early as 1969 by Goodman et al. [45]. The authors had posited that marked variation in the expression of this trait in genetically related individuals is consistent with an autosomal mode of transmission. 40–60% individuals with this entity report a positive family history which reflects its genetic transmission.

A few anatomical factors like structure of the bony orbit, thin eyelid skin, prominent underlying vasculature and orbicularis oculi muscle predispose to the appearance of periocular hyperpigmentation. With ageing, relative orbital rim recession occurs and fat volume decreases which increases hollowness and thereby increases shadowing specially in the inferomedial orbit or the tear trough area. Also, the infraorbital eyelid fluid accumulation further contributes to the darkened appearance. Accumulation of haemoglobin breakdown products increases the darkness. A variety of pathological and age-related changes are responsible for this vascular leakage. Post-inflammatory hyperpigmentation resulting due to allergic contact dermatitis and atopic dermatitis may cause it. It is seen to be precipitated or aggravated by sleep disorders. Other triggers include irregular menstrual cycle, episodes of illnesses and infections like viral hepatitis and varicella, eye strain, stress, hormonal changes, drugs like NSAID's and chemotherapeutic agents, excessive alcohol consumption, smoking, poor nutrition leading to vitamin deficiencies, anaemia and excessive sun exposure. Hyperpigmentation due to various other cutaneous conditions such as lichen planus pigmentosus, erythema dyschromicum perstans; fixed drug eruption, Nevus of Ota and melasma may sometimes produce the clinical picture of periocular hyperpigmentation. The pigment demarcation line F sometimes extends into the periorbital region and produces periocular hyperpigmentation. Periorbital muscle fatigue in myopes also plays a role in its causation. The condition worsens with ageing of skin. Thus, periocular hyperpigmentation may result from pathology of skin, soft tissues and skeletal elements or a combination of them. Interestingly, an Indian study by Malakar et al. reported that in 92% patients periorbital melanosis was an extension of pigmentary demarcation line (PDL-F). The study further expounded that periorbital melanosis and PDL-F occurred concurrently in 67% patients. In rest of the patients, the observation was made by dermatologist. The triggering factors noted were pregnancy (12 patients); acute illness such as viral hepatitis (3 patients), typhoid (2 patients) and chicken pox (1 patient). The authors noticed one singular hyperpigmented patch even in patients with coexisting POM and PDL-F that extended from around the eyes to the lateral side of the face. PDL-F usually remains unnoticed in childhood and becomes apparent only after some triggering factor(s) such as puberty, pregnancy and illnesses.

PDL-F were absent in their younger patients between 11 and 22 years in about 8% cases. The authors opined that in these patients triggering factors may not have stimulated the physiological line to appear as yet but they should be followed up to look for the appearance of same [46].

9.3.3 Clinical Features

Periocular hyperpigmentation appears clinically as bilateral round, homogenous, light to dark coloured brownish black pigmentation of the palpebral skin more often the lower eyelid which is distinctly apparent from the surrounding facial skin colour (Fig. 9.3). Manual stretching of the lower eyelid is helpful in distinguishing it from the shadow effect of the tear trough. True pigmentation retains its colour on stretching while that due to shadow effect wanes away. Wood's lamp is helpful in distinguishing the depth of melanin deposition, that is, epidermal and dermal component. Dermatoscopy is helpful in in vivo evaluation of the pattern of pigment, vasculature and skin changes and thus obviates the need for histopathological evaluation. Polarized dermatoscopy is better at identifying the cause of pigmentation, that is,

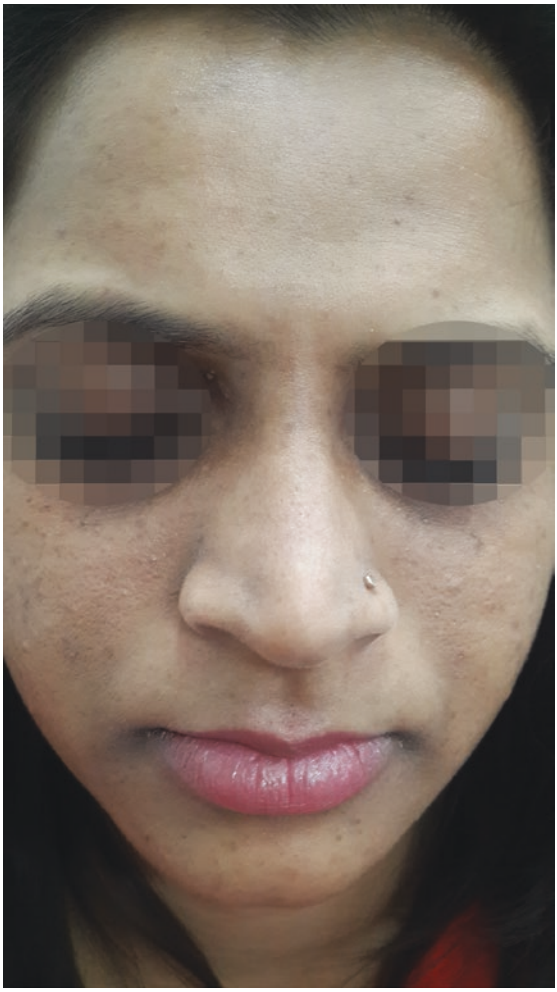

Fig. 9.3 Periorbital hyperpigmentation in an Indian female patient

whether its melanin or vascular cause and non-polarized is better at assessing surface changes. The different patterns of pigment noticed are blotches, exaggerated pigment network, coarse speckled, fine speckled and globules. Vascular pattern includes superficial veins which are bluish linear blood vessels of larger calibre as compared to telangiectasia. Skin changes observed include atrophy which is apparent as hypopigmented area with absent skin markings and exaggerated skin markings in some patients. Melanin index, erythema index and oxygenation index can be measured using reflectance meters for research purposes.

Recently a validated and reproducible photo numeric scale with written descriptors and corresponding representative images has been compiled from a database of facial images and the consensus opinion of a panel of expert evaluators to assess the severity of periocular hypermelanosis and to reduce the inter-observer bias in clinical assessment [47].

Clinically it is classified into pigmented, vascular, structural and mixed types. Pigmented type appears as predominantly infraorbital brown to black hue which may sometimes involve upper eyelid also. Vascular type appears as blue, pink or purple hue which accentuates on stretching the lower eyelid. Structural type is usually due to the shadow effect of the surrounding facial anatomic structure. The shadow effect vanishes on stretching the lower eyelid skin. Mixed type has features of more than one type [48]. Ranu et al. found vascular type to be the commonest type (41.8%) and those due to shadow effects to be least common (11.4%) [49].

9.3.4 Dermatoscopy

Dermatoscopy helps in finding origin of pigment whether it is due to melanin or due to underlying vasculature. Polarized dermatoscopy helps in evaluating pigment network and vascular structures, whereas non polarized dermatoscopy evaluates superficial skin changes such as scaling and fissuring.

Patterns of pigmentation observed in POH include blotches, coarse speckled, fine speckled, globular and exaggerated pattern. Accentuation of reticular pigment network pattern in terms of pigment deposition is noted on dermatoscopy. The pattern of vasculature consists of telangiectasia and superficial veins. Telangiectasia appears as finer branching erythematous vessels. Superficial veins appear as bluish, linear veins of larger calibre as compared to telangiectasia. Telangiectasia is associated generally with post steroid abuse, whereas the vascular type presents with superficial veins. Vascular type of POH occurs due to a combination of transparency of the overlying skin and dermal vascularity. Skin changes observed generally on dermatoscopy are atrophy and exaggerated skin markings. Atrophy appeared as hypopigmentation and lack of normal skin markings. Exaggerated skin markings appear as increase in crisscross lines of skin markings.

Jage M et al. reported dermatoscopic changes in pigmentation, vasculature, and skin changes in POH in Indian patients. Pigmentary alterations noted on

dermatoscopy included blotches (30%), exaggerated pigment network (28%), coarse speckled (24%), fine speckled (20%), and globules (16%). Pattern of telangiectasis (18%) and superficial dilated vessels (20%) were the main vasculature changes on dermatoscopy. Atrophy (18%) and exaggerated skin markings (22%) were noted in the skin of POH [50]. It was also noted in the instant study that in the constitutional type of periorbital pigmentation, the most common dermatoscopic pattern observed is exaggerated pigment network. Globules, coarse speckled and fine speckled, are found more commonly in postinflammatory type. The colour of pigment observed on dermatoscopy was dark brown in 48 cases and slate blue in 2 cases. On further examination, it was found that patients with slate blue pigmentation had aetiologies of lichen planus pigmentosus which implies dermal origin of pigment. Patients with postinflammatory type showed commonly blotches (20%), coarse speckled (20%), fine speckled (14%) and globule pigment pattern (10%).

Another recent Indian study corroborated similar dermatoscopic findings. Most common pigmentary pattern noted was scattered pigmented dots (56%) and exaggerated pigment network (31%). Other less common findings were globules (30%), and blotches (27%). Vascular changes noted were dilated veins and telangiectasia in 50% and 32% of their subjects, respectively. Most common change in skin of POH noted was exaggerated skin markings seen in 43% of subjects. Scattered pigmented dots were found to be significantly associated with vascular type of POH. The most frequent pigmentary pattern in post-inflammatory type of POM was exaggerated pigment network. Constitutional and shadow type of POM had pigment arranged in Globules while in shadow type of POM pigment was more commonly arranged in blotches [51].

9.3.5 Management

The primary aim is to figure out any precipitating factor and removing it. Complementary to the medical management, concealers help in matching the skin hue to that of the surrounding skin and boost the self-confidence. Makeup foundation may work as a concealer to blend the hyperpigmented area with the surrounding skin hue. Optical diffusers are molecules like mica, talc, titanium dioxide, zinc oxide which may be used in conjunction to concealers to reflect away light. Use of broad-spectrum sunscreen and UV-coated glasses are advisable to these patients.

Topical depigmenting creams are commonly used to decrease periocular pigmentation. Topical retinoids decrease dyschromia by decreasing melanogenesis and stimulating collagen synthesis. Topical hydroquinone is a competitive antagonist of tyrosinase and decreases melanin synthesis. Topical depigmenting creams containing azelaic acid and kojic acid are also employed for the treatment. Topical Caffeine based gels are seen to decrease oedema and pigmentation. Cosmeceutical peptides which include signal peptides, enzyme inhibitor peptides and carrier peptides promote collagen synthesis and improve the appearance of dark circles.

Chemical peels either as monotherapy or in combination with other modalities are also utilized for lightening the periocular pigmentation. Glycolic acid (20%), very low concentrations of TCA peel (3.75%) and lactic acid (15%) have been reported to be useful. A combination of 4% hydroquinone and 30% salicylic acid peel was reported to be safe and efficacious. Carboxytherapy and vitamin C mesotherapy have also shown promising results.

Intense Pulsed Light therapy utilizes wavelength of 500–1200 nm which targets haemoglobin and melanin in the epidermis and dermis. Radiofrequency devices are used to promote neo-collagenosis through their thermal effect and thus improve skin quality and hue. Q-switched lasers such as Q switched ruby laser (694 nm), Q switched alexandrite laser, and Nd: YAG laser (1064 nm) selectively disrupt melanosomes and thus are useful in treating pigmented type of dark circles. Recently a few studies have used novel picosecond alexandrite laser (755 nm). The results from these studies are encouraging as better pigment clearance is noticed. Also, side effects such as postprocedure pain and postinflammatory pigmentation occur less commonly. Pulse dyed lasers produce visible light of 585–595 nm and selectively targets haemoglobin as the chromophore. It is a suitable choice in patients having vascular etiology of periocular hyperpigmentation. Ablative laser resurfacing is also used to decrease pigmentation in periocular region. It produces controlled tissue injury and the subsequent repair process leads to collagen remodelling, decreased pigmentation and improved skin which conceal underlying vasculature and orbicularis oculi muscle.

Periocular melanosis resulting due to shadow effect can be mitigated to some extent by injecting hyaluronic acid fillers in the periorbital hollows. Fat transfer in the infraorbital rim hollow is another useful option. Lower eyelid blepharoplasty is especially useful where gravitational descent of lower eyelid produces shadows and gives an impression of periocular hyperpigmentation.

9.4 Lichen Planus Pigmentosus

An uncommon variant of lichen planus (LP) usually found in dark-skinned patients is Lichen planus pigmentosus (LPP). It presents clinically as dark brown to grey macules on sun exposed areas of the face, neck, and flexures [52]. Bhutani and colleagues coined the name lichen planus pigmentosus as these lesions exhibited histopathological similarity with lichen planus and exhibited association with other types of lichen planus in about one-third patients. Considerable overlap exists between ashy dermatosis and LPP and they are supposed to represent the same entity by some authors while others consider them as different entities. Despite the controversy the balance tilts in favour of considering them as distinct entities as specific differences in epidemiology, pathogenesis, clinical presentation, histopathological findings, prognosis, and response to treatment are pertinent.

9.4.1 Epidemiology

LPP is a chronic condition which predominantly affects people having skin phototypes III to VI. Thus it is common in geographic regions receiving high sun exposure such as India, Asia, Africa, and Latin America and it is rarely encountered in Caucasians. It is more common in females. Exposed sites are commonly affected. It deteriorates the quality of life of affected patients.

9.4.2 Etiopathogenesis

CD8+ T lymphocytes are the main effector cells which targets and damages the epidermal keratinocytes and leads to intense pigmentary incontinence. Initial inflammatory response quickly dissipates leaving behind dermal melanin which persists for months to years. A few associations have been noted with LPP such as hepatitis C virus infection, prolonged exposure to sun, environmental pollution, and use of mustard oil in food as well as its use as moisturiser. Mustard oil contains a photosensitizer (allyl-thiocyanate) which is incriminated in the causation of LPP. Other substances which can trigger its onset include contact with amla oil, henna, hair dye, cold cream, turmeric based powder/liquid and nickel. Recently, a case of childhood LPP was reported where a 10-year-old boy developed LPP involving more than 40% of his body surface area following mercury amalgam filling in his molar tooth. Patch test to mercury was positive, exclusion of other triggering factors for LPP and patient improved after amalgam removal. Hormonal factors might have a role in pathogenesis of LPP because it is commonly observed for the first time in some women around the time of menopause.

9.4.3 Clinical Features

LPP mainly affects the temporal and preauricular areas of the face and neck, at times extending onto the trunk (Fig. 9.4). Flexural areas are affected in one-fifth cases, mainly the axillae, followed by the inframammary folds and the inguinal creases (Inverse LPP). Arms can also be sometimes affected. The palms, soles, oral mucosa, scalp and nails are usually spared in LPP. Clinically the condition is usually asymptomatic and the patient presents with mostly cosmetic disfigurement with dark brown to grey or grey-blue, discrete as well as coalescent, round or oval macules with irregular and poorly-defined borders distributed symmetrically over all or some of the above-mentioned sites. Itching might be present in the initial and active phase of the disease.

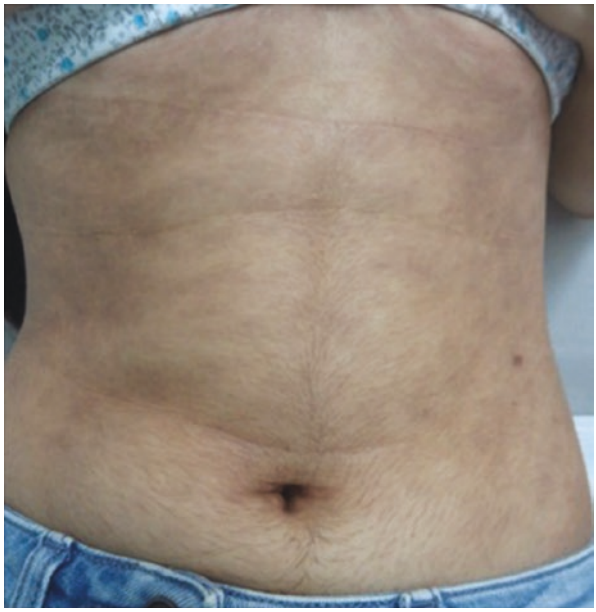

Fig. 9.4 Diffuse-brown hyperpigmentation over the infra-mammary area and abdomen in a young woman with lichen planus pigmentosus

LPP-inversus is considered as a variant of LPP which involves flexural and intertriginous areas. Friction at these sites is the probable cause. It has no predisposition to affect the sun-exposed areas unlike LPP. It usually affects women beyond 40 years of age. Linear or zosteriform LPP appears along Blaschko's lines and may affect the limbs, face or the trunk. Other patterns include diffuse, reticular and perifollicular. Follicular LPP usually affects younger age group and the most frequently involved sites are the upper limbs and trunk. Clinical lesions are pinpoint follicular macules on an apparently normal skin. Sometimes exaggerated skin markings are observed which may be produced by rubbing by the patient [53]. Lesions of lichen planus or lichen planopilaris may also be encountered in these patients.

LPP can coexist with classic lichen planus, frontal fibrosing alopecia (FFA), lichen planopilaris and mucosal lichen planus. LPP is also seen to be associated with a few endocrinal maladies such as type 2 diabetes (38%), thyroid disorders (22%), and dyslipidaemia (50%). A chronic inflammatory state in patients with LPP is hypothesized to predispose to these endocrinopathies [52]. LP with post-inflammatory hyperpigmentation is believed to be a distinct entity and is not included in LPP.

LPP has also been found to be uncommonly linked to a few autoimmune diseases such as vitiligo and lupus erythematosus and rarely to malignancies, acrokeratosis of Bazex, atopic dermatitis and nephrotic syndrome [54].

Though the course and duration are unpredictable, the disease usually runs a chronic course for 6 months to 3 years and is gradually progressive with remissions and relapses. Some cases may resolve spontaneously while others suffer from persistent pigmentation.

A few clinical condition may closely mimic clinical lesions of lichen planus pigmentosus and need to be considered during clinical work up of such a patient. These are idiopathic eruptive macular pigmentation, Ashy dermatosis/erythema dyschromicum perstans, Riehl's melanosis/pigmented contact dermatitis, Ochronosis, Hori nevus, Fixed drug reaction, melasma, and postinflammatory pigmentation. "acquired dermal macular hyperpigmentation" (ADMH) is proposed to decrease confusion associated with the diagnosis as Ashy dermatosis, erythema dyschromicum perstans, Riehl's melanosis, idiopathic eruptive macular pigmentation, and LPP have overlapping clinical and histopathological features Of late, an inclusive term "acquired dermal macular hyperpigmentation" (ADMH) is proposed when there are overlapping clinical and histopathological features and a definitive diagnosis of Ashy dermatosis, erythema dyschromicum perstans, Riehl's melanosis, idiopathic eruptive macular pigmentation, and LPP cannot be made [55]. These conditions have been clubbed together because all of them represent a lichenoid reaction pattern to chronic subclinical injury [53].

9.4.4 Dermatoscopy

Brown homogeneous areas on dermatoscopy represent epidermal pigmentation while pigmentary incontinence and melanophages in the papillary dermis is seen dermatoscopically as grey–brown or grey–blue dots and globules. Initial LPP lesions have diffuse black pepper–like pattern of grey dots. Long-standing lesions of LPP show reticular, linear and cobblestone patterns of grey dots. Lack of pigmentation in the follicular openings is seen as white dots. Pigment is characteristically absent in skin furrows probably due to lack of friction [56].

A recent study recorded the dermatoscopic features of facial lesions in LPP patients. Hem-like (20.9%) pattern, arcuate (18.6%), incomplete reticular (39.5%), complete reticular (7%) patterns of dots and/or globules (86%) were recorded in the maximum number of cases. Non-specific arrangement (14%) of dots and globules is also seen. Other less common dermatoscopic patterns were exaggerated pseudoreticular pattern, accentuation of pigmentation around follicular openings, targetoid appearance, and obliteration of the pigmentary network [57].

Wood's light examination: Since the location of melanin is predominantly dermal, there is no enhancement of the lesion with Wood's light.

9.4.5 Histopathology

Histopathology of LPP shows vacuolization of the epidermal basal cells, band-like lichenoid or perivascular lymphocytic infiltrates in the papillary dermis, pigmentary incontinence and melanophages in dermis.

9.4.6 Treatment

Most of the data of treatment response comes from case reports and case series. Patients are advised to avoid triggers and photoprotection with sunscreens is encouraged. Medium-high potency topical corticosteroids are used as anti-inflammatory agents once or twice a day for a short duration. LPP Inversus cases do not respond well to topical steroids. In one of the studies evaluating efficacy of topical steroids in LPPI, 2 out of 20 LPPI cases had moderate improvement, 11 had slight improvement and 7 had no improvement [58]. Tacrolimus (0.03 or 0.1%) ointment twice daily is seen to produce 50% improvement in 12 weeks [59]. It is therefore recommended to use topical tacrolimus for at least 8 weeks [58]. Depigmenting agents such as 4% hydroquinone, kojic acid, modified Kligman's formula (tretinoin 0.025% to 0.05%, hydroquinone 4%, 0.1% dexamethasone) inhibit melanogenesis and increases epidermal turnover and can serve as an adjuvant treatment when used in conjunction with an anti-inflammatory treatment. Q-switched Nd-YAG 1064 nm laser works on the principle of selective photothermolysis of melanin and has moderate efficacy in treating LPP. It can be combined with topical tacrolimus in cases of active LPP. A successful combination therapy of tacrolimus, hydroxychloroquine and picosecond laser for lichen planus pigmentosus is recently reported [60]. Oral anti-inflammatory agents used in the treatment of LPP include oral corticosteroids, dapsone and isotretinoin. Sindhura et al. from India retrospectively analysed 6 patients of follicular LPP who had received Oral mini pulse dexamethasone 2.5 mg twice weekly, topical mometasone furoate 1% cream, and topical tacrolimus 0.1% ointment. All cases had disease stabilised over a mean period of 10.7 weeks, after which oral mini pulse was tapered and ceased [61]. Only one patient showed satisfactory improvement in pigmentation. Verma et al. examined a series of 5 patients with lichen planus pigmentosus with successful response to a combination of topical tacrolimus 0.1% ointment twice daily and oral dapsone 100 mg once daily for 4 months. Improvement was noticed during the study period with no further progression in disease. Oral dapsone was well tolerated [62]. Muthu et al. treated 27 LPP patients with fixed low-dose (20 mg/day) oral isotretinoin for 6 months and topical sunscreen was used along with it. Moderate improvement (26–50%) in 15 patients (55.7%) followed by good (>50%) in seven (21.8%) and mild (<25%) in two (6.2%) patients was noted. It took about 2 weeks for pruritus to subside, and disease stabilized by 4–6 weeks. Better outcome was observed in patients with a shorter duration (≤5 years) of disease and with limited body area involvement. The authors opined that low-dose isotretinoin should be considered for use in early and limited LPP [63].

Recently, oral tranexamic acid 250 mg per day for 4 to 6 months was administered to 18 women and 2 men with LPP who were all phototype 3 or 4. Pruritus was present in 9 patients. Long-term photoprotection was advised to the patients. Evaluation at 6 months showed that 10 patients improved partially and 3 patients showed no response. Pruritus disappeared in all patients and no relapse was seen at 12 months. The authors suggested that tranexamic acid has a good safety profile and

efficacy in treatment of lichen planus pigmentosus [64]. However, larger-scale studies are needed to further explore this treatment option. Sonthalia et al. published the results of phenol combination peel done every 3 weeks, for residual post LPP hyperpigmentation in 17 patients. A total of 6 sessions of peel were done. Modified phenol peels were found to be effective in reduction of hyperpigmentation of LPP. Also, they were found to be safe and were well tolerated [65].

9.5 Pigmented Contact Dermatitis

Pigmented contact dermatitis (PCD) is a type of contact dermatitis characterized by appearance of hyperpigmentation with little or no signs of cutaneous inflammation. The term "pigmented contact dermatitis" was coined by Osmundsen, a Danish dermatologist in 1970 who documented several cases of peculiar facial hyperpigmentation in Copenhagen which was the result of contact dermatitis to an optical whitener, Tinopal CH 3566, in washing powder [66]. "pyrazoline" derivatives that seem to have a marked tendency to induce pigmented contact dermatitis. A mixture of two "pyrazoline" derivatives present in it was incriminated as the responsible chemical. Later on, the term pigmented cosmetic contact dermatitis was introduced by Nakayama, a Japanese dermatologist in 1973 for cases that developed the same clinical features after exposure to cosmetic contact allergens especially Brilliant Lake Red R [67]. Pigmented cosmetic dermatitis is now a well-recognised variant of PCD. Riehl′s melanosis is another presentation of PCD. It is clinically characterized by numerous fine, reticulate, acquired macules of pigmentation on the face, neck, and upper chest. The common allergens implicated in its causation include fragrances and chemicals in cosmetics. A recent global consensus statement emphasized that finely reticulated hyperpigmentation on the face and neck region should be labelled "pigmented contact dermatitis" if its appearance is preceded by relevant contact allergy [68]. It is demonstrated commonly with the help of patch tests. The limitations of this approach are that this is not always possible and patch tests may be positive in other conditions also such as LPP and EDP.

9.5.1 Etiopathogenesis

PCD is a common entity in dark-skinned individuals of Asian population as asymptomatic blotchy or reticulate slate-grey and brown hyperpigmentation often involving the face in middle-aged women. PCD commonly result following direct contact with the allergens (Table 9.3). Rarely it can occur after airborne spread. The well-known causes of PCD include dyes and textile allergens (azo dyes, Brilliant Lake Red R, Tinopal CH3566, Disperse Blue dyes, rubber components, kumkum/vermillion—Brilliant Lake Red R, Sudan I, aminoazobenzone, cananga oil, "chandan", etc. [69], naphthol, washing powders, henna (red—lawsone, brown—indigo plant leaves,

Table 9.3 Reported causes of Pigmented contact dermatitis

S. No	Substances	Responsible allergens
1.	Dyes and textiles	• Azo dyes—Brilliant Lake red R • Tinopal CH3566 (optical whitener) • Disperse blue dyes • Rubber components • Naphthol, washing powders
2.	Kumkum/ vermillion	Brilliant Lake red R, Sudan I, aminoazobenzone, cananga oil, "chandan"
3.	Henna	Red—Lawsone, brown—Indigo plant leaves, black—PPD
4.	Preservatives	Formaldehyde
5.	Fragrances	• Musk ambrette • Cananga oil (vermillion) • Benzyl salicylate • Benzyl alcohol • Sandalwood oil • Cinnamic alcohol • Jasmine absolute • Hydroxycitronellal • Ylang-ylang oil • Eugenol, geraniol oil, lavender oil, lemon oil
6.	Cosmetics	• Ricinoleic acid (lipstick) • Brilliant Lake Red R pigment • Yellow No. 10 and 11 pigment • Hair dyes • Castor oil acid • Deodorants
7.	Other substances	• Kojic acid • Minoxidil 5% • DPCP contact immunotherapy • Rubber products • Nickel • Chromium

black—PPD; preservatives (formaldehyde); fragrances (musk ambrette (even airborne through incense), cananga oil (vermillion), benzyl salicylate, benzyl alcohol, sandalwood oil, cinnamic alcohol, jasmine absolute, hydroxycitronella, ylang-ylang oil, eugenol, geraniol oil, lavender oil, lemon oil); cosmetics (ricinoleic acid (lipstick), Brilliant Lake Red R pigment, Yellow No. 10 and 11 pigment, hair dyes, castor oil acid, deodorants); other substances such as kojic acid, minoxidil 5%, DPCP contact immunotherapy, rubber products, nickel and chromium. A recent Indian study implicated cetrimonium, gallate mix, thimerosal, and skin lightening creams as the common chemicals responsible for PCD [57]. Cetrimonium is an antiseptic and a surfactant used widely in hair conditioning products. Gallate mix consists of dodecyl gallate, octyl gallate, and propyl gallate. These antioxidants are frequently used as preservatives in lipsticks, cleansers, skin lightening creams, conditioners, and makeup products. Samanta et al. recently conducted patch tests in biopsy proven

cases of PCD and among total 1216 (32 patches × 38 patients) patch applied, 42 (3.4%) showed positivity in 30 patients. Among allergen categories, colorant (PPD) was found to be most common (37%) followed by fragrances (18%), preservatives (15%), anti-microbial (11%) and emulsifier and anti-oxidants (each 8%). This study also reported lavender absolute as the most common allergen in fairness creams. The exact pathogenic mechanism is unclear. Nakayama postulated that hyperpigmentation due to contact dermatitis may develop due to 3 mechanisms, that is, incontinence pigmenti histologica, increased basal melanosis and haemorrhage around blood vessels which causes hemosiderin deposits and leads to Majocchi–Schamberg dermatitis [67]. It is postulated that persistent contact with low levels of allergenic chemicals produces type IV allergy which leads to basal layer cytolysis and consequently produces pigment incontinence and dermal melanophages. Cutaneous inflammation increases the number and size of the melanocytes and enhances their enzymatic activity [70]. Nagao et al. postulated that the allergen responsible for PCD may have a special affinity for melanin, inciting an inflammatory reaction first around the melanocytes and then around the cells incorporating melanin granules [71]. Osmundsen mentioned that PCD may reflect some idiosyncrasy of the patients and/or the mode of exposure to the allergen and/or some specific peculiarity of the allergen itself, the exact pathomechanism remaining uncertain [66].

9.5.2 Clinical Features

PCD usually presents as asymptomatic blotchy or reticulate slate-grey and brown hyperpigmentation usually involving the forehead (Fig. 9.5), zygomatic and temple area of the face. The central part of the face, including the periorbital area relative to the lateral part of the face, is relatively less affected. More commonly involved sites include hair margins (especially in hair dye associated), outer surface, helix & lobule of ears, preauricular area, temples, dorsum of neck, upper back, inframammary area and arms. Sparing of creases is noted. Patch test is found to be more often positive when these sites are involved [72]. Sometimes, dress or shirt dye dermatitis affects the axillary borders, sparing the vault; and trouser dye dermatitis presents initially on the anterior thigh [73].

Conspicuous absence of itching, predominant hyperpigmentation, and absence of signs of dermatitis are clinical features that distinguish PCD from allergic contact dermatitis to cosmetics. It can develop from 2 months to 2 years after sensitizer use. Temporal correlation is often difficult to establish. Other differential diagnosis which needs to be excluded based upon morphology, prior inflammation and lack of interface dermatitis include vitamin B12 deficiency, Addison's disease, Addisonian pigmentation, drug-induced reactions (FDE), PIH due to LP, macular amyloidosis, melasma, exogenous ochronosis, PIH, frictional melanosis and atopic dermatitis with PIH.

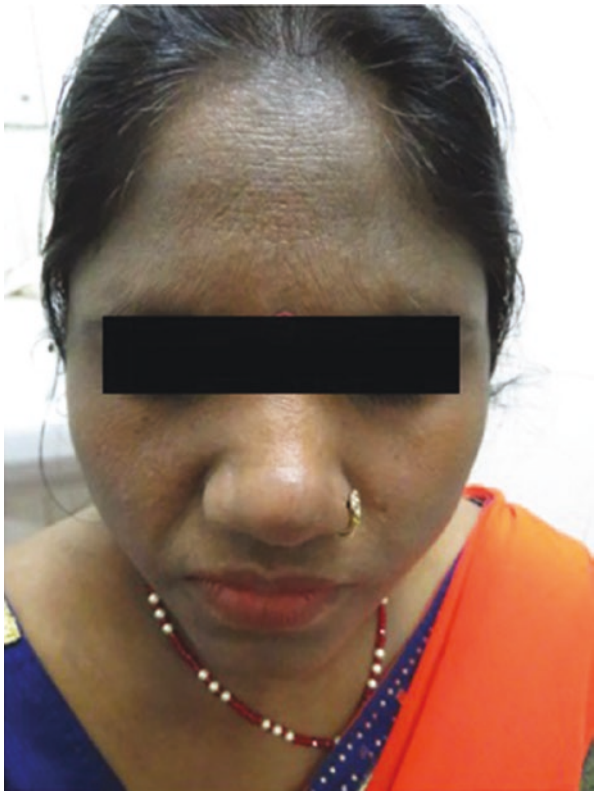

Fig. 9.5 Dark-brown hyperpigmentation in a North-Indian female with pigmented contact dermatitis to "sindoor" (vermillion) (applied by married ladies on the central hair margin)

9.5.3 Dermatoscopy

Dermatoscopy features usually overlap with LPP and EDP. It often reveals a pseudo-network with multiple grey dots. However, patchy and diffuse reticular pattern may also be observed. Surface scale, focal telangiectasia and follicular keratotic plug have also been noted. Regularly distributed pigment granules which are finer, more regular and darker when compared to LPP granules are evident. Hem-like pattern of brown, grey dots and globules are usually observed in extra facial lesions [74].

9.5.4 Histopathological Findings

Histopathological findings reveal liquefaction degeneration of the epidermal basal layer. Pigmentary incontinence and a scant perivascular inflammatory cell infiltrate in the papillary dermis are also observed. Mild epidermal atrophy with rete ridge flattening and necrotic keratinocytes may also be found in the epidermal basal layer. Recently, PCD in a 51-year-old man due to exposure to benzyl salicylate present in

his aftershave showed histopathologic features of a nonlichenoid focal interface dermatitis involving the epidermis and pilosebaceous unit, along with dermal melanophages [75]. Of late, an Indian study has shown that out of the 38 biopsy proven cases of PCD, 18 (47%) showed lichenoid features, 17 (45%) showed spongiotic features, 3 (8%) showed a mixed lichenoid and spongiotic pattern [76].

9.5.5 Role of Patch Test in PCD

Patch testing is central to the diagnosis of PCD. Closed patch testing is usually carried out with standard series, cosmetic series, fragrance series and the personnel products of the patients [73]. For "leave–on" cosmetics patch test is done "as is". For "wash-off" or "rinse-off" cosmetics, the suspected substance is used in the concentration of 10%. When the soaps and detergents are suspected, they are used in concentration of 1% for patch testing. Follow up at 1 month is warranted to look for development of delayed pigmented macule at patch-test site.

A study from Israel on the utility of screening patch test in PCD revealed highest yield with the European standard series and the Scandinavian photo series [77]. The cosmetic and fragrance series gave a low yield, with only 2 patients showing a relevant result to at least one allergen. Photo patch test should be done as a part of further evaluation. The International Contact Dermatitis Research Group (ICDRG) scoring system should be followed to record the reaction. Apart from a papule or vesicle, a brown pigment may develop at the site of patch test site. A brown pigment may develop at the patch test site (Osmundsen). The accepted criterion for relevance of a patch test is the disappearance of eczema on cessation of exposure to allergen. However, in PCD, pigmentation can persist for months-years even after withdrawal of the implicated allergen.

Other tests—The provocative usage test (PUT) or repeated open application test (ROAT) may identify a reaction if closed patch test reaction is equivocal. In repeated open application test (ROAT), the suspected cosmetic is applied twice daily for 7 days on upper arm. It is mostly needed for fragrance and preservative since a very low concentration present in patch test. Usage test is utilized if patch testing to a strongly suspected test substance is negative. The patients are asked to use the preparation again routinely as they would normally use it, especially bindis.

9.5.6 Management

The most effective general advice is to avoid the use of textiles and washing powders containing strong contact sensitizers, avoid cosmetics and other agents in daily use/salons with identified allergens. The treating physicians should prescribe skin care products without offending allergen. The task of allergen avoidance through the use of allergen controlled system (ACS) prevents contact with the main contact

sensitizers [78]. These include allergen controlled detergent for skin (ACD-S, "Minon"), allergen controlled cosmetics (ACC), allergen controlled wearing apparel (ACW) and allergen controlled detergent for wearing apparel (ACD-W). The affected person is asked to wear allergen-controlled wearing apparel (ACW) underwear if textile allergy is proven. The data of allergen control study by Nakayama who treated a total of 165 cases of pigmented cosmetic dermatitis solely with allergen controlled system showed complete cure in 52, almost complete cure in 21, and remarkable improvement in 51 patients. The rate of cure plus remarkable improvement reached 75%. The duration of follow-up was between 3 months and 5 years.

Strict legislations in various countries prohibit the use of PPD, phenyl-azonaphthol and Yellow 11, carbanilides and several perfumery sensitizers, among others. Unfortunately, such stringent laws are lacking in India leading to the rampant use of such allergens in various cosmetics.

Treatments that are aimed at removing pigment include topical therapy with hydroquinone and other topical depigmenting agents. Systemic therapies include oral glycyrrhizin 150 mg/day, oral vitamin C 100 mg/day, oral tranexamic acid 500 mg/day, oral dapsone, immunosuppressives. Procedures which have been used include 30% Salicylic acid peels and lasers such as IPL, QS Nd: YAG. In a recent pilot study conducted over 6 months, the efficacy and safety of a novel combination therapy with oral administration of tranexamic acid (TA) and Glycyrrhizin compound for recalcitrant Riehl's melanosis was evaluated. Seven out of ten patients received "marked improvement", while two received "moderate improvement" and one "minimal improvement" at the final visit. Reflectance confocal microscopy and dermatoscopy analyses confirmed the improvement of pigmentation and erythema with decreased pigment granules and telangiectatic vessels [79]. Triple combination therapy with salicylic acid peels, oral glycyrrhizin compound, and vitamin C has also been found to be safe and effective modality [80].

Moreover, triple combination therapy with a low-fluence 1064 nm Q-switched Nd: YAG laser, hydroquinone cream and oral tranexamic acid for recalcitrant Riehl's Melanosis was recently explored and found to be a viable option for Asian patients having Riehl's melanosis with high risk of post-inflammatory hyperpigmentation [81].

In a nutshell, the priority should be the control of the ongoing inflammation which is achieved with cessation of contact, anti-inflammatory agents, tacrolimus, moisturizers, topical and oral immunosuppressives and later on use of depigmenting agents and/or procedures to manage residual pigmentation.

References

1. Jin Y, Santorico SA, Spritz RA. Pediatric to adult shift in vitiligo onset suggests altered environmental triggering. J Invest Dermatol. 2020;140(1):241–243.e4.
2. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003;16(3):208–14.

3. Patil S, Gautam M, Nadkarni N, Saboo N, Godse K, Setia MS. Gender differences in clinicoepidemiological features of vitiligo: a cross-sectional analysis. ISRN Dermatol. 2014;2014(13):186197.
4. Dennin MH, Stein SL, Rosenblatt AE. Vitiligoid variant of lichen sclerosus in young girls with darker skin types. Pediatr Dermatol. 2018;35(2):198–201. https://doi.org/10.1111/pde.13399. Epub 2018 Jan 4
5. Rashighi M, Harris JE. Vitiligo pathogenesis and emerging treatments. Dermatol Clin. 2017;35(2):257–65.
6. Basak PY, Adiloglu AK, Ceyhan AM, Tas T, Akkaya VB. The role of helper and regulatory T cells in the pathogenesis of vitiligo. J Am Acad Dermatol. 2009;60(2):256–60.
7. Frisoli ML, Essien K, Harris JE. Vitiligo: mechanisms of pathogenesis and treatment. Annu Rev Immunol. 2020;26(38):621–48.
8. Nguyen JK, Schlichte MJ, Jogi R, Alikhan M, Patel AB. A case of new-onset vitiligo in a patient on tofacitinib and brief review of paradoxical presentations with other novel targeted therapies. Dermatol Online J. 2020;26(3):13030/qt1hk2x4j5.
9. Sollena P, Nikolaou V, Soupos N, Kotteas E, Voudouri D, Stratigos AJ, Fattore D, Annunziata MC, Orlandi A, Di Nardo L, Apalla Z, Deilhes F, Romano MC, Fabbrocini G, Sibaud V, Peris K. European network for cutaneous ADverse event of oncologic drugs (ENCADO) group. Vitiligo-like lesions in patients with advanced breast cancer treated with cycline-dependent kinases 4 and 6 inhibitors. Breast Cancer Res Treat. 2021;185(1):247–53.
10. Webb KC, Lyon S, Nardone B, West DP, Kundu RV. Influence of pregnancy on vitiligo activity. J Clin Aesthet Dermatol. 2016;9(12):21–5.
11. Zhen Y, Yao L, Zhong S, Song Y, Cui Y, Li S. Enhanced Th1 and Th17 responses in peripheral blood in active non-segmental vitiligo. Arch Dermatol Res. 2016;308(10):703–10. https://doi.org/10.1007/s00403-016-1690-3.
12. Horev A, Weintraub AY, Sergienko R, Wiznitzer A, Halevy S, Sheiner E. Pregnancy outcome in women with vitiligo. Int J Dermatol. 2011;50(9):1083–5.
13. Park KY, Kwon HJ, Wie JH, Lee HH, Cho SB, Kim BJ, Bae JM. Pregnancy outcomes in patients with vitiligo: a nationwide population-based cohort study from Korea. J Am Acad Dermatol. 2018;79(5):836–42.
14. Taieb A, Alomar A, Böhm M, Dell'anna ML, De Pase A, Eleftheriadou V, Ezzedine K, Gauthier Y, Gawkrodger DJ, Jouary T, Leone G, Moretti S, Nieuweboer-Krobotova L, Olsson MJ, Parsad D, Passeron T, Tanew A, van der Veen W, van Geel N, Whitton M, Wolkerstorfer A, Picardo M, Vitiligo European Task Force (VETF); European Academy of Dermatology and Venereology (EADV); Union Europe'enne des Me'decins Spe'cialistes (UEMS). Guidelines for the management of vitiligo: the European Dermatology Forum consensus. Br J Dermatol. 2013;168(1):5–19. https://doi.org/10.1111/j.1365-2133.2012.11197.x. Epub 2012 Nov 2
15. Bassiouny D, Hegazy R, Esmat S, Gawdat HI, Ahmed Ezzat M, Tawfik HA, Hegazy AA, Ibrahim S. Cosmetic camouflage as an adjuvant to vitiligo therapies: effect on quality of life. J Cosmet Dermatol. 2021;20(1):159–65.
16. Derbyshire E. Innovations in skin camouflaging techniques: where are we scientifically? Int J Cosmet Sci. 2019;41:526–33.
17. Gawkrodger DJ, Ormerod AD, Shaw L, Mauri-Sole I, Whitton ME, Watts MJ, Anstey AV, Ingham J, Young K. Vitiligo: concise evidence based guidelines on diagnosis and management. Postgrad Med J. 2010;86(1018):466–71. https://doi.org/10.1136/pgmj.2009.093278.
18. Khullar G, Kanwar AJ, Singh S, Parsad D. Comparison of efficacy and safety profile of topical calcipotriol ointment in combination with NB-UVB vs. NB-UVB alone in the treatment of vitiligo: a 24-week prospective right-left comparative clinical trial. J Eur Acad Dermatol Venereol. 2015;29(5):925–32. https://doi.org/10.1111/jdv.12726. Epub 2014 Sep 15
19. Bae JM, Jeong KH, Choi CW, Park JH, Lee HJ, Kim HJ, Lee SH, Oh SH, Shin J, Kang HY, Lee WJ, Ju HJ, Kim DH, Chang SE, Lee DY, Kim YC, Choi GS, Kim KH, Kim TH, Lee SC, Lee AY, Hann SK, Lee MH, Park CJ. Development of evidence-based consensus on critical issues in the management of patients with vitiligo: a modified Delphi study. Photodermatol

Photoimmunol Photomed. 2021;37(1):3–11. https://doi.org/10.1111/phpp.12598. Epub 2020 Sep 10. PMID: 32910540
20. Mohammad TF, Al-Jamal M, Hamzavi IH, Harris JE, Leone G, Cabrera R, Lim HW, Pandya AG, Esmat SM. The vitiligo working group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo. J Am Acad Dermatol. 2017;76(5):879–88. https://doi.org/10.1016/j.jaad.2016.12.041. Epub 2017 Feb 16
21. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. J Am Acad Dermatol. 2017;77(4):675–682.e1. https://doi.org/10.1016/j.jaad.2017.05.043. Epub 2017 Aug 18
22. Harris JE, Rashighi M, Nguyen N, Jabbari A, Ulerio G, Clynes R, Christiano AM, Mackay-Wiggan J. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). J Am Acad Dermatol. 2016;74(2):370–1. https://doi.org/10.1016/j.jaad.2015.09.073. Epub 2015 Dec 11
23. Rosmarin D, Pandya AG, Lebwohl M, Grimes P, Hamzavi I, Gottlieb AB, Butler K, Kuo F, Sun K, Ji T, Howell MD, Harris JE. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. Lancet. 2020;396(10244):110–20. https://doi.org/10.1016/S0140-6736(20)30609-7.
24. Relke N, Gooderham M. The use of janus kinase inhibitors in vitiligo: a review of the literature. J Cutan Med Surg. 2019;23(3):298–306. https://doi.org/10.1177/1203475419833609. Epub 2019 Mar 22
25. Phan K, Phan S, Shumack S, Gupta M. Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and meta-analysis. J Dermatolog Treat. 2020;2:1–5. https://doi.org/10.1080/09546634.2020.1735615. Epub ahead of print
26. Passeron T. First step in a new era for treatment of patients with vitiligo. Lancet. 2020;396(10244):74–5. https://doi.org/10.1016/S0140-6736(20)30747-9.
27. Wang G, Qiu D, Yang H, Liu W. The prevalence and odds of depression in patients with vitiligo: a meta-analysis. J Eur Acad Dermatol Venereol. 2018;32(8):1343–51.
28. Borimnejad L, Parsa Yekta Z, Nikbakht-Nasrabadi A, Firooz A. Quality of life with vitiligo: comparison of male and female muslim patients in Iran. Gend Med. 2006;3(2):124–30.
29. Osinubi O, Grainge MJ, Hong L, Ahmed A, Batchelor JM, Grindlay D, Thompson AR, Ratib S. The prevalence of psychological comorbidity in people with vitiligo: a systematic review and meta-analysis. Br J Dermatol. 2018;178(4):863–78. https://doi.org/10.1111/bjd.16049. Epub 2018 Feb 7
30. Ogbechie-Godec OA, Elbuluk N. Melasma: an up-to-date comprehensive review. Dermatol Ther (Heidelb). 2017;7(3):305–18.
31. Chung BY, Noh TK, Yang SH, Kim IH, Lee MW, Yoon TJ, Chang SE. Gene expression profiling in melasma in Korean women. Dermatology. 2014;229(4):333–42.
32. Gopichandani K, Arora P, et al. Hormonal profile of melasma in Indian females. Pigment Int. 2015;2:85–90.
33. Adalatkhah H, Amani F. The correlation between melasma, ovarian cysts and androgenic hormones (a case-control study). Res J Biol Sci. 2007;2:593–6.
34. Bolanca I, Bolanca Z, Kuna K, Vuković A, Tuckar N, Herman R, Grubisić G. Chloasma--the mask of pregnancy. Coll Antropol. 2008;32(Suppl 2):139–41.
35. Snyder A, Schiechert RA, Zaiac MN. Melasma associated with topical estrogen cream. J Clin Aesthet Dermatol. 2017;10(2):57–8.
36. Kwon SH, Na JI, Choi JY, Park KC. Melasma: updates and perspectives. Exp Dermatol. 2019;28(6):704–8.
37. Abdel Hay R, Mohammed FN, Sayed KS, Abd El Fattah NA, Ibrahim S. Dermoscopy as a useful tool for evaluating melasma and assessing the response to 1064-nm Q-switched Nd:YAG laser. Dermatol Ther. 2020;33(4):e13629. https://doi.org/10.1111/dth.13629. Epub 2020 Jun 13
38. Neema S, Chatterjee M. Dermoscopic characteristics of Melasma in Indians: a cross-sectional study. Int J Dermoscop. 2017;1(1):6–10.

39. Sarkar R, Gokhale N, Godse K, Ailawadi P, Arya L, Sarma N, Torsekar RG, Somani VK, Arora P, Majid I, Ravichandran G, Singh M, Aurangabadkar S, Arsiwala S, Sonthalia S, Salim T, Shah S. Medical management of melasma: a review with consensus recommendations by indian pigmentary expert group. Indian J Dermatol. 2017;62(6):558–77. https://doi.org/10.4103/ijd.IJD_489_17.
40. Kaur A, Bhalla M, Sarkar R. Tranexamic acid in melasma:a review. Pigment Int. 2020;7:12–25.
41. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efficacy and safety of tranexamic acid in Melasma: a meta-analysis and systematic review. Acta Derm Venereol. 2017;97(7):776–81. https://doi.org/10.2340/00015555-2668.
42. McKesey J, Tovar-Garza A, Pandya AG. Melasma treatment: an evidence-based review. Am J Clin Dermatol. 2020;21(2):173–225. https://doi.org/10.1007/s40257-019-00488-w.
43. Sarkar R, Arsiwala S, Dubey N, Sonthalia S, Das A, Arya L, Gokhale N, Torsekar RG, Somani VK, Majid I, Godse K, Ravichandran G, Singh M, Aurangabadkar S, Salim T, Shah S, Sinha S. Chemical peels in melasma: a review with consensus recommendations by indian pigmentary expert group. Indian J Dermatol. 2017;62(6):578–84. https://doi.org/10.4103/ijd.IJD_490_17.
44. Kartha NS, Kunjukunju BP. A clinic epidemiological study of periocular hyperpigmentation. J Evolution Med Dent Sci. 2020;9(09):687–91.
45. Goodman RM, Belcher RW, Periorbital hyperpigmentation. An overlooked genetic disorder of pigmentation. Arch Dermatol. 1969;100(2):169–74.
46. Malakar S, Lahiri K, Banerjee U, Mondal S, Sarangi S. Periorbital melanosis is an extension of pigmentary demarcation line-F on face. Indian J Dermatol Venereol Leprol. 2007;73(5):323–5. https://doi.org/10.4103/0378-6323.34009.
47. O'Mahony MM, Sladen C, Crone M, Banner E, Newton VL, Allen A, Bell M, Marlow I, Acevedo SF, Jiang LI. A validated photonumeric scale for infraorbital dark circles and its application in evaluating the efficacy of a cosmetic treatment product in a split-face randomized clinical trial. Int J Cosmet Sci. 2021;43(1):48–56.
48. Sarkar R, Das A. Periorbital hyperpigmentation: what lies beneath? Indian Dermatol Online J. 2018;9(4):229–30.
49. Ranu H, Thng S, Goh BK, Burger A, Goh CL. Periorbital hyperpigmentation in Asians: an epidemiologic study and a proposed classification. Dermatol Surg. 2011;37:1297–303.
50. Jage M, Mahajan S. Clinical and dermoscopic evaluation of periorbital hyperpigmentation. Indian J Dermatopathol Diagn Dermatol. 2018;5:42–7. Available from: https://www.ijdpdd.com/text.asp?2018/5/1/42/232952
51. Ramakrishnan S, Hegde SP, Shenoy MM, Pinto M, AA MI, Amin VB. A cross-sectional study on clinico-dermoscopic features of periorbital melanosis in a tertiary care hospital. J Cosmet Dermatol. 2021;20(9):2917–23. https://doi.org/10.1111/jocd.13979. Epub ahead of print
52. Robles-Méndez JC, Rizo-Frías P, Herz-Ruelas ME, Pandya AG, Ocampo CJ. Lichen planus pigmentosus and its variants: review and update. Int J Dermatol. 2018;57(5):505–14. https://doi.org/10.1111/ijd.13806. Epub 2017 Oct 26
53. Kumaran MS, Dabas G, Parsad D, Vinay K. Lichen planus pigmentosus - an appraisal. Int J Dermatol. 2018;57(6):748–50. https://doi.org/10.1111/ijd.13982. Epub 2018 Apr 6
54. Feng H, Gutierrez D, Rothman L, Meehan S, Sicco KL. Lichen planus pigmentosus. Dermatol Online J. 2018;24(12):13030/qt0wz1v2kd.
55. Vinay K, Bishnoi A, Parsad D, et al. Dermatoscopic evaluation and histopathological correlation of acquired dermal macular hyperpigmentation. Int J Dermatol. 2017;56:1395–9.
56. Badyal R, Kushwaha RK, Rajput AS, Jain SK, Nyati A, Yadav D. A clinicoepidemological study of lichen planus pigmentosus and its association with metabolic syndrome and cutaneous manifestations in Indian population. Pigment Int. 2020;7:26–31.
57. Sharma VK, Gupta V, Pahadiya P, Vedi KK, Arava S, Ramam M. Dermoscopy and patch testing in patients with lichen planus pigmentosus on face: a cross-sectional observational study in fifty Indian patients. Indian J Dermatol Venereol Leprol. 2017;83(6):656–62. https://doi.org/10.4103/ijdvl.IJDVL_469_16.

58. Wu A, Vaidya S. Literature review of treatment outcomes for lichen planus Pigmentosus, erythema Dyschromicum Perstans, and ashy dermatosis. J Cutan Med Surg. 2018;22(6):643–5. https://doi.org/10.1177/1203475418782132.
59. Al-Mutairi N, El-Khalawany M. Clinicopathological characteristics of lichen planus pigmentosus and its response to tacrolimus ointment: an open label, non-randomized, prospective study. J Eur Acad Dermatol Venereol. 2010;24:535–40.
60. Wu CY, Lin FL. A successful combination therapy of tacrolimus, hydroxychloroquine and picosecond laser for lichen planus pigmentosus. Australas J Dermatol. 2019;60(4):e336–7. https://doi.org/10.1111/ajd.13060. Epub 2019 Apr 22
61. Sindhura KB, Vinay K, Kumaran MS, Saikia UN, Parsad D. Lichen planus pigmentosus: a retrospective clinico-epidemiologic study with emphasis on the rare follicular variant. J Eur Acad Dermatol Venereol. 2016;30:e142–4.
62. Verma P, Pandhi D. Topical tacrolimus and oral dapsone combination regimen in lichen planus pigmentosus. Skinmed. 2015;13:351–4.
63. Muthu SK, Narang T, Saikia UN, Kanwar AJ, Parsad D, Dogra S. Low-dose oral isotretinoin therapy in lichen planus pigmentosus: an open-label non-randomized prospective pilot study. Int J Dermatol. 2016;55(9):1048–54. https://doi.org/10.1111/ijd.13293. Epub 2016 Apr 7
64. Zenjari L, Elfetoiki FZ, Hali F, Skalli H, Chiheb S. Acide tranexamique oral dans le traitement du lichen pigmentogène [Oral tranexamic acid in the treatment of lichen planus pigmentosus: A prospective study of 20 cases]. Ann Dermatol Venereol. 2020;147(12):818–22. https://doi.org/10.1016/j.annder.2020.06.017. Epub 2020 Jul 31
65. Sonthalia S, Vedamurthy M, Thomas M, Goldust M, Jha AK, Srivastava S, Aggarwal I. Modified phenol peels for treatment-refractory hyperpigmentation of lichen planus pigmentosus: a retrospective clinico-dermoscopic analysis. J Cosmet Dermatol. 2019; https://doi.org/10.1111/jocd.12862. Epub ahead of print
66. Osmundsen PE. Pigmented contact dermatitis. Br J Dermatol. 1970;83:296–301.
67. Nakayama H, Harada R, Toda M. Pigmented cosmetic dermatitis. Int J Dermatol. 1976;15(9):673–5. https://doi.org/10.1111/j.1365-4362.1976.tb01825.x.
68. Kumarasinghe SPW, Pandya A, Chandran V, Rodrigues M, Dlova NC, Kang HY, Ramam M, Dayrit JF, Goh BK, Parsad D. A global consensus statement on ashy dermatosis, erythema dyschromicum perstans, lichen planus pigmentosus, idiopathic eruptive macular pigmentation, and Riehl's melanosis. Int J Dermatol. 2019;58(3):263–72. https://doi.org/10.1111/ijd.14189. Epub 2018 Sep 3
69. Nath AK, Thappa DM. Kumkum-induced dermatitis: an analysis of 46 cases. Clin Exp Dermatol. 2007;32(4):385–7. https://doi.org/10.1111/j.1365-2230.2007.02422.x. Epub 2007 Apr 8
70. Papa CM, Kligman AM. The behavior of melanocytes in inflammation. J Invest Dermatol. 1965;45:465–73.
71. Nagao S, Iijima S. Light and electron microscopic study of Riehl's melanosis. Possible mode of its pigmentary incontinence. J CutanPathol. 1974;1:165–75.
72. Bishnoi A, Vinay K, Arshdeep PD, Handa S, Saikia UN, Sendhil KM. Contact sensitization to hair colours in acquired dermal macular hyperpigmentation: results from a patch and photopatch test study of 108 patients. J Eur Acad Dermatol Venereol. 2019;33(7):1349–57. https://doi.org/10.1111/jdv.15576. Epub 2019 Apr 3
73. Shenoi SD, Rao R. Pigmented contact dermatitis. Indian J Dermatol Venereol Leprol. 2007;73:285–7.
74. Neema S, Chatterjee M. Nonmelanoma facial melanoses. In: Chatterjee M, Neema S, Malakar S, editors. Dermoscopy in darker skin. Delhi: Jaypee Publishers Pvt. Ltd.; 2017. p. 27–30.
75. Zaaroura H, Bergman R, Nevet MJ. Pigmented facial contact dermatitis to benzyl salicylate: a comparative histopathological and Immunohistochemical study of the involved skin and the positive patch test site. Am J Dermatopathol. 2019;41(6):443–7. https://doi.org/10.1097/DAD.0000000000001258.

76. Samanta A, Agarwal K, Naskar BN, De A. The role of patch testing with indian cosmetic series in patients with facial pigmented contact dermatitis in India. Indian J Dermatol. 2021;66:81–6.
77. Trattner A, Hodak E, David M. Screening patch tests for pigmented contact dermatitis in Israel. Contact Dermatitis. 1999;40:155–7.
78. Ninomiya F, Nakayama H. Effects of allergen controlled cosmetics on hyperpigmented dermatitis. Aesthet Plast Surg. 1982;6(4):211–5. https://doi.org/10.1007/BF01570649.
79. Xu Z, Xing X, Zhang C, Chen L, Flora XL. A pilot study of oral tranexamic acid and glycyrrhizin compound in the treatment of recalcitrant Riehl's melanosis. J Cosmet Dermatol. 2019;18(1):286–92. https://doi.org/10.1111/jocd.12797. Epub 2018 Oct 19
80. Wang L, Wen X, Hao D, Li Y, Du D, Jiang X. Combination therapy with salicylic acid chemical peels, glycyrrhizin compound, and vitamin C for Riehl's amelanosis. J Cosmet Dermatol. 2020;19(6):1377–80. https://doi.org/10.1111/jocd.13153. Epub 2019 Sep 16
81. Kwon HH, Ohn J, Suh DH, Park HY, Choi SC, Jung JY, Kwon IH, Park GH. A pilot study for triple combination therapy with a low-fluence 1064 nm Q-switched Nd:YAG laser, hydroquinone cream and oral tranexamic acid for recalcitrant Riehl's melanosis. J Dermatolog Treat. 2017;28(2):155–9. https://doi.org/10.1080/09546634.2016.1187706. Epub 2016 Jun 27

Chapter 10
Eczemas in Women

Paula Carolina Luna and Maria Emilia Debernardi

10.1 Atopic Dermatitis (Atopic Eczema)

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory skin disease characterized by recurrent eczematous lesions and itch. Although it is more common in children, it can affect all ages. It has been described in all ethnicities. AD can cause an important psychosocial burden on patients and their families.

The prevalence of AD may differ among authors, but it has been referred to be 20% in children and 10% in adults of high-income countries [1, 2] or around 15–20% of children and 2–5% of adults [3]. Between 10 and 20% of patients suffer severe disease [4].

Data about gender differences are inconsistent. The prevalence of AD in childhood has been reported to be slightly higher in boys (8.7%) than in girls (5.6%) at <4 years old in the Netherlands [5]. A study in Japan has shown that after puberty, there was a slightly higher prevalence of AD in females (8.1%) than in men (5.7%) [6]. A study considering both Europe and the USA has also shown a higher prevalence in adolescent girls (8.01%) vs boys (6.04%) [7].

When evaluating the specific relation to gender, several authors have observed that AD prevalence tends to be equal between both sexes during the first years of life (up to 10 years old). At 18 years of age, the prevalence showed to be statistically significantly higher in girls, compared with boys [8, 9]. This tendency also is observed in other Th-2 shifted diseases, mainly asthma [10].

This slightly higher prevalence among females was confirmed in the Phase 3 ISAAC study, which evaluated more than one million children in two age groups. One group from 6 to 7 and the other from 13 to 14-year-old. Slightly higher rates of current eczema symptoms were found in girls compared to boys and was more

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Table 10.1 Effect of different sex hormones on skin barrier impairment and immune profile. Adapted from Kanda et al. [11].

Hormone	Th1	Th2	Th17	Treg	Skin barrier Impairment
Androgen	M −	M −	M −	M +	M +
Estrogen	D	S +	D	S +	S −
Progesterone	S −	S +	M −	S +	M +
DHEA	M +	M −	B	B	B
Total activity	M > F	M ≪ F	B	B	M ≫ F

Th1 T helper 1 cells, *Th2* T helper 2 cells, *Th17* T helper 17 cells, *Treg* regulatory T cells. *M* Moderate suppression, *S* strong suppression, *M* moderate stimulation, *S* strong stimulation, *B* ambiguous, *D* effect dependent on tissue concentration or context, *M−* moderate reduction, *M+* moderate elevantion

noticeable in the older age group [1]. Nevertheless, these findings vary greatly across different studies.

It has been suggested that the skin barrier and/or the immune response in childhood might be less susceptible to the influence of sex hormones compared to those in adolescence or adulthood (Table 10.1) [11]. These findings suggest that progesterone and/or estrogen may be the reason for preponderance of dermatitis in females.

A higher incidence of intrinsic AD with enhanced Th1 activity as well as of nickel allergy and without increased serum IgE values or filaggrin mutation [14] in women exists in all generations. Worsening of AD before menstruation has been frequently reported.

Th2 and Tregs activities are enhanced by estrogen and progesterone, while Th1 and Th17 activities are suppressed by these hormones, to prepare the female body not to reject the allogeneic fetus during pregnancy [12]. On the other hand, androgens such as testosterone or dihydrotestosterone (DHT) downregulate Th1, Th2, and Th17 activities while inducing Treg activity thus they are mostly immunosuppressive. The magnitude of stimulation or suppression by female hormones is mostly higher than that by male hormones [13]. During adolescence and adulthood, Th1 activities are lower in women than in men with much lower Th2 activities in men than in women [13]. Differences in Th17 or Treg activities in men and women are ambiguous. The adrenal cortex produces dehydroepiandrosterone (DHEA) that enhances Th1 responses shifting the balance towards Th1-dominant immunity [15]. Amounts of steroid sulfatase converting dehydroepiandrosterone sulfate (DHEAS) to active DHEA are higher in females making them more susceptible to the influence of DHEA than males [16]. The influence of sexual hormones on IL-22 produced by Th22 cells has not been yet evaluated.

The course of AD can range from early transient to chronic persistent and from rapidly relapsing–remitting AD to long periods of remission followed by recurrence [17, 18]. Although most patients first develop AD during their early childhood that resolves in early life, some adult patients may also have AD either as persistent or new-onset disease.

Being a female, together with a history of atopy, a low socioeconomic status, nonwhite ethnicity, and young age of onset were shown to be significant predictors

of "persistently active" subgroup according to a meta-analysis by Abuabara et al. [19].

Advances in the knowledge of AD have shown that it involves several factors such as epidermal barrier disfunction, unbalanced skin microbiome and immune dysregulation favoring type-2 activity. Most of these aspects might be due to genetic predisposition [20]. At present the strongest genetic risk factor for AD is associated with mutations in the FLG gene that encodes the skin barrier protein filaggrin [21, 22]. This loss-of-function mutations only affects around 20–40% of patients with AD, which implies there are many other genes responsible for this condition.

Asthma, allergic rhinitis, and food allergies, are more frequent type 2 comorbidities in AD. Other non–type 2 comorbidities such different types of health and psychosocial involvement and different type of infections are also more frequent in these patients [23].

Exclusive and prolonged breastfeeding, antigen avoidance diets during pregnancy and lactation, and specific cow's milk hydrolysates have shown conflicting results when evaluating their effect in primary prevention of AD [24, 25], that is, prevention of development of AD in a high-risk newborn.

Clinical manifestations of AD are mostly similar in males and females. Xerosis, eczema, fissures, oozing, crusting, scaling, lichenification, pruritus, and pain show no predilection for both sexes, but the distribution of lesions is dependent of the age of the patient. Infantile eczema usually affects the face and scalp first spreading to symmetrically involve the trunk and the extensor surface of the limbs. In children, AD tends to be distributed mainly in a flexural pattern (affecting more commonly the antecubital, popliteal, and neck area). The face, hands, wrists, back, and dorsal feet tend to be affected after puberty (Figs. 10.1 and 10.2).

Female patients might be at a higher risk of developing atopic lesions in some areas such as vulva and nipple (Fig. 10.3).

Vulvar itch might be due to great number of conditions, being the most common noninfectious causes AD and contact dermatitis both irritant (ICD) and allergic (ACD). ICD is responsible of up to 50% of cases of chronic cases in adult women [26] while in prepubertal girls both AD and ICD are the most common vulvar disorders [27]. It is very important to be able to identify the underlying condition appropriately to deliver the correct treatment and improve the patient's quality of life and save costs.

AD is the most common dermatoses of pregnancy, with an incidence of 36% to 49% of all gestational dermatoses [28]. AD can be triggered by pregnancy. To prevent fetal rejection, during pregnancy the balance between Th1 and Th2 cytokine response is altered with a decrease in Th1 and an increase in Th2 response and a reduction in the maternal cell-mediated immune function. All these physiological responses to pregnancy are thought to explain the worsening of AD severity during this period [29] (Fig. 10.4).

AD diagnosis is relatively straightforward and mainly clinical [30]. Different diagnostic criteria have been developed. Epidemiological studies in children use mainly the UK Working Party criteria [31], while others, such as the Hanifin and

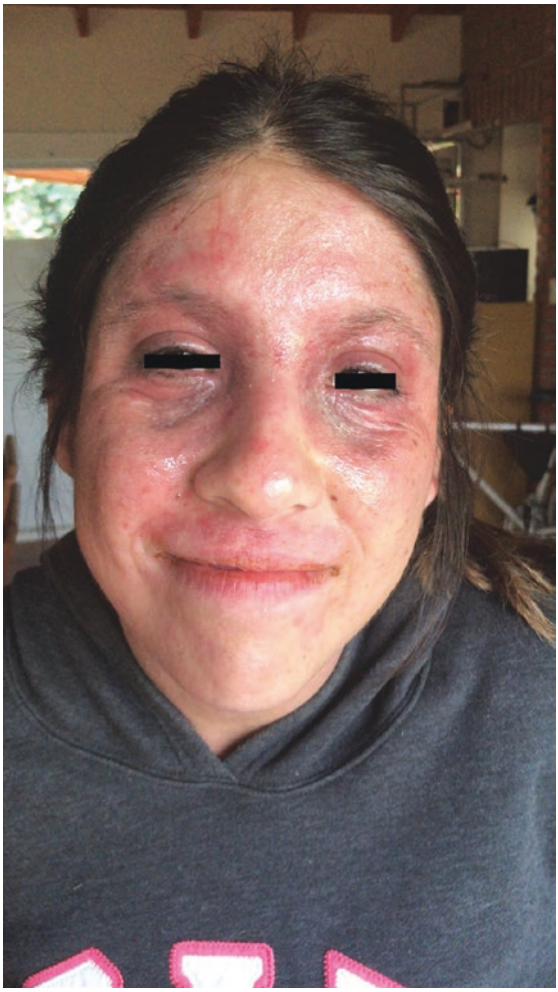

Fig. 10.1 AD affecting facial area in a young patient

Rajka criteria [32] and its simplified version the AAD criteria (a simpler version of the latter) [33] are frequently used in clinical evaluations. All criteria include the main 3 features of the disease: eczematous lesions, pruritus, and a chronic or relapsing course (Table 10.2) [34].

Clinical assessment is the basis to characterize the severity of AD and to evaluate therapeutic outcomes. Objective signs and subjective symptoms are taken into consideration when evaluating the overall disease severity via a physician evaluation and the recollection of patient-reported manifestations and QoL outcomes. The most worldwide used tools for evaluating severity include Eczema Area and Severity Index (EASI); Body Surface Area (BSA); SCORing Atopic Dermatitis (SCORAD) which apart from the physician's perspective includes two cardinal symptoms such as pruritus and sleep disturbances; Physician Global Assessment (PGA); and from

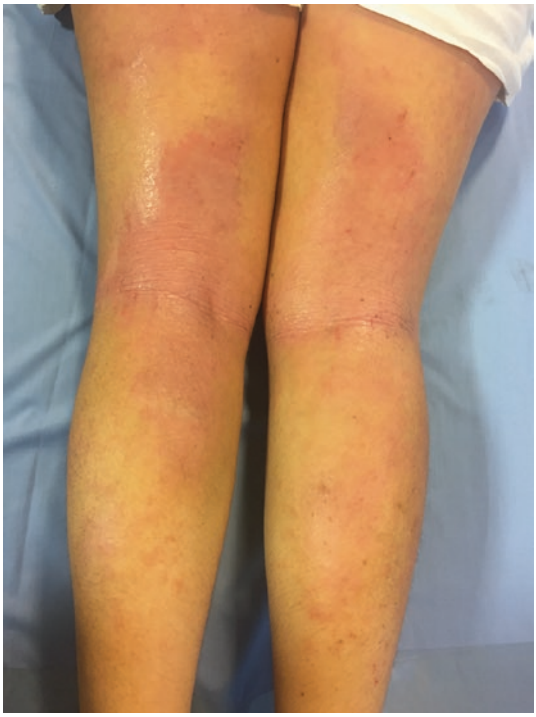

Fig. 10.2 AD with a typical distribution over popliteal area

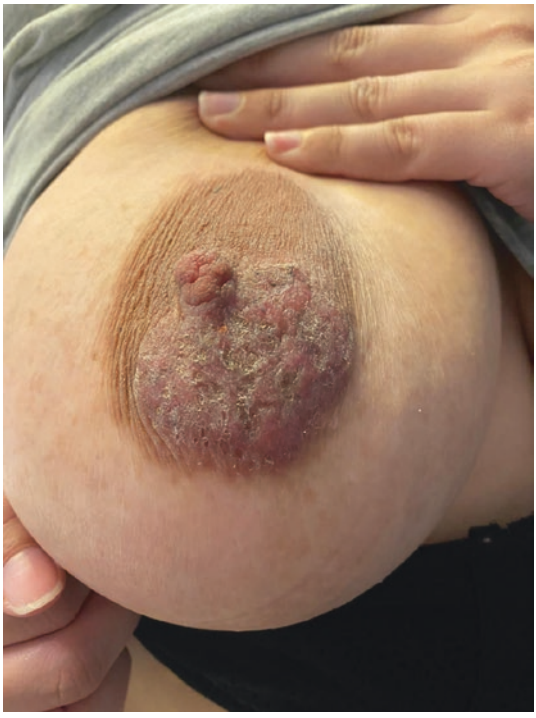

Fig. 10.3 Nipple eczema on a female patient with AD

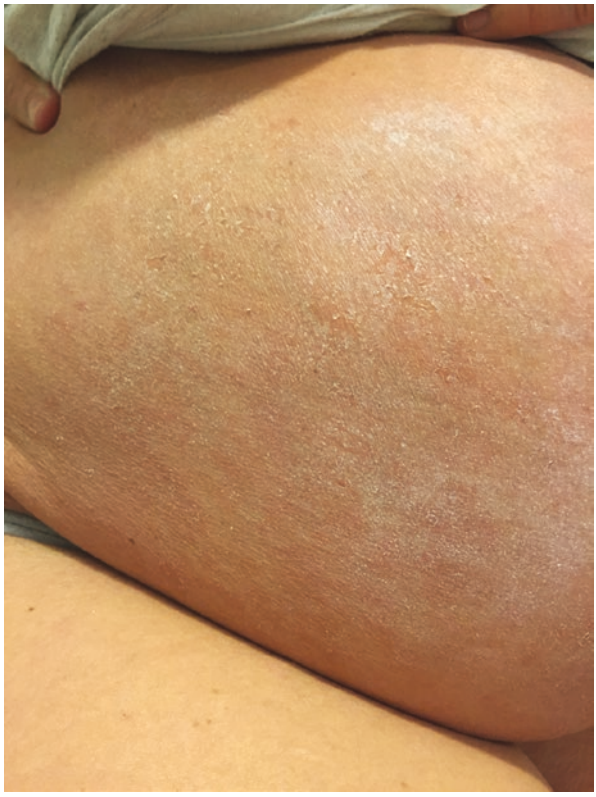

Fig. 10.4 AD of pregnancy. Patient with a history of mild AD showing worsening during pregnancy

a patient's perspective; Dermatology Life Quality Index (DLQI); and pruritus Numerical Rating Scale (NRS).

Long-term disease control is the main objective in the treatment of AD. Strategies should be built considering each individual patient and include skin barrier restoration using moisturizer and avoidance of individual trigger factors (Fig. 10.5) [35].

Regular use of moisturizers improves barrier function, increase hydration, reduce xerosis, itch, and flares, apart from reducing the need for topical steroid application [36].

Emollients are topical formulations lacking active ingredients. Emollients usually contain a humectant such as urea or glycerol, that promotes the hydration of the stratum corneum together with substances that reduce evaporation, known as occludents (e.g., petrolatum). Topical formulations with nonactive (vehicle-type) ingredients and additional actives, nonmedicated substances, are known as "emollients plus." Among these active substances we can mention, for example, bacterial lysates from *Vitreoscilla filiformis* or *Aquaphilus dolomiae* that have shown to improve AD lesions and help balance the skin microbiome of AD patients [35, 37].

Table 10.2 Features to be considered for the diagnosis of AD [34]

ESSENTIAL FEATURES	IMPORTANT FEATURES	ASSOCIATED FEATURES
(Must be present): • **Pruritus** • **Eczema (acute, subacute, chronic)** • **Typical morphology and age-specific patterns*** • **Chronic or relapsing history** **Patterns include:* 1. Facial, neck, and extensor involvement in infants and children 2. Current or previous flexural lesions in any age group 3. Sparing of the groin and axillary regions	(Seen in most cases, adding support to the diagnosis): • **Early age of onset** • **Atopy** **- Personal and/or family history** **- Immunoglobulin E reactivity** • **Xerosis**	(Suggest the diagnosis of AD but are too nonspecific): • **Atypical vascular responses (facial pallor, white dermographism, delayed blanch response)** • **Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis** • **Ocular/periorbital changes** • **Other regional findings (perioral changes/periauricular lesions)** • **Perifollicular accentuation/ lichenification/prurigo lesions**

EXCLUSIONARY CONDITIONS (Diagnosis of AD depends on excluding conditions):
• **Scabies** • **Seborrheic dermatitis** • **Contact dermatitis (irritant or allergic)** • **Ichthyoses** • **Cutaneous T-cell lymphoma** • **Psoriasis** • **Photosensitivity dermatoses** • **Immune deficiency diseases** • **Erythroderma of other causes**

All patients should be prescribed adequate amounts of emollients. Adult patients require a minimum of 250 g per week, that should be used as needed, at least once a day [35].

All patients should use emollients as a background therapy. Given they do not have active compounds, they can be freely used at any age and sex (even in pregnant women). Emollient use over inflamed areas should be avoided given the fact that they are usually poorly tolerated; individual acute lesions should be then treated with an active compound and emollients applied avoiding these lesions [35].

Topical corticosteroids (TCS) are the first-line anti-inflammatory treatment for AD.

When choosing a TCS, several factors should be considered including potency, vehicle, patient age, and body area to treat. Another factor to consider is that pregnant women (Fig. 10.6) should only use less than 200 g/month of Class II/II TCS (avoiding Fluticasone propionate) and only use class IV TCS as rescue treatment [38]. They are usually well tolerated and, if used accordingly, have a very good safety profile. The possibility of a wrong use of these compounds should be always considered and patients and caregivers should be trained in their correct use.

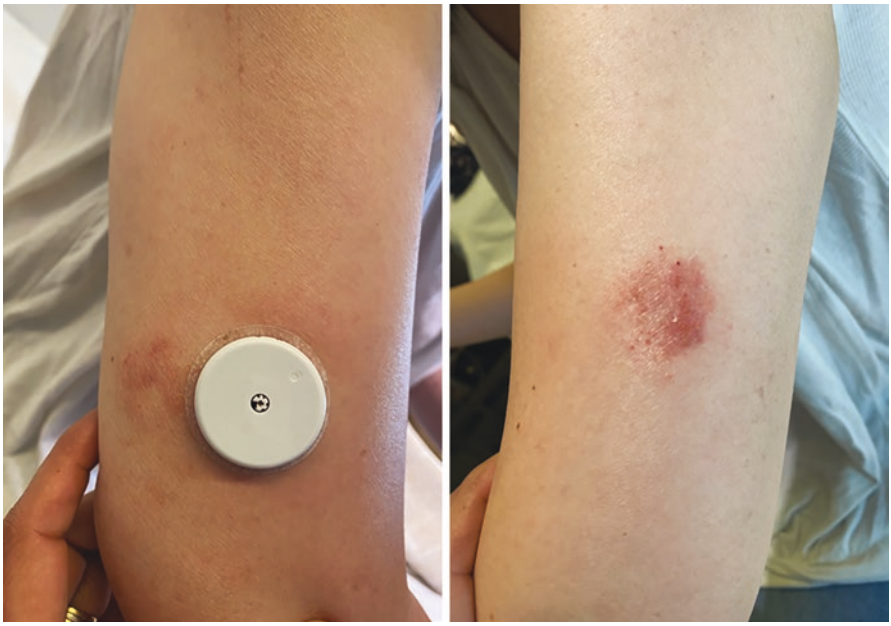

Fig. 10.5 Allergic contact dermatitis secondary to a glucose sensor in a type 1 diabetes patient

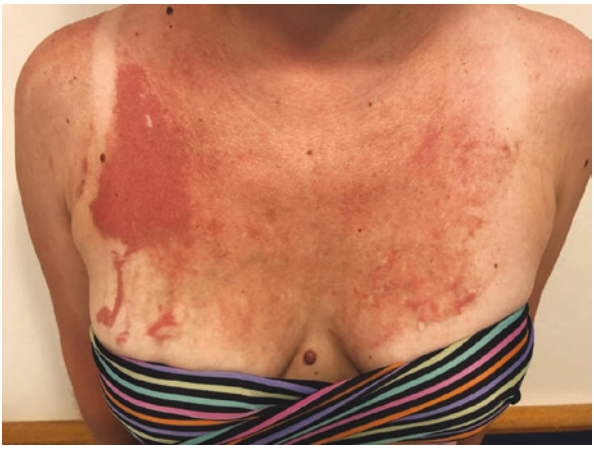

Fig. 10.6 Berloque dermatitis due to perfume and sun exposure in a female patient

It is advisable to explain the patient about the correct amount of TCS to be applied. It is useful to follow the fingertip unit rule. A fingertip unit (FTU) refers to the amount of substance expelled from a 5-mm-diameter nozzle tube applied from the tip of the index finger to the distal skin crease. Two adult palms correspond to a FTU, which represents 2% of an adult body surface area [39].

Tacrolimus ointment and pimecrolimus cream, are both topical calcineurin inhibitors (TCI) that have been specifically approved for the treatment of AD. They

have shown effectiveness and safety in treating AD but are not as potent as TCS [40, 41]. TCI safety profile has shown to not produce skin atrophy, glaucoma or cataract, therefore they are recommended for areas of sensitive skin (periocular, genitals, and intertriginous areas) and specially as a proactive treatment in those patients with frequent flareups [35]. A transient heat, tingling, or burning sensation at the application site that tends to disappear within a few days has been described as the most bothersome side effect of TCI. No restrictions for its use have been reported in pregnant women.

Crisaborole is the first topical phosphodiesterase (PDE4) inhibitor that has been approved for AD. No data specifically regarding the use of crisaborole in preconceptive women or during pregnancy has been published yet and the rate of excretion into breast milk or the effect of crisaborole on the breastfeeding baby has not yet been studied either. So, until it is correctly studied, crisaborole is not recommended in preconceptive, pregnant, or breastfeeding women [42].

The classical approach to topical treatment, known as "reactive treatment," has been to apply it only to lesional skin and either stop it or taper it down once eczemas had healed. There are some other alternatives, such as the "proactive treatment," that consists of the use of a long-term anti-inflammatory treatment after an initial remission of the lesions, applied usually twice a week to previously affected areas of skin, in combination with liberal use of emollients on the entire body. The duration of this approach will depend on the severity and persistence of the disease [35].

Phototherapy is an alternative treatment when topicals alone fail to control AD. Ultraviolet light has a local immunosuppressive and anti-inflammatory effect on the skin. The most effective type of phototherapy for AD are narrow-band ultraviolet B (NB-UVB) and medium-dose ultraviolet A1 (UVA1). Phototherapy has shown to be both effective and safe and it might be considered as the treatment of choice in patients with moderate to severe disease that also have an impaired immunity or other comorbid conditions where systemic immunosuppressants are contraindicated. For these reasons, phototherapy might be particularly useful in pregnant or lactating women. The main limiting factor for its use is the need for frequent sessions (3 to 5 times per week) in a specialized center for 2 to 3 months. Apart from this limitation, the long-term use of UVA1 might pose a higher risk of photodamage, skin carcinogenesis, and melanoma induction, but this risk in minimal with the standard dose [35].

When the use of topical treatments and UV light therapy are not effective enough to control the disease or there is a contraindication for its use, systemic therapy should be considered. Immunosuppressives such as methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil are the most frequently used conventional systemic treatments [35]. Other newer treatments such as dupilumab and Jak inhibitors, are other alternatives for patients with moderate to severe disease.

Oral or parenteral corticosteroids should not be used except there are no other available treatments, for short periods of time, during a flare or when starting a systemic treatment that has some latency in the onset of action. Its use is specially discouraged during pregnancy.

Cyclosporine is the only classic immunosuppressive that has been specifically approved for the treatment of AD in several countries. It is highly effective with a mean improvement of clinical severity scores of 55% from baseline after 6–8 weeks of treatment [43] and has the extra benefit of a rapid onset of action. Its main adverse effects are renal toxicity, risk of arterial hypertension and cumulative risk of malignancy. For this reason, most guidelines recommend limiting its use to less than 1–2 years. Although not specifically approved, cyclosporine can be used during pregnancy and lactation, although breast secretion of cyclosporine has been confirmed [44]. During pregnancy, a strict maternal control, especially of arterial hypertension, should be performed.

Methotrexate and azathioprine appear to be effective and safe off-label treatments for severe AD, even in children. They have a slow onset of action, with maximum benefits appearing after 4–8 weeks for azathioprine and 8–12 weeks for methotrexate. With the correct monitoring, both drugs can be used for prolonged periods of time. Methotrexate is contraindicated during pregnancy and lactation due to its potentially teratogenic effect, using a "safety first" criteria methotrexate should be stopped at least six months before pregnancy [42].

Dupilumab is the first biologic treatment approved for managing moderate-to-severe AD (it was originally approved for adults, but it's use has expanded to children too). Dupilumab is a human monoclonal antibody of the IgG 4 subclass that inhibits the signaling of interleukin (IL)-4 and IL-13, key cytokines in the pathophysiology of AD. As it is a biologic, dupilumab is applied subcutaneously every 2 weeks and has shown to be both effective and safe in the management of AD. The most common side effect of dupilumab is injection site reaction, and the most specific side effect is conjunctivitis [20, 45]. The European Summary of Product Characteristics (SmPC) states "dupilumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." Recent case reports of the use of dupilumab during pregnancy in patients after weighting risk–benefit ratio have been published [29, 46]. Data about safety of breastfeeding while on dupilumab are lacking. Breastfeeding by mothers treated with other biologics (TNF-α inhibitors, IL 12/23, and IL 17 inhibitors) is considered safe because of low amounts of the medication in breast milk and further protein degradation by the infant's gastric acid, but no specific studies have been done with dupilumab [46–49].

More than half of adult patients have a moderate to severe disease which needs to be approached with more than just topicals. Patients are many times undertreated for many reasons, which might be especially true in women with childbearing potential due to the fear of potentially affecting the fetus with the different treatments without considering the burden of chronic inflammation in the patient and in the outcome of the potential pregnancy.

Little is known about the risk of prenatal, obstetric and birth complications in mothers with AD, as well as about the specific treatment trends in these patients. A large cohort study of 10,441 mother–child binomial were retrospectively identified through the Danish Medical Birth Registry and matched 1:1 with non-AD pairs. Although the study is retrospective and does not consider maternal disease severity, they conclude that the presence of maternal AD was positively associated with

premature rupture of membranes [1.15 (1.05–1.27)] and staphylococcal neonatal septicemia [2.45 (1.33–4.49)]. They also found it was inverse association with gestational diabetes [OR 0.79, 95% CI (0.68–0.92)]. No associations were found with preeclampsia, prematurity, low or high birth weight, or neonatal Group B streptococcal septicaemia [48].

Some specific considerations should be taken when treating female patients. The main difference relies on the pregnancy status: patients with no risk of getting pregnant (premenarche, or under highly effective contraceptive measures), patients willing to get pregnant shortly (preconceptive), pregnant patients, or lactating patients. In patients with nonwillingness to get pregnant all treatments are nonrestricted (if there are no other contraindications).

Table 10.3 shows a summary of the recommendations from the European Task Force on Atopic Dermatitis (ETFAD) position paper for the treatment of parental atopic dermatitis during preconception, pregnancy, and lactation period [50]. These recommendations were given with the "safety-first" precept and that is why some of the statements are arguable. Considering that every year around 3% of pregnancies are stillbirths and 6% of babies are born with a congenital birth defect, malformations and stillbirths can happen even when using a drug that is considered safe during pregnancy in patients with AD and patients who are treated with a specific and "safe" drug. 5wq+s.

Although AD tends to worsen during pregnancy, the previous cited registry study involving 10,441 pregnancies evaluated the trends in use of treatments in pregnant AD patients and revealed a decreased use systemic treatments and TCI together with an increase in the use of TCS and ultraviolet light treatments, when comparing to previously to pregnancy. It has been suggested that this trend reflects a tendency of patients and treating doctors to be more cautious and have a more restricted approach to treatment during this period [48] (Table 10.4).

Table 10.3 Adapted from Wollenberg et al. [35]

SEVERE: SCORAD >50 or persistent disease	Hospitalizations, cyclosporine A, short course oral corticosteroids, dupilumab, methotrexate, azathioprine, mycophenolate mofetil, PUVA,
MODERATE: SCORAD 25-50 or recurrent disease	Proactive therapy with type II or III TCS, TCI, wet wrap therapy, UV therapy, psychologic counseling
MILD: SCORAD <25 or transient disease	Reactive therapy with type II TCS, TCI, antiseptics
ALL PATIENTS/ ALL THE TIME	Therapeutic education, emollients, bath oils, avoidance of individually confirmed relevant allergens

Table 10.4 Adapted from Vestergaard et al. [50]

Drug	Preconceptive Women	Pregnant women	Lactating women	Preconceptive Men
Topical corticosteroids	No restrictions	TCS class II/III are recommended If more than 200 g/month, consider Adding UV treatment Class IV may be used as rescue therapy, or over longer periods on limited skin areas Avoid fluticasone propionate	Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding	No restrictions
Topical calcineurin inhibitors	No restrictions	No restrictions	Apply immediately after breastfeeding; nipples should be cleaned correctly before every feeding	No restrictions
Topical PDE-4 inhibitors (Crisaborole)	Not recommended	Not recommended	Not recommended	No restrictions
UVB-NB	Yes	Yes	Yes	Yes
Cyclosporine A	May be used	May be used under strict control. Considered first-line therapy for long-term control	May be used under strict control	No restrictions
Azathioprine	May be used	May be used under strict indications if no other therapy is possible. It is not recommended to initiate therapy during pregnancy where other therapies should be used	May be used It is recommended to discard milk produced within 4 h after drug intake	No restrictions

Table 10.4 (continued)

Drug	Preconceptive Women	Pregnant women	Lactating women	Preconceptive Men
Methotrexate	When no local/national guideline exists follow a safety-first approach. Stop at least 6 months prior to desired time of conception. If local/national guideline exists follow those instead	Contraindicated	Contraindicated	Treatment must be stopped 3 months prior to desired time of conception
Mycophenolate mofetil	Therapy must be stopped 3 months prior to desired time of conception	Contraindicated	Contraindicated	Therapy must be stopped 3 months prior to desired time of conception
Systemic corticosteroids	May be used as rescue therapy, or as bridging until effect of other systemic or biological medicaments	May be used as rescue therapy, or for short periods of time (2–3 weeks), not exceeding 0.5 mg/kg/day. Prednisolone is the preferred drug	May be used as rescue therapy	No restrictions
Dupilumab	No restrictions	Not recommended as a first choice Not enough data available May be used after careful risk–benefit assessment	Not recommended as a first Not enough data available May be used after careful risk–benefit assessment	No restrictions

Although they are usually used in patients with AD, H1R antihistamines (both first- and second-generation) have no pathophysiologic background so they should be restricted for the treatment of pruritus if standard treatment with TCS and emollients is not sufficient [35].

10.2 Burden of Mothers of Children with AD

Having a child with AD is significantly associated with psychological distress, depression, and sleep disturbances [51]. Although the tendency is slowly changing, most home care tasks still mainly rely on the mothers, so they tend to be the more severely affected family member influenced by the burden of disease. For the first

decade of their children's, mothers are more likely to have both impaired sleep quality and difficulty falling asleep with a feeling of subjectively insufficient sleep, and an obvious increased daytime exhaustion. These sleep outcomes parallel the disease severity. The worst the severity, the worst the sleep quality. The implications of these findings affect not only the mothers QoL but given that maternal emotional and psychosocial well-being is linked to the child's health, development, and cognitive and social functioning, it once again, directly affects the child.

A caregiver who is chronically sleep-deprived, exhausted, and/or depressed is also less equipped to implement time-consuming treatment regimens, regulate their child's behavior, and help the child cope with their disease.

For this reason, family-oriented care should be provided, addressing the needs of the entire family and promoting family functioning to optimize child outcomes and the overall family health.

When caring for children with AD, (specially in severe patients) treating physicians should ask about the caregiver's well-being, sleep disturbances and fatigue and evaluate the possibility of offering psychosocial support not only for the patient but also for the caregiver [51].

10.3 Contact Dermatitis

Contact dermatitis (CD) is a very common inflammatory skin disorder produced after the contact of the skin with a physical or weak chemical agent. Around 95% of all occupational skin diseases fall into this category.

It can be classified as either irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD) depending on its pathophysiology, being ICD far more common. While ICD is an inflammatory reaction caused directly by the irritating substance and is not immunologically driven, ACD is a type IV-mediated hypersensitivity to a specific allergen, with its secondary inflammatory response with exposure [52]. It is sometimes hard to distinguish between these two types of CD.

10.4 Irritant Contact Dermatitis

Eighty percent of all patients with CD belong to the ICD group. This type of CD is due to the direct effect of the irritant on epidermis. As it is not an immune mediated type of CD prior sensitization is not required. Several factors depending on the patient such as previous history of atopy, age, sex, and certain body regions, may predispose to ICD. Factors depending on the irritant itself are also important (amount of exposure, concentration, duration, repetition, and the presence of overlying environmental and mechanical factors). Under certain circumstances, anyone can develop ICD after a sufficient exposure to an irritant.

Although ICD is nonimmunological in nature it might predispose the patient to ultimately develop contact sensitization to allergens and subsequently ACD [52].

We define irritant as a substance either physical or chemical that can potentially generate cellular damage after contacting the skin at high concentrations or for prolonged periods of time. Frequently described irritants may include animal products, cosmetics, degreasing agents, detergents, dusts, foods, friction, low humidity, metalworking fluids, solvents, tear gases, topical medications, and water and wet work.

There are two mechanisms of action by which an irritant can cause its damage. Either by its direct toxicity to epidermal keratinocytes (e.g., sodium lauryl sulfate) or disrupt the epithelial barrier by depleting its lipids (e.g., acetone) [53]. When this injury becomes chronic, due to repetitive exposure to an irritant not strong enough to produce a burn, it activates the innate immune response releasing several proinflammatory cytokines including IL-1α, IL-1β, TNF-α, GM-CSF, IL-6, and IL-8 from the keratinocytes [54]. In turn, these cytokines activate Langerhans cells, dermal dendritic cells, and endothelial cells that release chemokines which results in the recruitment of neutrophils, lymphocytes, macrophages, and mast cells to the epidermis which causes further inflammation.

ICD can be both acute and chronic. The latter is the most frequent and is due to the repetitive exposure to a weak irritant over long periods of time. Its clinical manifestation usually consists of dry, dull, red, scaly rash, and lichenified lesions [55].

Given the ICD lesions appear at the site of contact even after a single exposure to a strong irritant or after several contacts with a weak irritant, the distribution of the cutaneous lesions is the single most relevant clue when considering CD.

In some patients AD or ACD may coexist with ICD, given most patients with ACD and AD usually show a lower inflammatory threshold to the different irritants and are then prone to developing ICD.

Cutaneous lesions in ICD are well demarcated and limited to the area that has been in direct contact with the irritant. Itching is not usually the main symptom while other manifestations such as pain, burning or stinging are more common. ICD typically have onset of symptoms within minutes to hours of exposure to an irritant.

In contrast in ACD, although the lesions at the beginning might be well-demarcated, the reaction might exceed the site of contact.

ICD is usually and exclusion diagnosis when other type I and type IV hypersensitivity have been ruled out.

The adequate treatment of ICD is the identification and avoidance of the underlying cause. A healthy skin barrier also helps to prevent irritation, so moisturizers are also useful by increasing hydration and prevent trans epidermic water loss [56].

The use of TCS in these circumstances might be useful for treating the secondary inflammation although it is controversial apart from the exclusion of the irritant [52].

10.5 Allergic Contact Dermatitis

ACD is considered a common dermatosis with a reported prevalence of around 20% [57].

There are several risk factors for the development of ACD as not everyone will become sensitized after being exposed to an allergen. Main risk factors are personal or family history of AD or ACD and prior sensitization to another allergen.

There is a higher prevalence in women due to the higher incidence of early contact with nickel from jewelry as well as a higher contact with cosmetics [58, 59].

On some occasions ACD can be considered an occupational dermatosis. Some jobs such as hairdressers, health-care workers, food handlers, building and construction workers, and metal workers have an increased risk of developing ACD due to their frequent contact with common allergens.

As ACD is not immediate, a correct diagnosis is sometimes difficult. An extensive history should be performed when ACD is suspected interrogating about possible causes and frequently used substances. Hobbies, occupation, and introduction of new products in the daily care should always be considered. The behavior of the rash during vacations or weekends should also be considered.

The presentation of the rash may differ depending on its evolution. Acute lesions usually manifest as an acute eczema with erythema and vesicles and some severe patients might even develop true bullae. More chronic ACD manifests with signs of long-lasting inflammation, such as lichenification, scaling, and fissuring or erythema and scales. In between these two sides of the spectrum, we find subacute ACD, which may show an addition of both types of lesions.

When looking for clues for the diagnosis, certain distributions should call our attention. Lesions appearing over the eyelid, lateral face, central face, neck, or hands should make us consider ACD.

The gold standard for the diagnosis of ACD is patch testing (its complexity is beyond the scope of this chapter).

CD usually affects the hands. Most CD that affects the hands is ICD and typically involves the dorsal aspect of the hands and fingers. In a less extent CD can affect the palms (where the stratum corneum is thicker and more resistant to irritants) or the interdigital spaces, where irritants can get caught. ACD of the hand usually presents as well-demarcated plaques and vesicles involving the dorsal hands, fingers and wrists. A systemic contact dermatitis after the ingestion of certain foods containing metals to which the patient might be sensitized (e.g., nickel) can also manifest as a vesicular dermatitis.

The most important aspect of ACD treatment is the avoidance of the offending allergen. Because many agents are found in everyday products, avoidance can be difficult, even if the allergen has been identified.

To help patients with the avoidance in the everyday life, two databases with a list of different products that can replace those that contain the substance to which the patient has tested positive to. These databases are: The Contact Allergen Management Program *(https://www.contactderm.org/resources/acds-camp*) developed by the

American Contact Dermatitis Society and the Contact Allergen Replacement Database (*www.AllergyFreeSkin.com*).

Apart from avoidance, TCS can be used. For the nature of the reaction, they are even more useful in ACD than in ICD. In severe and generalized reactions, systemic corticosteroids may be needed. TCI should be used in chronic cases and over certain areas such as face, eyelid, and neck, and are the treatment of choice in patients allergic to TCS. Allergy to TCS has been described to affect 0.5% to 5.8% of patients [60].

Restoring the skin barrier is very important to minimize the possibility of recurrence and the risk of further sensitization.

In refractory cases, phototherapy can be considered and in severe patients systemic treatments such as methotrexate, cyclosporine, or dupilumab may be needed.

10.6 Photocontact Dermatitis

As with other contact dermatitis, photocontact dermatitis can be divided into allergic or irritant (phototoxic) dermatitis, most frequently being the latter.

Phytophotodermatitis is the prototype of phototoxic dermatitis. It is due to non–immunologically mediated inflammation, which develops after exposure to both furocoumarin-producing plants (e.g., limes, celery, figs, parsley, and parsnips) and UVA radiation [61, 62]. After coming in contact with the photosensitizer and the exposition to UVA radiation, the activated furocoumarin damages the DNA and membranes with the subsequent cell death and epidermal injury [63].

Lesional morphology is very evocative of this type of eruption: irregularly shaped well-demarcated patches with blisters/vesicles or plaques that are burning or painful and that can evolve into hyperpigmentation.

In women a very frequent type of phototoxic reaction is known as Berloque dermatitis, it is due to the contact of perfume or cosmetics and subsequent UV exposure. Lesions typically appear over the neck and chest and might be misdiagnosed with another dermatosis.

10.7 Drug Photosensitivity

The reaction elicited by a drug with the subsequent exposure to sunlight is known as drug-induced photosensitivity. Several drugs, including different classes of antimicrobials, (NSAIDs), agents for hypertension or arrythmias, and neuropsychiatric drugs have been implicated. Drug-induced photosensitivity can be divided into either phototoxic or photoallergic [64].

Analogous to ICD, in phototoxic reactions tissue is directly damaged by the activation of the drug by the UVR. This type of reaction typically begins minutes to hours after exposure to UVR manifesting similar to sunburn and is limited to the sun exposed skin. It does not require previous sensitization.

On the other hand, although photoallergic reactions are also due to the interaction of the sun and the UVR, they only occur after previous sensitization to the agent. They manifest as eczematous, pruritic lesions, not only confined to the areas previously exposed to the sun and develops 24–72 h after exposure.

10.8 Dyshidrotic Eczema

Dyshidrotic eczema (DE) or acute palmoplantar eczema is an intensely pruritic, vesiculobullous disorder of the palms and soles, which was originally thought to be related to the sweat glands, hence its denomination [65]. It is now considered a special type of eczema, with a pronounced spongiosis and accumulation of edema fluid in regions with a thick epidermis and an even thicker overlying horny layer with no relation to the sweat glands [66].

This type of eczema is more frequent in female than in males and it accounts for approximately 5–20% of the causes of hand eczema.

It typically presents as intensely pruritic vesicles over the lateral and dorsal aspect of fingers and toes, of abrupt onset. Lesions are deep-seated and can be true multilocular vesicles or coalesce into bullae.

The diagnosis of DE is usually clinic, and a biopsy is only required when treatments fail to succeed or in atypical cases. Spongiosis is the main pathologic finding. Although rare, secondary infection of the lesions may occur mainly due to scratching.

The definite cause of DE is yet to be elucidated, but several risk factors such as a history of AD, sensitization to allergens or contact with irritants, hyperhidrosis, and smoking have been described [67, 68].

The treatment of DE is focused on managing acute eruptions and in preventing further flares and is mainly dependent on disease severity [69].

Mild to moderate cases, with few lesions, mild erythema and slight pruritus with no significant pain or discomfort can be managed with TCS and/or TCI. When the disease is severe or disabling, systemic corticosteroids, immunosuppressants, retinoids, or phototherapy might be of help. As sweating has been shown to be an aggravating factor, botulinum toxin has shown to be an effective coadjuvant when managing vesiculation and erythema [70].

References

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC phase three. J Allergy Clin Immunol. 2009;124:1251–8. https://doi.org/10.1016/j.jaci.2009.10.009.
2. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132(5):1132–8. https://doi.org/10.1016/j.jaci.2013.08.031.

3. Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, et al. European task force on atopic dermatitis/EADV eczema task force. ETFAD/EADV eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. J Eur Acad Dermatol Venereol. 2016;30(5):729–47. https://doi.org/10.1111/jdv.13599. Epub 2016 Mar 23. PMID: 27004560
4. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy. 2018;73(6):1284–93. https://doi.org/10.1111/all.13401. Epub 2018 Feb 13. PMID: 29319189
5. Dirven-Meijer PC, Glazenburg EJ, Mulder PG, Oranje AP. Prevalence of atopic dermatitis in children younger than 4 years in a demarcated area in Central Netherlands: the west Veluwe study group. Br J Dermatol. 2008;158(4):846–7. https://doi.org/10.1111/j.1365-2133.2007.08407.x. Epub 2008 Jan 30. PMID: 18241282
6. Saeki H, Tsunemi Y, Fujita H, Kagami S, Sasaki K, Ohmatsu H, et al. Prevalence of atopic dermatitis determined by clinical examination in Japanese adults. J Dermatol. 2006;33(11):817–9. https://doi.org/10.1111/j.1346-8138.2006.00187.x. PMID: 17074002
7. Harrop J, Chinn S, Verlato G, Olivieri M, Norbäck D, Wjst M, et al. Eczema, atopy and allergen exposure in adults: a population-based study. Clin Exp Allergy. 2007;37(4):526–35. https://doi.org/10.1111/j.1365-2222.2007.02679.x. PMID: 17430349
8. Ziyab AH, Raza A, Karmaus W, Tongue N, Zhang H, Matthews S, Arshad SH, Roberts G. Trends in eczema in the first 18 years of life: results from the Isle of Wight 1989 birth cohort study. Clin Exp Allergy. 2010;40(12):1776–84. https://doi.org/10.1111/j.1365-2222.2010.03633.x.PMID: 21059120
9. Gough H, Grabenhenrich L, Reich A, Eckers N, Nitsche O, Schramm D, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr Allergy Immunol. 2015;26(5):431–7. https://doi.org/10.1111/pai.12410. PMID: 26011739; PMCID: PMC4744942
10. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy. 2008;63(11):1418–27. https://doi.org/10.1111/j.1398-9995.2008.01880.x. PMID: 18925878
11. Kanda N, Hoashi T, Saeki H. The roles of sex hormones in the course of atopic dermatitis. Int J Mol Sci. 2019;20(19):4660. https://doi.org/10.3390/ijms20194660. PMID: 31547021; PMCID: PMC6802354
12. Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev. 2012;11(6–7):A502–14. https://doi.org/10.1016/j.autrev.2011.12.003. Epub 2011 Dec 13. PMID: 22193289; PMCID: PMC3431799
13. Roved J, Westerdahl H, Hasselquist D. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. Horm Behav. 2017;88:95–105. https://doi.org/10.1016/j.yhbeh.2016.11.017. Epub 2016 Dec 9. PMID: 27956226
14. Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. J Dermatol Sci. 2010;58(1):1–7. https://doi.org/10.1016/j.jdermsci.2010.02.008. Epub 2010 Feb 16. PMID: 20207111
15. Solano ME, Sander VA, Ho H, Motta AB, Arck PC. Systemic inflammation, cellular influx and up-regulation of ovarian VCAM-1 expression in a mouse model of polycystic ovary syndrome (PCOS). J Reprod Immunol. 2011;92(1–2):33–44. https://doi.org/10.1016/j.jri.2011.09.003. Epub 2011 Oct 21. PMID: 22018827
16. Namazi MR. The Th1-promoting effects of dehydroepiandrosterone can provide an explanation for the stronger Th1-immune response of women. Iran J Allergy Asthma Immunol. 2009;8(1):65–9. PMID: 19279363
17. Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, Wijga AH, Henderson AJ, Koppelman GH, Brown SJ. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. J Allergy Clin Immunol. 2018;141(3):964–71. https://doi.org/10.1016/j.jaci.2017.09.044. Epub 2017 Nov 10. PMID: 29129583; PMCID: PMC5840507

18. Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrländer C, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. JAMA Pediatr. 2017;171(7):655–62. https://doi.org/10.1001/jamapediatrics.2017.0556. PMID: 28531273; PMCID: PMC5710337
19. Abuabara K, Hoffstad O, Troxel AB, Gelfand JM, McCulloch CE, Margolis DJ. Patterns and predictors of atopic dermatitis disease control past childhood: an observational cohort study. J Allergy Clin Immunol. 2018;141(2):778–780.e6. https://doi.org/10.1016/j.jaci.2017.05.031.
20. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. Nat Genet. 2015;47(12):1449–56. https://doi.org/10.1038/ng.3424. Epub 2015 Oct 19. PMID: 26482879; PMCID: PMC4753676
21. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38(4):441–6. https://doi.org/10.1038/ng1767. Epub 2006 Mar 19. PMID: 16550169
22. Rodríguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. J Allergy Clin Immunol. 2009;123(6):1361–70.e7. https://doi.org/10.1016/j.jaci.2009.03.036. PMID: 19501237
23. Williams HC, editor. Atopic dermatitis: the epidemiology, causes and prevention of atopic eczema. Cambridge: Cambridge University Press; 2000.
24. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. Br J Dermatol. 2009;161(2):373–83. https://doi.org/10.1111/j.1365-2133.2009.09049.x. Epub 2009 Feb 23. PMID: 19239469
25. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev. 2006;4:CD003664. https://doi.org/10.1002/14651858.CD003664.pub3. Update in: Cochrane Database Syst Rev. 2017 Mar 15;3:CD003664. PMID: 17054180
26. Farage MA, Miller KW, Ledger WJ. Determining the cause of vulvovaginal symptoms. Obstet Gynecol Surv. 2008;63(7):445–64. https://doi.org/10.1097/OGX.0b013e318172ee25. PMID: 18559121
27. Fischer G, Rogers M. Vulvar disease in children: a clinical audit of 130 cases. Pediatr Dermatol. 2000;17(1):1–6. https://doi.org/10.1046/j.1525-1470.2000.01701.x. PMID: 10720979
28. Babalola O, Strober BE. Treatment of atopic dermatitis in pregnancy. Dermatol Ther. 2013;26(4):293–301. https://doi.org/10.1111/dth.12074. PMID: 23914886
29. Kage P, Simon JC, Treudler R. A case of atopic eczema treated safely with dupilumab during pregnancy and lactation. J Eur Acad Dermatol Venereol. 2020;34(6):e256–7. https://doi.org/10.1111/jdv.16235. Epub 2020 Feb 21. PMID: 31990389
30. Dizon MP, Yu AM, Singh RK, Wan J, Chren MM, Flohr C, et al. Systematic review of atopic dermatitis disease definition in studies using routinely collected health data. Br J Dermatol. 2018;178(6):1280–7. https://doi.org/10.1111/bjd.16340. Epub 2018 Apr 25. PMID: 29336013; PMCID: PMC6033033
31. Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. U.K. diagnostic criteria for atopic dermatitis working party. Br J Dermatol. 1996;135(1):12–7. PMID: 8776351
32. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1980;59:44–7.
33. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. Br J Dermatol. 2008;158(4):754–65. https://doi.org/10.1111/j.1365-2133.2007.08412.x. Epub 2008 Jan 30. PMID: 18241277
34. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of

atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338–51. https://doi.org/10.1016/j.jaad.2013.10.010. Epub 2013 Nov 27. PMID: 24290431; PMCID: PMC4410183
35. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657–82. https://doi.org/10.1111/jdv.14891. Erratum in: J Eur Acad Dermatol Venereol 2019;33(7):1436. PMID: 29676534
36. van Zuuren EJ, Fedorowicz Z, Arents BWM. Emollients and moisturizers for eczema: abridged Cochrane systematic review including GRADE assessments. Br J Dermatol. 2017;177(5):1256–71. https://doi.org/10.1111/bjd.15602. Epub 2017 Oct 1. PMID: 28432721
37. Gueniche A, Knaudt B, Schuck E, Volz T, Bastien P, Martin R, Röcken M, Breton L, Biedermann T. Effects of nonpathogenic gram-negative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. Br J Dermatol. 2008;159(6):1357–63. https://doi.org/10.1111/j.1365-2133.2008.08836.x. Epub 2008 Sep 15. PMID: 18795916
38. Chi CC, Kirtschig G, Aberer W, Gabbud JP, Lipozenčić J, Kárpáti S, Haustein UF, Zuberbier T, Wojnarowska F. Evidence-based (S3) guideline on topical corticosteroids in pregnancy. Br J Dermatol. 2011;165(5):943–52. https://doi.org/10.1111/j.1365-2133.2011.10513.x. Epub 2011 Sep 29. PMID: 21729030
39. Gelmetti C, Wollenberg A. Atopic dermatitis - all you can do from the outside. Br J Dermatol. 2014;170(Suppl 1):19–24. https://doi.org/10.1111/bjd.12957. Epub 2014 May 9. PMID: 24720530
40. Reitamo S, Rustin M, Ruzicka T, Cambazard F, Kalimo K, Friedmann PS, Schoepf E, Lahfa M, Diepgen TL, Judodihardjo H, Wollenberg A, Berth-Jones J, Bieber T. European tacrolimus ointment study group. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. J Allergy Clin Immunol. 2002;109(3):547–55. https://doi.org/10.1067/mai.2002.121832. PMID: 11898005
41. Cury Martins J, Martins C, Aoki V, Gois AF, Ishii HA, da Silva EM. Topical tacrolimus for atopic dermatitis. Cochrane Database Syst Rev. 2015;2015(7):CD009864. https://doi.org/10.1002/14651858.CD009864.pub2. PMID: 26132597; PMCID: PMC6461158
42. Heilskov S, Deleuran MS, Vestergaard C. Immunosuppressive and immunomodulating therapy for atopic dermatitis in pregnancy: an appraisal of the literature. Dermatol Ther (Heidelb). 2020;10(6):1215–28. https://doi.org/10.1007/s13555-020-00457-w. Epub 2020 Nov 2. PMID: 33140290; PMCID: PMC7649192
43. Schmitt J, Spuls P, Boers M, Thomas K, Chalmers J, Roekevisch E, Schram M, Allsopp R, Aoki V, Apfelbacher C, Bruijnzeel-Koomen C, Bruin-Weller M, Charman C, Cohen A, Dohil M, Flohr C, Furue M, Gieler U, Hooft L, Humphreys R, Ishii HA, Katayama I, Kouwenhoven W, Langan S, Lewis-Jones S, Merhand S, Murota H, Murrell DF, Nankervis H, Ohya Y, Oranje A, Otsuka H, Paul C, Rosenbluth Y, Saeki H, Schuttelaar ML, Stalder JF, Svensson A, Takaoka R, Wahlgren CF, Weidinger S, Wollenberg A, Williams H. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. Allergy. 2012;67(9):1111–7. https://doi.org/10.1111/j.1398-9995.2012.02874.x. Epub 2012 Jul 30. PMID: 22844983
44. Mazzuoccolo LD, Andrada R, Pellerano G, Neglia V, Abeldaño A. Levels of cyclosporine in breast milk and passage into the circulation of the infant of a mother with psoriasis. Int J Dermatol. 2014;53(3):355–6. https://doi.org/10.1111/j.1365-4632.2012.05534.x. Epub 2013 Jan 22. PMID: 23336105
45. Seegräber M, Srour J, Walter A, Knop M, Wollenberg A. Dupilumab for treatment of atopic dermatitis. Expert Rev Clin Pharmacol. 2018;11(5):467–74. https://doi.org/10.1080/17512433.2018.1449642. Epub 2018 Mar 20. PMID: 29557246
46. Mian M, Dunlap R, Simpson E. Dupilumab for the treatment of severe atopic dermatitis in a pregnant patient: a case report. JAAD Case Rep. 2020;6(10):1051–2. https://doi.org/10.1016/j.jdcr.2020.08.001. PMID: 32995444; PMCID: PMC7509357

47. Porter ML, Lockwood SJ, Kimball AB. Update on biologic safety for patients with psoriasis during pregnancy. Int J Womens Dermatol. 2017;3(1):21–5. https://doi.org/10.1016/j.ijwd.2016.12.003. PMID: 28492050; PMCID: PMC5419021
48. Tirelli LL, Luna PC, Cristina E, Larralde M. Psoriasis and pregnancy in the biologic era, a feared scenario. What do we do now? Dermatol Ther. 2019;32(6):e13135. https://doi.org/10.1111/dth.13137.
49. Hamann CR, Egeberg A, Wollenberg A, Gislason G, Skov L, Thyssen JP. Pregnancy complications, treatment characteristics and birth outcomes in women with atopic dermatitis in Denmark. J Eur Acad Dermatol Venereol. 2019;33(3):577–87. https://doi.org/10.1111/jdv.15256. Epub 2018 Oct 8. PMID: 30242910
50. Vestergaard C, Wollenberg A, Barbarot S, Christen-Zaech S, Deleuran M, Spuls P, Flohr C, et al. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. J Eur Acad Dermatol Venereol. 2019;33(9):1644–59. https://doi.org/10.1111/jdv.15709. Epub 2019 Jun 23. Erratum in: J Eur Acad Dermatol Venereol 2020 Feb;34(2):426–427. PMID: 31231864
51. Ramirez FD, Chen S, Langan SM, Prather AA, McCulloch CE, Kidd SA, et al. Assessment of sleep disturbances and exhaustion in mothers of children with atopic dermatitis. JAMA Dermatol. 2019;155(5):556–63. https://doi.org/10.1001/jamadermatol.2018.5641. PMID: 30892577; PMCID: PMC6506883
52. Bains SN, Nash P, Fonacier L. Irritant contact dermatitis. Clin Rev Allergy Immunol. 2019;56(1):99–109. https://doi.org/10.1007/s12016-018-8713-0. PMID: 30293200
53. Yang L, Mao-Qiang M, Taljebini M, Elias PM, Feingold KR. Topical stratum corneum lipids accelerate barrier repair after tape stripping, solvent treatment and some but not all types of detergent treatment. Br J Dermatol. 1995;133(5):679–85. https://doi.org/10.1111/j.1365-2133.1995.tb02738.x. PMID: 8555016
54. Smith HR, Basketter DA, McFadden JP. Irritant dermatitis, irritancy and its role in allergic contact dermatitis. Clin Exp Dermatol. 2002;27(2):138–46. https://doi.org/10.1046/j.1365-2230.2002.00997.x. PMID: 11952708
55. Seyfarth F, Schliemann S, Antonov D, Elsner P. Dry skin, barrier function, and irritant contact dermatitis in the elderly. Clin Dermatol. 2011;29(1):31–6. https://doi.org/10.1016/j.clindermatol.2010.07.004. PMID: 21146729
56. Chew AL, Maibach HI. Occupational issues of irritant contact dermatitis. Int Arch Occup Environ Health. 2003;76(5):339–46. https://doi.org/10.1007/s00420-002-0419-0. Epub 2003 Jun 25. PMID: 12827369
57. Alinaghi F, Bennike NH, Egeberg A, Thyssen JP, Johansen JD. Prevalence of contact allergy in the general population: a systematic review and meta-analysis. Contact Dermatitis. 2019;80(2):77–85. https://doi.org/10.1111/cod.13119. Epub 2018 Oct 29. PMID: 30370565
58. Nethercott JR, Holness DL, Adams RM, Belsito DV, De Leo VA, Emmett EA, et al. Patch testing with a routine screening tray in North America, 1985 through 1989: II. Gender and response. Am J Contact Dermat. 1991;2(2):130–4.
59. Alani JI, Davis MD, Yiannias JA. Allergy to cosmetics: a literature review. Dermatitis. 2013;24(6):283–90. https://doi.org/10.1097/DER.0b013e3182a5d8bc. PMID: 24201464
60. Zmudzinska M, Czarnecka-Operacz M, Silny W. Contact allergy to glucocorticosteroids in patients with chronic venous leg ulcers, atopic dermatitis and contact allergy. Acta Dermatovenerol Croat. 2008;16(2):72–8. PMID: 18541102
61. Pomeranz MK, Karen JK. Images in clinical medicine. Phytophotodermatitis and limes. N Engl J Med. 2007;357(1):e1. https://doi.org/10.1056/NEJMicm053778. PMID: 17611200
62. Quaak MS, Martens H, Hassing RJ, van Beek-Nieuwland Y, van Genderen PJ. The sunny side of lime. J Travel Med. 2012;19(5):327–8. https://doi.org/10.1111/j.1708-8305.2012.00644.x. Epub 2012 Aug 8. PMID: 22943277
63. Derraik JG, Rademaker M. Phytophotodermatitis caused by contact with a fig tree (Ficus carica). N Z Med J. 2007;120(1259):U2658. PMID: 17721568

64. Monteiro AF, Rato M, Martins C. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. Clin Dermatol. 2016;34(5):571–81. https://doi.org/10.1016/j.clindermatol.2016.05.006. Epub 2016 May 20. PMID: 27638435
65. Lofgren SM, Warshaw EM. Dyshidrosis: epidemiology, clinical characteristics, and therapy. Dermatitis. 2006;17(4):165–81. https://doi.org/10.2310/6620.2006.05021. PMID: 17150166
66. Calle Sarmiento PM, Chango Azanza JJ. Dyshidrotic eczema: a common cause of palmar dermatitis. Cureus. 2020;12(10):e10839. https://doi.org/10.7759/cureus.10839. PMID: 33173645; PMCID: PMC7647841
67. Guillet MH, Wierzbicka E, Guillet S, Dagregorio G, Guillet G. A 3-year causative study of pompholyx in 120 patients. Arch Dermatol. 2007;143(12):1504–8. https://doi.org/10.1001/archderm.143.12.1504. PMID: 18086998
68. Kotan D, Erdem T, Acar BA, Boluk A. Dyshidrotic eczema associated with the use of IVIg. BMJ Case Rep. 2013;2013:bcr2012008001. https://doi.org/10.1136/bcr-2012-008001. PMID: 23417935; PMCID: PMC3604565
69. Tzaneva S, Kittler H, Thallinger C, Hönigsmann H, Tanew A. Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema. Photodermatol Photoimmunol Photomed. 2009;25(2):101–5. https://doi.org/10.1111/j.1600-0781.2009.00419.x. PMID: 19292787
70. Wollina U. Pompholyx: a review of clinical features, differential diagnosis, and management. Am J Clin Dermatol. 2010;11(5):305–14. https://doi.org/10.2165/11533250-000000000-00000. PMID: 20642293

Chapter 11
Metabolic Syndrome: Dermatological Aspects in Women

Dillion Mintoff and Anupam Das

11.1 Introduction

Metabolic syndrome (MetS) refers to a constellation of signs and biochemical markers which collectively increase the risk of cardio- and neuro-vascular disease and malignant disease. According to National Health and Nutrition Examination Survey (NHANES) carried out by the Centre for Disease Control and Prevention, the prevalence of MetS has been rising, with the overall prevalence calculated at 34.2% of the 14.374 participants recruited between 2007 and 2012. Among women, the prevalence was calculated to be 34.9% [1]. Various diagnostic criteria have been established to make a diagnosis of MetS, the most established of which have been summarized in Table 11.1.

Components of the MetS are associated with cutaneous manifestations such as acanthosis nigricans (AN), acrochordons, xanthelasma and striae distensae. MetS also predisposes to inflammatory conditions of the skin such as hidradenitis suppurativa (HS) and psoriasis. Dermatologists are therefore in a unique position which enables them to recognize cutaneous manifestations of the MetS, allowing them to screen target patients for the condition as well as treat associated cutaneous comorbidities.

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Table 11.1 Diagnostic criteria for metabolic syndrome

WHO [2]	ATP-III [3]	IDF
Impaired glucose tolerance OR diabetes OR insulin resistance AND 2 or more of the following: 1. Blood pressure ≥ 160/90 mmHg 2. Raised plasma triglycerides (≥1.7 mmol/L; 150 mg/dL AND/OR low HDL-cholesterol ≥0.9 mmol/L or 35 mg/dL in men; <1.0 m/mol, 39 mg/dL in women) 3. Central obesity (waist to hip ratio > 0.90 in males, >0.85 in females) AND/OR BMI > 30 kg/m^2 4. Microalbuminuria (urinary albumin excretion rate ≥20 mcg/min or albumin–creatinine ratio ≥20 mg/g)	3 or more of the following: 1. Fasting glucose ≥110 mg/dL 2. Blood pressure ≥130/85 mmHg 3. Triglycerides ≥150 mg/dL 4. High-density lipoprotein cholesterol (<40 mg/dL in men or <50 mg/dL in women) 5. Abdominal obesity (waist circumference > 102 cm in men, >88 cm in women)	Central obesity and 2 or more of the following: 1. Fasting glucose of >100 mg/dL or an established diagnosis of type 2 diabetes 2. Blood pressure ≥135/85 mmHg 3. Triglycerides >150 mg/dL or on specific treatment for this lipid abnormality 4. High-density lipoprotein <50 mg/dL or on specific treatment for this lipid abnormality

11.2 Acrochordons

Acrochordons are cutaneous appendages which can vary in size from a few millimetres to centimetres in length. Acrochordons are commoner in patients with the MetS [4, 5], with up to 40% of patients having multiple skin tags having the disease [6].

These projections, also called fibroepithelial polyps (FEPs) or "skin tags", are most commonly found in areas of friction such as the neck and axillae. In women, acrochordons are documented to arise anywhere within the perineum, including the labia [7–9]. FEPs of the labia have been described to grow to massive sizes during pregnancy [10]. Even though the lesions are more characteristic of middle-aged to elderly patients, giant, ulcerated acrochordons of the labia have been described in females as young as 15 years old [11]. The majority of acrochordons of the perineum are acquired, however such lesions have also been diagnosed prenatally by ultrasonography [12]. Notwithstanding, acrochordons in the perineum are an uncommon finding, with nil discovered in a prospective, observational study in 100 females [13].

In a cohort of 350 women with a poor obstetric history, acrochordons were associated with a higher risk of comorbid immunological disease [14]. Pregnant women diagnosed with skin tags have a non-statistically significant (p 0.18) higher odds ratio of developing gestational diabetes [15]. Other associated conditions include hypertension and diabetes [16].

The differential diagnosis of acrochordons is narrow. Acrochordons have been described to be scattered among polypoidal basal cell carcinomas in the perineum of a woman with Gorlin–Goltz syndrome [17]. Acrochordons have also been

likened to squamous cell carcinoma [18]. They have also been described to arise in a linear fashion [19].

The pathophysiology of acrochordon formation is not completely understood. Known association with insulin resistance has suggested that the formation of these projections is associated. This is supported by the findings of increased tissue expression Insulin-like growth factor 1 Receptor and insulin-like growth factor 2 Receptor in diabetic patients.

11.3 Acanthosis Nigricans

Definition: Acanthosis nigricans (AN) is characterised by symmetric, dark, coarse, thickened, velvety appearing plaques commonly distributed on the neck, axillae, antecubital and popliteal fossae, inframammary and groin areas, sometimes on the face (Fig. 11.1) [20]. Recently, Karadag et al. have devised a scoring system for AN severity (SCANS) to evaluate AN and skin tags, their correlation with obesity or diabetes [21].

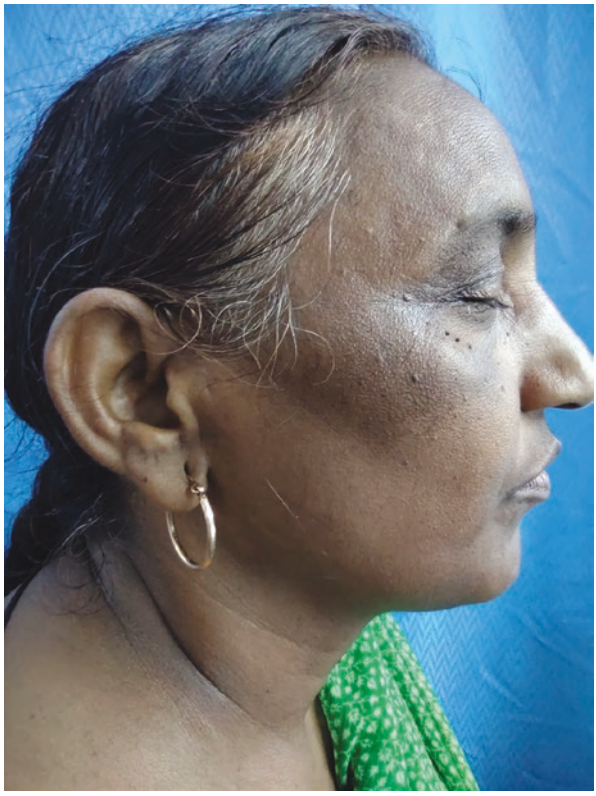

Fig. 11.1 A middle-aged lady presenting with facial acanthosis nigricans, acrochordons and dermatosis papulosis nigra

AN most commonly affects the intertriginous skin and knuckles [22]. Case reports document AN in rare sites such as conjunctiva [23], hands and feet [24], vulva [25] and oral mucosa [26] in women. AN in MetS is acquired (obesity, repeated trauma [27], drugs [28]; however, autosomal dominant forms of disease can occur [29].

Women with AN are significantly more likely to suffer from MetS [30, 31], obesity and insulin resistance [31]. Has been documented in women as young as 6 years old [32]. Acanthosis nigricans can present in syndromic form consistent hyperandrogenism, Insulin resistance and AN (HAIR-AN). AN is a composite marker of cardiometabolic risk [33]. Women having such syndromic forms are at risk of suffering from comorbid hyperandrogenaemia, hyperinsulinemia and insulin resistance [34, 35]. Acanthosis can also affect lean women with Type B insulin resistance [36].

The odds ratio of a patient with AN to have gestation diabetes mellitus has been estimated at 5.5 (p 0.001) [15].

AN may represent a cutaneous manifestation of an underlying malignancy, particularly of the gastrointestinal tract [37]. Malignant AN has also been documented to be a parneoplastic manifestation of endometrial [38, 39], fallopian tube [40], ovarian [41–43] and (metastatic) mammary carcinoma in women [44]. Acanthosis nigricans of the neck may be a predictor of pre-eclampsia [45].

Liraglutide can be an option for females with HAIR-AN, resulting in significant improvement in insulin resistance, androgen levels and menstrual cycle [46].

Treatment options include trichloroacetic acid peels [47], glycolic acid peels, lasers [48], 10% urea + 0.025% tretinoin [49], topical rapamycin [50]/topical sirolimus [51], and melatonin [52].

11.4 Hirsutism

Hirsutism (defined as a mFG score >5) was identified in 10% of 2988 Chinese women aged 20–45 [31]. Hirsutism has not been found to significantly impact the QoL of women when assessed by DLQI [53]. It is quite frequently found in women presenting with metabolic syndrome.

11.5 Hidradenitis Suppurativa

HS is a chronic suppurative condition of the pilosebaceous unit. Patients present with recurrent nodules, abscesses, and sinuses, mostly in intertriginous skin. The condition is not only more prevalent in women but is also associated with MetS, with the odds ratio of patients having co-morbid disease being at 2.66 (95%CI,

Table 11.2 HS is a chronic suppurative condition of the pilosebaceous unit (Reproduced with permission from Mintoff et al. (2021)

Study	MetS diagnostic criteria	% MetS in HS group	% MetS in control group	OR (95%CI)
Ozkur 2020 [54]	NCEP-ATP III	32.4% (12/37)	5.4% (2/37)	8.4 (1.73–40.89)
Duran-Vian 2019 [55]	NCEP-ATP III	37.1% (26/70)	9.3% (14/150)	5.74 (2.76–11.95)
Gonzalez-Lopez 2019 [56]	NCEP-ATP III	34.2% (26/76)	11.5% (7/61)	4.01 (1.60–10.05)
Akdogan 2018 [57]	International diabetes federation	50.0% (20/40)	17.5% (7/40)	4.71 (1.69–13.13)
Chiricozzi 2018 [58]	N/A	4.4% (11/253)	N/A	N/A
Loo 2018 [59]	NCEP-ATP III	19.4% (12/62)	24.2% (15/62)	1.33 (0.56–3.13)
Shalom 2015 [60]	NCEP-ATP-III	10.4% (334/3207)	7.1% (453/612)	1.53 (1.32–1.77)
Miller 2014 [61]	NCEP-ATP IIII	32.2% (105/326)* 53.1% (17/32)**	21.5%(3192/14,851)	2.08 (1.61–2.69) 3.89 (1.90–7.98
Gold 2014a [62]	NCEP-ATP III	50.6% (123/243)	30.2% (67/222)	2.37 (1.62–3.47)
Sabat 2012 [63]	NCEP-ATP III	40.0% (32/80)	13.0% (13/100)	4.46 (2.02–9.96)

1.90–3.72) based on studies summarized in Table 11.2. HS and MetS share a similar adipokine milieu specifically raised leptin, resistin and visfatin together with a lower serum adiponectin level. This share profile promotes inflammation and obesity through chemokines such as IL-2, IL-6, IL-1B, TNF alpha and interferon gamma.

11.6 Androgenetic Alopecia

It is a specific pattern of hair loss in males and females [64]. Insulin resistance is characterised by increased levels of insulin leading to vasoconstriction and nutritional deficiency in the hair follicles, which accentuates the action of dihydrotestosterone on miniaturisation of hair follicles [65]. A case–control study demonstrated higher prevalence of MetS ($P = 0.001$) and higher levels of triglycerides and blood pressure ($P < 0.05$) [64]. Another study concluded that there is a statistically significant correlation between female pattern hair loss, hypertension and central obesity [66]. Therefore, patients presenting with female pattern hair loss must be investigated for MetS, and lowering of insulin resistance and losing weight might help improve hair growth.

11.7 Rosacea

Patients suffering from rosacea have been found to have higher levels of total cholesterol, LDL-cholesterol and C reactive proteins, in comparison to controls [67, 68]. Moreover, these patients are more likely to have a family history of cardiovascular disease, insulin resistance, dysregulated sympathetic nervous system and hypertension [67–69].

11.8 Acne Vulgaris

The etiopathogenesis of acne revolves around increased production of sebum, follicular hyperkeratinisation, colonisation of *Propionibacterium acnes* and inflammatory cascade [70, 71]. It has been documented that acne and insulin resistance have a common stem of activation of mammalian target of rapamycin complex 1 signaling [72]. Thus, acne in women is thought to have a significant correlation with insulin resistance and dyslipidaemia [73–75].

11.9 Systemic Lupus Erythematosus

Female patients suffering from SLE, have been shown to have five times higher risk of acquiring coronary artery disease, and subsequently metabolic syndrome [76, 77]. Hypertriglyceridemia and hypertension have the strong correlation with SLE [77].

11.10 Atopic Dermatitis

A cross-sectional study in Korean women suffering from atopic dermatitis demonstrated a significant association with MetS ($P = 0.02$) and hypertriglyceridemia ($P = 0.05$) [78]. This is possibly attributed to an altered cytokine profile, in both the conditions.

11.11 Miscellaneous Dermatoses

Some of the other dermatological conditions which have been linked to metabolic syndrome in women include lichen planus, seborrhoeic dermatitis, squamous cell carcinoma and xanthelasma palpebrarum [79–84].

11.12 Conclusion

The prevalence of metabolic syndrome is on the rise, attributed to the altered lifestyle and many other factors. Cutaneous manifestations often herald the diagnosis of metabolic syndrome in females; therefore, dermatologists and physicians of allied disciplines should be aware of the association of acanthosis nigricans, acrochordons, hirsutism, hidradenitis suppurativa, psoriasis and so on with MetS.

References

1. Moore JX. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. Prev Chronic Dis. 2017;14:E24. Available from: https://www.cdc.gov/pcd/issues/2017/16_0287.htm
2. Alberti KGMM, Zimmet PZ. Definition, Diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med. 1998;15(7):539–53.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.
4. Akpinar F, Dervis E. Association between acrochordons and the components of metabolic syndrome. Eur J Dermatol. 2012;22(1):106–10.
5. Shah R, Jindal A, Patel N. Acrochordons as a cutaneous sign of metabolic syndrome: a case-control study. Ann Med Health Sci Res. 2014;4(2):202–5.
6. Sari R, Akman A, Alpsoy E, Balci M. The metabolic profile in patients with skin tags. Clin Exp Med. 2010;10(3):193–7.
7. Deng YQ, Xu JX, He YM, Xiong X. A rare vulval manifestation of acrochordons in a young woman. Australas J Dermatol. 2018;59(3):e221–2.
8. Garg S, Baveja S. Giant Acrochordon of labia majora: an uncommon manifestation of a common disease. J Cutan Aesthet Surg. 2015;8(2):119–20.
9. Asad N, Mushtaq A, Bano R. Skin tag (acrochordon) on labium majus in an infertile female. J Coll Physicians Surg Pak. 2012;22(9):613–4.
10. Eris Eken Z, Oltulu P, Alper S, Taskin B, Cay O. Case report of a very large skin tag in an unusual location that grew rapidly during pregnancy. J Dermatol. 2014;41(4):366.
11. Ozkol HU, Bulut G, Gumus S, Calka O. Ulcerated giant labial acrochordon in a child. Indian Dermatol Online J. 2015;6(1):60–1.
12. Bord A, Valsky DV, Yagel S. Prenatal sonographic diagnosis of congenital perineal skin tag: case report and review of the literature. Prenat Diagn. 2006;26(11):1065–7.
13. Singh N, Thappa DM, Jaisankar TJ, Habeebullah S. Pattern of non-venereal dermatoses of female external genitalia in South India. Dermatol Online J. 2008;14(1):1.
14. Beksac B, Donmez HG, Cagan M, Unal C, Fadiloglu E, Beksac MS. Acrochordons and autoimmunity: significance of preconceptional counseling. Hum Antibodies. 2020;28(4):335–9.
15. Yılmaz E, Kelekci KH, Kelekci S. Skin tag and acanthosis nigricans: do they have a predictive value for gestational diabetes mellitus? Exp Clin Endocrinol Diabetes. 2011;119(7):419–22.
16. Fang CEH, Crowe C, Murphy A, O'Donnell M, Finucane FM. Cross-sectional study of the association between skin tags and vascular risk factors in a bariatric clinic-based cohort of Irish adults with morbid obesity. BMC Res Notes. 2020;13(1):156.
17. Wang SQ, Goldberg LH. Multiple polypoid basal cell carcinomas on the perineum of a patient with basal cell nevus syndrome. J Am Acad Dermatol. 2007;57(2 Suppl):S36–7.

18. Schwartz RA, Tarlow MM, Lambert WC. Keratoacanthoma-like squamous cell carcinoma within the fibroepithelial polyp. Dermatol Surg. 2004;30(2 Pt 2):349–50.
19. Singh S, Sahoo AK, Bhari N, Yadav S. Vulvar acrochordons arranged in a linear pattern. J Obstet Gynaecol. 2018;38(2):287–8.
20. Das A, Datta D, Kassir M, Wollina U, Galadari H, Lotti T, Jafferany M, Grabbe S, Goldust M. Acanthosis nigricans: a review. J Cosmet Dermatol. 2020;19(8):1857–65.
21. Karadag AS, Uzuncakmak TK, Ozlu E, Takir M, Karadag R, Kostek O, et al. Introduction of a novel quantitative scoring system for acanthosis nigricans and its validation in a pilot study. Dermatol Ther. 2020;33(6):e14450.
22. González-Saldivar G, Rodríguez-Gutiérrez R, Ocampo-Candiani J, González-González JG, Gómez-Flores M. Skin manifestations of insulin resistance: from a biochemical stance to a clinical diagnosis and management. Dermatol Ther (Heidelb). 2017;7(1):37–51.
23. Huang N, Yin HY, Swan R. Paraneoplastic conjunctival acanthosis Nigricans: a case report. Cornea. 2021;40(3):377–9.
24. Bishnoi A, Parsad D. Velvety hyperpigmentation on hands and feet of a young girl: Acral acanthosis Nigricans. J Cutan Med Surg. 2018;22(3):323.
25. Grasinger CC, Wild RA, Parker IJ. Vulvar acanthosis nigricans: a marker for insulin resistance in hirsute women. Fertil Steril. 1993;59(3):583–6.
26. Canjuga I, Mravak-Stipetić M, Kopić V, Galić J. Oral acanthosis nigricans: case report and comparison with literature reports. Acta Dermatovenerol Croat. 2008;16(2):91–5.
27. Bomar L, Lewallen R, Jorizzo J. Localized acanthosis nigricans at the site of repetitive insulin injections. Cutis. 2020;105(2):E20–2.
28. Mourad AI, Haber RM. Drug-induced acanthosis nigricans: a systematic review and new classification. Dermatol Ther. 2021;21:e14794.
29. Tahara U, Yasuda M, Yamada Y, Aoki S, Sato S, Amagai M, et al. Autosomal dominant familial acanthosis nigricans caused by a C-terminal nonsense mutation of FGFR3. J Hum Genet. 2021;66(8):831–4.
30. Ayaz T, Baydur Şahin S, Şahin OZ. Relation of acanthosis nigricans to metabolic syndrome in overweight and obese women. Metab Syndr Relat Disord. 2014;12(6):320–3.
31. Dong Z, Huang J, Huang L, Chen X, Yin Q, Yang D. Associations of acanthosis nigricans with metabolic abnormalities in polycystic ovary syndrome women with normal body mass index. J Dermatol. 2013;40(3):188–92.
32. Murphy R, Smith G, Isaac I, Hutchinson D, Semple RK. Novel mutation in insulin receptor gene identified after muscle biopsy in a Niuean woman with severe insulin resistance. Diabet Med. 2015;32(10):e24–8.
33. Lopez-Alvarenga JC, Chittoor G, Paul SFD, Puppala S, Farook VS, Fowler SP, et al. Acanthosis nigricans as a composite marker of cardiometabolic risk and its complex association with obesity and insulin resistance in Mexican American children. PLoS One. 2020;15(10):e0240467.
34. Agrawal K, Mathur R, Purwar N, Mathur SK, Mathur DK. Hyperandrogenism, insulin resistance, and acanthosis Nigricans (HAIR-AN) syndrome reflects adipose tissue dysfunction ('Adiposopathy' or 'sick fat') in Asian Indian girls. Dermatology. 2021;14:1–9.
35. Sadeghian G, Ziaie H, Amini M, Ali NM. Evaluation of insulin resistance in obese women with and without acanthosis nigricans. J Dermatol. 2009;36(4):209–12.
36. Rao G, Chauhan YV, Varthakavi PK, Bhagwat N. A lean lady with acanthosis Nigricans and uncontrolled diabetes mellitus. Cureus. 2020;12(11):e11330.
37. Yuan C, Liu L, Wang M. Widespread thickened, verrucous, Hyperpigmented plaques in a woman with weight loss. JAMA Oncol. 2019;5(7):1055–6.
38. Quint KD, Edelbroek JRJ, Gelderblom AJH, van Doorn R, Vermeer MH. A woman with paraneoplastic dermatoses; signs of recurrent malignancy. Ned Tijdschr Geneeskd. 2013;157(38):A6560.
39. Deen J, Moloney T, Burdon-Jones D. Severe, malignant acanthosis Nigricans associated with adenocarcinoma of the endometrium in a young obese female. Case Rep Dermatol. 2017;9(1):30–7.

40. West L, Carlson M, Wallis L, Goff HW. The sign of Leser-Trelát and malignant acanthosis Nigricans associated with fallopian tube carcinoma. Obstet Gynecol. 2018;132(5):1116–9.
41. Garzitto A, Ricceri F, Pescitelli L, Tripo L, Prignano F. Vitiligo masks malignant acanthosis nigricans in a woman with ovarian cancer. Int J Dermatol. 2015;54(11):1300–2.
42. Singh SK, Rai T. A rare case of malignant acanthosis nigricans in a lady with ovarian cancer. Indian Dermatol Online J. 2013;4(2):125–7.
43. Oh CW, Yoon J, Kim CY. Malignant acanthosis Nigricans associated with ovarian cancer. Case Rep Dermatol. 2010;2(2):103–9.
44. Arellano J, Iglesias P, Suarez C, Corredoira Y, Schnettler K. Malignant acanthosis nigricans as a paraneoplastic manifestation of metastatic breast cancer. Int J Womens Dermatol. 2019;5(3):183–6.
45. Hoirisch-Clapauch S, Benchimol-Barbosa PR. Markers of insulin resistance and sedentary lifestyle are predictors of preeclampsia in women with adverse obstetric results. Braz J Med Biol Res. 2011;44(12):1285–90.
46. Livadas S, Androulakis I, Angelopoulos N, Lytras A, Papagiannopoulos F, Kassi G. Liraglutide administration improves hormonal/metabolic profile and reproductive features in women with HAIR-AN syndrome. Endocrinol Diabetes Metab Case Rep. 2020;4:2020.
47. Baldissera RL, Yang EJ, Schmitt JV, Lin E, de Jesus FE, Silva Enokihara MM SE, et al. Trichloroacetic acid peels for the treatment of acanthosis nigricans. J Am Acad Dermatol. 2021;86(1):203–4.
48. Zaki NS, Hilal RF, Essam RM. Comparative study using fractional carbon dioxide laser versus glycolic acid peel in treatment of pseudo-acanthosis nigricans. Lasers Med Sci. 2018;33(7):1485–91.
49. Treesirichod A, Chaithirayanon S, Chaikul T, Chansakulporn S. The randomized trials of 10% urea cream and 0.025% tretinoin cream in the treatment of acanthosis nigricans. J Dermatolog Treat. 2021;32:837–42.
50. Coerdt KM, Todd SP, DeKlotz CMC. Topical rapamycin for acanthosis nigricans in the Fitzpatrick IV/V adolescent population. Pediatr Dermatol. 2021;38(1):296–8.
51. Dodds M, Maguiness S. Topical sirolimus therapy for epidermal nevus with features of acanthosis nigricans. Pediatr Dermatol. 2019;36(4):554–5.
52. Sun H, Wang X, Chen J, Gusdon AM, Song K, Li L, et al. Melatonin treatment improves insulin resistance and pigmentation in obese patients with acanthosis Nigricans. Int J Endocrinol. 2018;2018:2304746.
53. Kutlu Ö. Evaluation of quality of life of patients with hirsutism among Turkish women: a single-center cross-sectional study. J Cosmet Dermatol. 2020;19(11):3053–7.
54. Özkur E, Erdem Y, Altunay İK, Demir D, Dolu NÇ, Serin E, et al. Serum irisin level, insulin resistance, and lipid profiles in patients with hidradenitis suppurativa: a case-control study. An Bras Dermatol. 2020;95(6):708–13.
55. Durán-Vian C, Arias-Loste MT, Hernández JL, Fernández V, González M, Iruzubieta P, et al. High prevalence of non-alcoholic fatty liver disease among hidradenitis suppurativa patients independent of classic metabolic risk factors. J Eur Acad Dermatol Venereol. 2019;33(11):2131–6.
56. González-López MA, Vilanova I, Ocejo-Viñals G, Arlegui R, Navarro I, Guiral S, et al. Circulating levels of adiponectin, leptin, resistin and visfatin in non-diabetics patients with hidradenitis suppurativa. Arch Dermatol Res. 2020;312(8):595–600.
57. Akdogan N, Alli N, Uysal PI, Topcuoglu C, Candar T, Turhan T. Visfatin and insulin levels and cigarette smoking are independent risk factors for hidradenitis suppurativa: a case-control study. Arch Dermatol Res. 2018;310(10):785–93.
58. Chiricozzi A, Giovanardi G, Caposiena Caro DR, Iannone M, De Simone C, Cannizzaro MV, et al. Characterization of comorbid conditions burdening hidradenitis suppurativa: a multicentric observational study. G Ital Dermatol Venereol. 2020;155(3):335–40.

59. Loo CH, Tan WC, Tang JJ, Khor YH, Manikam MT, Low D-E, et al. The clinical, biochemical, and ultrasonographic characteristics of patients with hidradenitis suppurativa in northern peninsular Malaysia: a multicenter study. Int J Dermatol. 2018;57(12):1454–63.
60. Shalom G, Freud T, Harman-Boehm I, Polishchuk I, Cohen AD. Hidradenitis suppurativa and metabolic syndrome: a comparative cross-sectional study of 3207 patients. Br J Dermatol. 2015;173(2):464–70.
61. Miller IM, Ellervik C, Vinding GR, Zarchi K, Ibler KS, Knudsen KM, et al. Association of metabolic syndrome and hidradenitis suppurativa. JAMA Dermatol. 2014;150(12):1273–80.
62. Gold DA, Reeder VJ, Mahan MG, Hamzavi IH. The prevalence of metabolic syndrome in patients with hidradenitis suppurativa. J Am Acad Dermatol. 2014;70(4):699–703.
63. Sabat R, Chanwangpong A, Schneider-Burrus S, Metternich D, Kokolakis G, Kurek A, et al. Increased prevalence of metabolic syndrome in patients with acne inversa. PLoS One. 2012;7(2):e31810.
64. Banger HS, Malhotra SK, Singh S, Mahajan M. Is early onset androgenic alopecia a marker of metabolic syndrome and carotid artery atherosclerosis in young Indian male patients? Int J Trichol. 2015;7:141–7.
65. Abdelmawla MY, Esawy A, Khater E, Khalifa N. Insulin resistance in androgenetic alopecia and acne vulgaris. Egypt J Dermatol Venerol. 2019;39:83.
66. El Sayed MH, Abdallah MA, Aly DG, Khater NH. Association of metabolic syndrome with female pattern hair loss in women: a case-control study. Int J Dermatol. 2016;55:1131–7.
67. Akin BA, Ozbas GS, Akbaba G, Etgu F, Dogan G. The relationship between rosacea and insulin resistance and metabolic syndrome. Eur J Dermatol. 2016;26(3):260–4.
68. Duman N, Ersoy ES, Atakan N. Rosacea and cardiovascular risk factors: a case control study. J Eur Acad Dermatol Venereol. 2014;28(9):1165–9.
69. Leroith D. Pathophysiology of the metabolic syndrome: implications for the cardiometabolic risks associated with type 2 diabetes. Am J Med Sci. 2012;343(1):13–6.
70. Bhat YJ, Latief I, Hassan I. Update on etiopathogenesis and treatment of acne. Indian J Dermatol Venereol Leprol. 2017;83(3):298–306.
71. Bagatin E, Freitas THP, Machado MCR, Ribeiro BM, Nunes S, Rocha MADD. Adult female acne: A guide to clinical practice. An Bras Dermatol. 2019;94(1):62–75.
72. Melnik BC, John SM, Plewig G. Acne: risk indicator for increased body mass index and insulin resistance. Acta Derm Venereol. 2013;93(6):644–9.
73. Emiroğlu N, Cengiz FP, Kemeriz F. Insulin resistance in severe acne vulgaris. Postepy Dermatol Alergol. 2015;32(4):281–5.
74. Kartal D, Yildiz H, Ertas R, Borlu M, Utas S. Association between isolated female acne and insulin resistance: a prospective study. G Ital Dermatol Venereol. 2016;151(4):353–7.
75. Roth MM, Leader N, Kroumpouzos G. Gynecologic and andrologic dermatology and the metabolic syndrome. Clin Dermatol. 2018;36(1):72–80.
76. Parker B, Urowitz MB, Gladman DD, Lunt M, Donn R, Bae SC. Impact of early disease factors on metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis. 2015;74(8):1530–6.
77. Hallajzadeh J, Khoramdad M, Izadi N, Karamzad N, Almasi-Hashiani A, Ayubi E. The association between metabolic syndrome and its components with systemic lupus erythematosus: a comprehensive systematic review and meta-analysis of observational studies. Lupus. 2018;27(6):899–912.
78. Lee JH, Jung HM, Do HK, Lee SH, Lee JY, Park YG, et al. Association between metabolic syndrome and atopic dermatitis in Korean adults. Acta Derm Venereol. 2017;97:77–80.
79. Arias-Santiago S, Buendía-Eisman A, Aneiros-Fernández J, Girón-Prieto MS, Gutiérrez-Salmerón MT, Mellado VG. Cardiovascular risk factors in patients with lichen planus. Am J Med. 2011;124(6):543–8.
80. Imamoglu B, Hayta SB, Guner R, Akyol M, Ozcelik S. Metabolic syndrome may be an important comorbidity in patients with seborrheic dermatitis. Arch Med Sci Atheroscler Dis. 2016;1(1):e158–61.

81. Nagel G, Bjørge T, Stocks T, Manjer J, Hallmans G, Edlinger M. Metabolic risk factors and skin cancer in the metabolic syndrome and cancer project (me-can). Br J Dermatol. 2012;167(1):59–67.
82. Kavoussi H, Ebrahimi A, Rezaei M, Ramezani M, Najafi B, Kavoussi R. Serum lipid profile and clinical characteristics of patients with xanthelasma palpebrarum. An Bras Dermatol. 2016;91(4):468–71.
83. Misitzis A, Cunha PR, Kroumpouzos G. Skin disease related to metabolic syndrome in women. Int J Womens Dermatol. 2019;5(4):205–12.
84. Fatima F, Das A, Kumar P, Datta D. Skin and metabolic syndrome: an evidence based comprehensive review. Indian J Dermatol. 2021;66:302–7.

Chapter 12
Body Dysmorphic Disorder in Females

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12.1 Introduction

Body dysmorphic disorder (BDD) is primarily a psychiatric disease presenting to dermatologists with a primary complaint of defect in appearance. It was previously known as dysmorphophobia, dermatological hypochondria or dermatological non-disease, but these terms are considered best not used, as these do not accurately reflect the condition.

There is characteristic preoccupation with a real or imagined external defect, with concern being out of proportion to the defect, if any. This preoccupation, though trivial to an onlooker, may consume entire waking hours and affect quality of life of the patient [1].

12.2 History

This condition was initially documented by Enrico Morselli in 1891 as dysmorphophobia (Greek Dysmorphia—ugliness) [2]. Later many other documentations were made, including the famous "Wolf man" of Sigmund Freud [3]. It was varyingly described as obsession, hypochondria, somatoform disorder and hypochondriacal psychosis [2].

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12.3 Current Status

The Diagnostic and Statistical Manual of Mental Disorders, DSM-V of 2013, categorizes BDD as an obsessive-compulsive spectrum disorder [4].

12.4 Epidemiology

Though there is lack of comprehensive data from many countries, the global prevalence is estimated to be 0.7–2.4% with a higher prevalence of 4.9–36% in dermatology patients [5]. It is disproportionately more in those with comorbid psychiatric problems (8–37%) [6] with an almost equal gender distribution [7], though concerns and comorbidities differ [8]. Younger patients (<50 years) have more associated morbidity [5].

12.5 Aetiopathogenesis

Pathogenesis involves a complex interplay of biologic, psychosocial, cultural and genetic factors. The key processes include impaired frontostriatal and temporoparietooccipital pathways, impaired visual processing by orbitofrontal cortex, abnormality in caudate nucleus and decrease in the neurotransmitter serotonin. Genetic predilection, psychosocial factors like childhood adverse events, personality traits, and gender and culture roles also are implicated [9].

12.6 Clinical Features

BDD has been described variously as "obsession with perfection" [10], and a condition which is "rich in symptoms, but poor in signs" [11].

Characteristic features are as follows [12].

1. Preoccupation with a minor or perceived body defect.
2. Complaints mostly related to face, breast, hair, body weight and shape.
3. Spends too much time contemplating the condition and elaborate and repetitive remedial strategies like prolonged grooming, excessive make-up, concealing, dressing up, mirror checking.
4. This preoccupation affects psychosocial well-being and quality of life.

DSM-V criteria for BDD is given in Table 12.1 [4].

Table 12.1 DSM-V criteria for BDD

DSM-V criteria for body dysmorphic disorder
(A) Preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others
(B) At some point during the course of the disorder, the individual has performed repetitive behaviours (e.g. mirror checking, excessive grooming, skin picking, reassurance seeking) or mental acts (e.g. comparing his or her appearance with that of others) in response to the appearance concerns
(C) The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
(D) The appearance preoccupation is not better explained by concerns with body fat or weight in an individual whose symptoms meet diagnostic criteria for an eating disorder

In addition to these, the level of insight (absent to good) and presence of muscle dysmorphophobia (exclusive to men) should also be counted

12.7 Areas of Concern in Females

Though any body part may be subject to scrutiny, those that are major components in body imagery are most affected, the common areas of concern being skin, hair, acne, nose shape and size, facial wrinkles, facial and body hair, breast size. Complaints pertaining to face include shape of nose and teeth, flushing, redness, greasiness, dilated veins, pores, facial hair, acne, pigmentation and scarring. Scalp hair loss and burning sensation is also a common complaint [11].

Some have concerns regarding to only one body part, some have concerns with multiple parts and in some, concerns keep on shifting from one area of focus to another [13]. The thoughts are invariably repetitive, bothersome and time-consuming, collectively lasting for up to 3 to 8 h per day [14].

Thoughts lead to repetitive time-consuming and uncontrollable behaviour like mirror checking, camouflaging, dressing up to hide the “defect”, skin picking or comparing the body parts to others’. Mirror gazing occurs in up to 80% cases, and the sessions may be much prolonged than normal [15]. Skin picking was seen in upto 27% in a series of cases [16]. This is particularly harmful in that it may lead to scars and pigmentation, thereby actually inducing deformity where there was none. BDD patients also indulge in repetitive and excessive make up, grooming, hiding defects with clothes, glasses or caps, hair styling and using concealers.

Repeated reassurance seeking from family and friends is also characteristically seen.

Compared to men, women are more preoccupied with breast and legs, and indulge more in camouflaging and mirror checking. They suffer more from anxiety, panic and bulimia [8].

Most women have pervasive shame, guilt and loss of hope, and do not easily share it with doctors. They request repeated cosmetic or surgical procedures in the hope that the appearance will improve. Eventually they avoid social interaction, isolate themselves and fail in relationships.

In recent years, compulsive "selfie" image clicking and posting on social media is also found to be an increasing trend in patients with BDD. Such women have negative self-image and low self-esteem [17].

There is impairment in various spheres of life like psychosocial functioning, education and occupation, and interpersonal relationships and quality of life decreases. Advanced cases become isolated and housebound [14]. Extreme cases indulge in self-mutilating behaviour in a self-attempt to correct the defect [18].

Up to 30% with BDD have poor insight. If insight is absent, delusions may set in. The patients are quite convinced that others are scrutinizing, discussing or mocking their "defects". Such cases are more resistant to treatment and develop more morbidity [1]. Those with good insight may realise that their defect appears more ugly to them than to others, but still cannot help obsessing about it [19].

Types of BDD

(a) With insight versus without insight (delusional).
(b) BDD by proxy: here a patient is concerned about the appearance of another closely associated person, for example, a wife concerned about a husband's baldness, a mother concerned that her unborn foetus has body defects [20], a mother concerned about child's ugliness [21].
(c) Familial BDD, wherein the patient imposes the delusional idea upon one or more family members [22].
(d) Folie a deux, wherein both partners suffer from BDD.

12.8 Differential Diagnosis

Other conditions that can be mistaken for BDD include:

Obsessive-compulsive disorder, eating disorders, skin picking, trichotillomania, major depressive disorder, anxiety disorder and hypochondriasis.

Those with concerns about actual physical defects too should not be labelled as BDD [13]. The main point in differentiation is the time spent obsessing about the condition and history of compensatory behaviour like mirror gazing and camouflaging.

BDD may have associated social anxiety and depression, which has to be differentiated from primary anxiety and depression.

Olfactory reference syndrome, wherein the patient has a fixed belief that she has foul body odour, is not considered a part of BDD [4].

12.9 Comorbidities

BDD is often associated with anxiety, depression, social avoidance, OCD, eating disorders and substance abuse [23, 24]. This may be a chance association, or due to the shared aetiology and pathogenic mechanisms. Depression is tenfold and anxiety

is fourfold seen in BDD patients than in non BDD subsets, especially if concerns are related to the face [5].

The life time association with BDD for depression is 75%, and for OCD it is 32%. Social phobia can occur in 37–39% of BDD sufferers, irrespective of the BDD attribute [25]. There is an overlap between BDD and eating disorders in the form of preoccupation with a distorted body image. Upto 12% patients with severe eating disorders have BDD [26], and 30–50% have a lifetime prevalence of substance abuse [27].

12.10 Adverse Effects/Complications

These include direct or indirect consequences like the following [11].

- Repeated doctor shopping.
- Unnecessary, multiple cosmetic and surgical procedures leading to drain of finance, family conflict.
- Extreme isolation, severe social phobia.
- Acts of self-mutilation in severe BDD.
- Suicidal tendency (24%).

Complications for the treating dermatologist: violence against treating doctor and multiple lawsuits are much more common. A survey among aesthetic surgeons revealed that with nearly 2% were physically threatened and 29% faced lawsuits by irate BDD sufferers [28].

12.11 Prognosis

BDD is a psychologically debilitating condition with chronic course and poor prognosis, with high rates of suicide. It typically starts in adolescence or early adulthood, though the patient may present to the doctor much later, and has chronic course with average duration of illness being more than 16 years [29]. Bad prognostic factors include younger age of onset, severe symptoms, longer duration of symptoms and associated psychiatric comorbidities [10].

12.12 Diagnosis of BDD

Diagnosis of BDD is essentially by clinical suspicion and correlation.

Multiple scales have been used to evaluate BDD, as it is essential to exclude BDD before performing cosmetologic and plastic surgical procedures. There are dermatologic and cosmetologic versions, as well as self-administered questionnaires [13,

Table 12.2 The Body Dysmorphic Disorder Questionnaire (BDDQ)

(1) Are you worried about how you look? if yes, please list the body areas you don't like If no, you are done with the questionnaire
(2) Is your main concern with how you look that you aren't thin enough or that you might get too fat? Yes/No
(3) How has this problem with how you look affected your life? Has it often upset you a lot? Yes/No • Has it often gotten in the way of doing things with friends, dating, your relationships with people, or your social activities? Yes/No –If yes: Describe how • Has it caused you any problems with school, work, or other activities? Yes/No –If yes: What are they? • Are there things you avoid because of how you look? Yes/No –If yes: What are they?
(4) On an average day, how much time do you usually spend thinking about how you look? (a) Less than 1 h a day. (b) 1–3 h a day. (c) More than 3 h a day

Patient is likely to have BDD if Question 1: Yes to both parts, Question 3: Yes to any of the questions, Question 4: Answers b or cQuestion 2: Yes can indicate either BDD or Eating disorder, and patient has to be further evaluated
Modified from: Phillips, K.A., Atala, K.D., Pope, H.G., 1995. Diagnostic instruments for body dysmorphic disorder. New Research Program and Abstracts, American Psychiatric Association 148th annual meeting. Miami: American Psychiatric Association

30]. A simple self-administered questionnaire which can be filled online, with automatic calculation of scores is available at Body Dysmorphic Disorder Foundation website. If the score is less than 30, out of total 72, the possibility of BDD is negligible [31]. The Body Dysmorphic Disorder Questionnaire (BDDQ) which is 100% sensitive and 89–94% specific is easy to use by the dermatologists [32] (Table 12.2).

12.13 Management of BDD

The main aim of treatment is to reduce dysfunctional thoughts, prevent unnecessary procedures and surgeries, treat associated psychiatric comorbidities and improve psychosocial functioning.

It is essential to categorise the type of BDD, whether predominantly obsessive-compulsive or delusional in nature to plan the most suitable approach. Depending upon the severity of the condition, it can be managed either with non-pharmacological measures alone or combined with psychotropics. It is imperative for all patients to be referred to a mental health professional as it can sometimes co-exist with psychiatric comorbidities which have to be tackled along with BDD.

12.13.1 Non-pharmacological Management

Cognitive-behaviour therapy (CBT) is an evidence based non-pharmacological treatment of BDD [33]. Our actions are usually governed by our thoughts. The principle of CBT is to identify and work on the disturbing thoughts to bring about changes in the behaviour patterns. The key therapeutic strategy of CBT used in BDD is Exposure and Response Prevention E/RP, others being motivational interviewing, psychoeducation, cognitive restructuring and mirror retraining/attention training [34–37].

CBT is the standard treatment for BDD. It is usually administered weekly on an individual basis, over 18 to 22 weeks. As a first step the therapist/clinician should do a thorough assessment of the patients with respect to their concerns, feelings, behaviour as well as the distress experienced. Subtle clues such as scars or excoriations on the face or use of heavy make-up to "hide" the defects should be noted. The therapist should screen for delusions of reference (e.g. "I feel all are staring at me when I go out"), panic attack (e.g. "I feel dizzy and think I am passing out when somebody looks at me"), depression, suicidal ideations, substance abuse, social phobia and also history of frequent cosmetic treatments.

12.13.2 Motivational Interviewing (MI) [38]

It is an effective counselling method which enhances motivation of the patient by resolving ambivalence. Ambivalence is the state where patient has contradictory feelings, that is, she wants to change her thoughts/actions but simultaneously not wanting to.

The four guiding principles of MI are represented by the acronym RULE where R = Resist the righting reflex, U = Understand the patient's own motivation, L = Listen with empathy, E = Empower the patient.

12.13.2.1 Resist the Righting Reflex

The health professionals usually have a tendency to be judgemental and advise the patients as to what is right and wrong. This can be viewed as criticism by patients with further strengthening of their thoughts and behaviours. By avoiding this attitude, the patient's motivation to change can be understood.

12.13.2.2 Understanding the Patient's Own Motivation

It is better to understand the patient's perspective and reasons for wanting to change and also the difficulties faced in this regard.

12.13.2.3 Listen with Empathy

Listening with concern forms the key. Rule of the thumb in MI is giving equal time for listening as well as talking.

12.13.2.4 Empower the Patient

The doctor needs to empower his patients to actively take part in treatment choices by openly discussing about their ideas to bring about the desired change.

12.14 Psychoeducation

Before initiating treatment, it is essential to provide psychoeducation to the patient on BDD. Psychoeducation is an evidence-based therapeutic intervention for the patient and family members or care-givers where they are given information about BDD, specifically how to distinguish BDD from normal appearance and body image concerns, role of perception regarding body image, outline of the cycle of BDD with emphasis on various behaviours that maintain distress [39]. Providing information aids in empowerment of patients and treatment compliance.

12.15 Exposure and Response Prevention (E/RP) [40]

The main principles of this treatment is to expose the client to the feared situation in a graded fashion until he/she becomes habituated to it with the assumption that gradually the aversion reduces and tolerance develops. It means encouraging the client to go out in public places and mingle with others without trying to hide the perceived flaws. Response prevention entails not giving in to behaviour such as gazing into the mirror, asking for reassurances from friends and family, consulting dermatologists and aestheticians for "correcting" the "flaws".

E/RP therapy starts with a detailed interview with the client to discuss their thoughts, feelings and behaviours related to their BDD. The treatment is conducted in four phases. In the first phase consisting of three weeks, the patient is given a self-rating scale to complete and is also told to self monitor [41] both the thoughts as well as BDD related behaviour. The self-reported diary [40] consists of 5 items

which the client rates once daily on a scale of 1 to 8: (1) rate the amount of time you had obsessions related to your appearance during the day; (2) rate the amount of distress you experienced due to the obsessions; (3) rate the amount of time you spent on compulsions during the day; (4) rate your ability to control the compulsions; (5) rate your degree of avoidance due to appearance concerns during the day. A daily mean score is calculated. Every week these self-report diaries are checked by the therapist and at the end of three weeks, a self-rating scale is filled. The common self-rating scales used in practice include the body dysmorphic disorder modification of the Yale–Brown obsessive-compulsive inventory scale [42], the Sheehan disability scale [43] and The MADRS-S [44, 45].

The second phase is over three weeks and the client meets the therapist twice weekly to reflect upon her thoughts and behaviours, while the therapist continues to motivate the patient to maintain the diary. In the third phase over seven weeks, E/RP is introduced with exposure in the initial weeks and response prevention strategies in the last few weeks. Exposure consists of carrying out the feared and dreaded activities such as going to crowded places such as malls, restaurants and parks without hiding the face in clothing or using make-up. Response prevention strategies consist of avoiding the use of make-up, avoiding looking into mirrors, reducing hours spent on reading about cosmetic products and cosmetic surgeries and also not seeking reassurance from family members about appearance. Fourth phase is the renewed self-monitoring phase consisting of three weeks where client continues to maintain the diary without any sessions with the therapist.

12.16 Cognitive strategies [46]

These include identifying maladaptive thoughts, assessing them and creating different thoughts. The therapist helps client to recognise their thoughts, for example, “The scars on my face make me look very ugly”. They may also harbour cognitive errors such as “My colleagues always stare at my face and think how bad I look”. After the client learns to identify them, the therapist works with the client to assess the soundness of the thoughts as well as their usefulness. For example, the client has to ask herself, “Has anyone ever told me that I look ugly because of my scars?” or “What is the evidence that others are looking at me and judging my looks?” Once the client learns to identify the thoughts and appearance related beliefs, the deeper core thoughts will be addressed. For example, in a client who believes his nose is big and crooked, the therapist will repeatedly question him, “What would it mean if people noticed your nose as big?” until the client expressed his core belief as, “If people noticed that my nose was big, they would not like me and this would mean that I am unlovable.” [3] By constantly working with the client, the therapist makes her understand her self-worth and make her realize that her skills and achievements are more important than the appearance.

12.17 Mirror Retraining and Attention Training

In BDD clients check out their image in the mirror to focus only on their perceived defect. In mirror retraining the client is trained to look at the mirror in a holistic manner. One learns to observe and describe the parts of the body in a non-judgemental manner without thinking as ugly, bad etc. In attention training, instead of focussing on their external 'flaws' and thinking how they will appear to others, they are trained to redirect their attention externally to the activity at hand and their environment. This enables them to enjoy their activities and interpersonal relations.

Based on case series, open studies and controlled studies, CBT is the first choice among psychotherapies recommended for clients with BDD [47]. In a first controlled study on group therapy in BDD, 54 clients were randomized to receive either CBT or to a waiting list. The former group showed significant reduction in the symptoms after 8 two hour sessions [48]. In a randomized controlled trial of 94 patients to either therapist-guided internet based CBT programme or an online supportive therapy, found the former therapy superior to the latter [49]. An open 12-week trial of smart-phone delivered CBT showed improvement in symptom severity, insight, functional status and quality of life in 90% of subjects [50].

A proportion of clients with BDD either do not respond to psychological measures are suffer from relapses. In such persons a visual training programme is under investigation based on visual perception abnormalities reported to be a key feature in BDD [51].

12.18 Medical Management (Pharmacotherapy) of BDD

As BDD is classified under the new Obsessive-Compulsive and related disorders, just as OCD, it is treated with Selective serotonin reuptake inhibitors (SSRIs). As in OCD, doses higher than that needed for depression have to be used, sometimes double or triple the antidepressant dose [52]. It is essential to use the highest tolerated dose for at least 3–4 months before switching to alternative treatments.

SSRIs such as citalopram, escitalopram, fluoxetine, fluvoxamine and tricyclic antidepressant clomipramine have been found useful. Among them escitalopram and fluoxetine have been the best studied and well tolerated drugs in BDD. In a 12-week open-label trial of citalopram in 15 subjects with BDD, responders constituted 73% and the drug was well tolerated in a dose of 20–40 mg/day [53]. In an open-label study of escitalopram, 10–30 mg/day in 100 patients of BDD, response was seen in 58% of cases. The 58 responders were then subjected to a randomised double blind study and a significant improvement was observed at the end of 6 months [54]. In a double-blind placebo controlled study of 67 patients with BDD treated with fluoxetine 20–80 mg per day, significant improvement was seen in 53 patients at week 8, continuing at weeks 10 and 12 [55]. In an open clinical trial of

fluvoxamine (100–300 mg/day) in 15 patients, 10 markedly improved at week 10 [56]. A double-blind crossover trial of clomipramine versus desipramine (selective norepinephrine reuptake inhibitor) found the former to be more effective than the latter and also useful in delusional patients [57].

12.18.1 SSRI Augmentation Therapies

When SSRIs alone show suboptimal response, or in cases with suicidal ideations, depressive features or delusions, additional treatments such as CBT or other psychotropics may be added to augment the effect. Adding an anxiolytic such as buspirone a 5HTA1 antagonist may help [58]. Addition of an atypical antipsychotic aripiprazole 10 mg/day has helped a case of BDD resistant to fluvoxamine alone [59]. Olanzapine 5 mg added to paroxetine 40 mg/day has greatly benefitted a female with severe BDD [60].

Pharmacotherapeutic guidelines in BDD [61]

1. Recognise and diagnose BDD: The diagnosis is usually missed in clinical practice. When patient is unusually concerned about minor or non-existent flaws, BDD has to be suspected. Simple questioning or use of standard questionnaires aids in the diagnosis.
2. Providing psychoeducation: It helps to educate the patient about the nature of the condition, measures to tackle it, complications if it is left untreated and the general course of the condition. Proper knowledge assists the patient to choose suitable treatment.
3. Begin treatment with an SSRI even in delusional patients.
4. Use maximum SSRI dose recommended or tolerated unless a lower dose works, for example, up to 80 mg of fluoxetine may be tried.
5. Continue the SSRI for at least a year.
6. Gradually taper the SSRI and do not stop abruptly.
7. If one SSRI fails try another.
8. Consider augmentation therapies.
9. Consider benzodiazepines in agitated or anxious patients.
10. Although medications are always needed for severely ill, severely depressed and highly suicidal patients, CBT can be tried as adjuvant treatment in all cases of BDD.

The role of oxytocin in the treatment needs to be investigated based on recent data [62]. Neurostimulation is another promising area for study [63]. Electroconvulsive therapy may be helpful in patients with BDD and depressive features [64].

12.18.2 Therapeutic Prognosis

Although BDD is a chronic disorder, it does respond to evidence-based treatments. A response rate of 50–80% has been observed with pharmacotherapy [65]. The BDD scoring instruments help in assessing the effect of treatment. Relapses can be prevented by long-term therapy.

Key Points

- BDD is an intrusive and obsessive primary psychiatric condition, mostly seen in young adults.
- Although not uncommon, it is frequently missed in clinical settings.
- Detailed history and questionnaires help in diagnosis.
- Associated psychiatric co-morbidities should be sought and treated.
- The severity of BDD is proportionate to the loss of insight which may vary from minimal to complete.
- Severe BDD can disrupt the patient's life in all spheres including psychosocial and occupational.
- Unwarranted cosmetic surgeries need to be avoided.
- In many a case, treatment is difficult, especially so in delusional patients who are unwilling to approach mental health professionals.
- CBT and SSRIs are standard treatment modalities.
- Dermatologists, aestheticians and plastic surgeons need to be especially careful in identifying and dealing with BDD patients as they are prone to physical violence or indulge in legal lawsuits.
- A BDD patient should be delicately handled by empathizing with them, firm refusal in offering unnecessary cosmetic and aesthetic procedures, and directing to a mental health expert.
- In patients with insight as well as in patient's family members, awareness of the disease may lead to acceptance of the diagnosis and better compliance with treatment.

References

1. Phillips KA, Didie ER, Feusner J, Wilhelm S. Body dysmorphic disorder: treating an underrecognized disorder. Am J Psychiat. 2008;165:1111–8.
2. Hsu SH, Vashi NA. Body Dysmorphic disorder: historical aspects. Chapter 6. In: Vashi NA, editor. Beauty and body dysmorphic disorder: a clinician's guide. Switzerland: Springer; 2015. p. 95–102.
3. Gardiner M. The wolf-man and Sigmund Freud. London: Pelican/Penguin Books; 1973.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
5. Herbtst I, Jemec GBE. Body dysmorphic disorder in dermatology: a systematic review. Psych Quart. 2020;91:1003–10.
6. Brohede S, Wingren G, Wijma B, Wijma K. Prevalence of body dysmorphic disorder among Swedish women: a population-based study. Compr Psychiatry. 2015;58:108–15.

7. Phillips KA, Diaz SF. Gender differences in body dysmorphic disorder. J Nerv Ment Dis. 1997;185(9):570–7.
8. Perugi G, Akiskal HS, Giannotti D, Frare F, Di Vaio S, Cassano GB. Gender-related differences in body dysmorphic disorder (dysmorphophobia). J Nerv Ment Dis. 1997 Sep;185:578–82.
9. Weiffenbach A, Kundu RV. Body dysmorphic disorder: etiology and pathophysiology. Chapter 8. In: Vashi NA, editor. Beauty and body dysmorphic disorder: a clinician's guide. Switzerland: Springer; 2015. p. 114–26.
10. Vashi NA. Obsession with perfection: body dysmorphia. Clin Dermatol. 2016;34:788–91.
11. Prabhu S, Balachandran C, Hameed S, Rao R, Sripathi H. Dermatological non disease. J Pak Assoc Dermatol. 2007;17:182–6.
12. Toh WL, Castle DJ, Mountjoy RL, Buchanan B, Farhall J, Rossell SL. Insight in body dysmorphic disorder (BDD) relative to obsessive-compulsive disorder (OCD) and psychotic disorders: revisiting this issue in light of DSM-5. Compr Psychiatry. 2017;77:100–8.
13. Jafferany M, Franca K, Vashi NA. Diagnosis of body dysmorphic disorder. Chapter 7. In: Vashi NA, editor. Beauty and body dysmorphic disorder: a clinician's guide. Switzerland: Springer; 2015. p. 103–11.
14. Phillips KA, Wilhelm S, Koran LM, Didie ER, Fallon BA, Feusner J, et al. Body dysmorphic disorder: some key issues for DSM-V. Depress Anxiety. 2010;27:573–91.
15. Veale D, Riley S. Mirror, mirror on the wall, who is the ugliest of them all? The psychopathology of mirror gazing in body dysmorphic disorder. Behav Res Ther. 2001;39:1381–93.
16. Phillips KA, Taub SL. Skin picking as a symptom of body dysmorphic disorder. Psychopharmacol Bull. 1995;31(2):279–88.
17. Khanna A, Sharma MK. Selfie use: the implications for psychopathology expression of body dysmorphic disorder. Ind Psychiatry J. 2017;26:106–9.
18. Chan JK, Jones SM, Heywood AJ. Body dysmorphia, self-mutilation and the reconstructive surgeon. J Plast Reconstr Aesthet Surg. 2011;64:4–8.
19. Shiffman MA. Body dysmorphic disorder. Am J Cosm Surg. 2008;25:269–71.
20. Laugharne R, Upex T, Palazidou E. Dysmorphophobia by proxy. J R Soc Med. 1998;91(5):266. https://doi.org/10.1177/014107689809100507.
21. Bakhla AK, Prakriti S, Kumar PA. A case of body dysmorphic disorder by proxy. Prim Care Companion CNS Disord. 2012;14(4):PCC.12l01347. https://doi.org/10.4088/PCC.12l01347.
22. Seaton ED, Baxter KF, Cunliffe WJ. Familial dysmorphophobia. Br J Dermatol. 2001;144:439–40.
23. Phillips KA, McElroy SL. Personality disorders and traits in patients with body dysmorphic disorder. Compr Psychiatry. 2000;41:229–36.
24. Gunstad J, Phillips KA. Axis I comorbidity in body dysmorphic disorder. Compr Psychiatry. 2003;44(4):270–6.
25. Coles ME, Phillips KA, Menard W, Pagano ME, Fay C, Weisberg RB, et al. Body dysmorphic disorder and social phobia: cross-sectional and prospective data. Depress Anxiety. 2006;23:26–33.
26. Hrabosky JI, Cash TF, Veale D, Neziroglu F, Soll EA, Garner DM, et al. Multidimensional body image comparisons among patients with eating disorders, body dysmorphic disorder, and clinical controls: a multisite study. Body Image. 2009;6:155–63.
27. Grant JE, Menard W, Pagano ME, Fay C, Phillips KA. Substance use disorders in individuals with body dysmorphic disorder. J Clin Psychiatry. 2005;66:309–16.
28. Sarwer DB. Awareness and identification of body dysmorphic disorder by aesthetic surgeons: Results of a survey of American society for aesthetic plastic surgery members. Aesth Surg J. 2022;22:531–5.
29. Phillips KA, McElroy SL, Hudson JI, Pope HG Jr. Body dysmorphic disorder: an obsessive-compulsive spectrum disorder, a form of affective spectrum disorder, or both? J Clin Psychiatry. 1995;56(Suppl 4):41–51.
30. Dufresne RG, Phillips KA, Vittorio CC, Wilkel CS. A screening questionnaire for body dysmorphic disorder in a cosmetic dermatologic surgery practice. Dermatol Surg. 2001;27:457–62.

31. COPS—Do I have BDD? Body Dysmorphic Disorder Questionnaire. Body Dysmorphic Disorder Foundation. Available at: https://bddfoundation.org/helping-you/questionnaires-do-i-have-bdd/. Accessed 28 Jan 21
32. Phillips KA, Atala KD, Pope HG. Diagnostic instruments for body dysmorphic disorder. New research program and abstracts, American Psychiatric Association 148th annual meeting. Miami: American Psychiatric Association; 1995.
33. Krebs G, Fernández de la Cruz L, Mataix-Cols D. Recent advances in understanding and managing body dysmorphic disorder. Evid Based Ment Health. 2017;20:71–5.
34. Veale D. Cognitive behavioral therapy for body dysmorphic disorder. Psychiatric Annals. 2010;40(7):333–40. Available from https://www.healio.com/psychiatry/journals/psycann/2010-7-40-7/%7Beba821e5-dfc9-4073-9b89-183b6c430dc5%7D/cognitive-behavioral-therapy-for-body-dysmorphic-disorder#divReadThis. https://doi.org/10.3928/00485713-20100701-06y.
35. Wilhelm S, Phillips KA, Steketee G. A cognitive-behavioral treatment manual for body dysmorphic disorder. New York: The Guilford Press; 2013.
36. Wilhelm S, Bulhman U, Hayward LC, Greenberg JL, Dimaite R. A cognitive- behavioural treatment approach for body dysmorphic disorder. Cognitive Behavioural Practice. 2010;17(3):241–7.
37. Veale D, Gournay K, Dryden W, Boocock A, Shah F, Willson R, et al. Body dysmorphic disorder: a cognitive behavioural model and pilot randomised controlled trial. Behav Res Ther. 1996;34(9):717–29.
38. Rollnick S, Miller WR, Butler CC. Motivational interviewing in health care. In: Helping patients change behavior. New York: The Guilford Press; 2008.
39. Turner C, Cadman J. When adolescents feel ugly: cognitive behaviour therapy for body dysmorphic disorder in youth. J Cogn Psychother. 2017;31(4):242–54. https://doi.org/10.1891/0889-8391.31.4.242.
40. Folke F, Bahr MV, Assadi-Talaremi V, Ramnero J. The exposure and response prevention in the treatment of body dysmorphic disorder—a case series. Pragmatic Case Studies Psychother. 2012;8(4):255–87.
41. Wilhelm S, Otto MW, Lohr B, Deckersbach T. Cognitive—behavior therapy for body dysmorphic disorder—a case series. Behav Res Ther. 1999;37:71–5.
42. Phillips KA, Hollander E, Rasmussen SA, Aronowitz BR, DeCaria C, Goodman WK. A severity rating scale for body dysmorphic disorder: development, reliability, and validity of a modified version of the Yale-Brown obsessive compulsive scale. Psychopharmacol Bull. 1997;33:17–22.
43. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11(Suppl 3):89–95.
44. Svanborg P, Åsberg M. A new self-rating scale for depression and anxiety states based on the comprehensive psychopathological rating scale. Acta Psychiatr Scand. 1994;89:21–8.
45. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134(4):382–9. https://doi.org/10.1192/bjp.134.4.382.
46. Hartmann A, Greenberg J, Wilhelm S. A therapist's guide for body dysmorphic disorder. International OCD Foundation; 2021. Available from https://bdd.iocdf.org/professionals/therapists-guide-to-bdd-tx/
47. Allen A. Cognitive-behavioral treatment of body dysmorphic disorder. Prim Psychiatry. 2006;13:70–6.
48. Rosen JC, Reiter J, Orosan P. Cognitive-behavioral body image therapy for body dysmorphic disorder. J Consult Clin Psychol. 1995;63:263–9.
49. Enander J, Andersson E, Mataix-Cols D, Lichtenstein L, Andersson G, Ruck C. Therapist guided internet based cognitive behavioural therapy for body dysmorphic disorder: single blind randomised controlled trial. BMJ. 2016;352:i241. Available from https://www.bmj.com/content/352/bmj.i241

50. Wilhelm S, Weingarden H, Greenberg JL, McCoy TH, Ladis I, Summers BJ, et al. Development and pilot testing of a cognitive-behavioural therapy digital service for body dysmorphic disorder. Behav Ther. 2020;51:15–26.
51. Beilharz F. Visual processing in body dysmorphic disorder: investigating eye movements and piloting a novel training programme. 2019. Available from https://researchbank.swinburne.edu.au/file/540da7d1-18bc-4371-9517-d324972a7baf/1/francesca_beilharz_thesis.pdf.
52. Sjogren M. An update on psychopharmacological treatment of body dysmorphic disorder. J Psychol Clin Psychiatry. 2019;10:228–32.
53. Phillips KA, Najjar F. An open-label study of citalopram in body dysmorphic disorder. J Clin Psychiatry. 2003;64:715–20.
54. Phillips KA, Keshaviah A, Dougherty DD, et al. Pharmacotherapy: relapse prevention in body dysmorphic disorder: a double-blind placebo-controlled trial. Am J Psychiatry. 2016;173:887–95.
55. Phillips KA, Albertini RS, Rasmussen SA. A randomised placebo-controlled trial of fluoxetine in body dysmorphic disorder. Arch Gen Psychiatry. 2002;59:381–8.
56. Perugi G, Gianotti D, Vaio SD, Frare F, Saetonni M, Cassano GB. Fluvoxamine in the treatment of body dysmorphic disorder. Int Clin Psychopharmac. 1996;11:247–54.
57. Hollander E, Allen A, Kwon J, et al. Clomiprmaine v/s desipramine crossover trial in body dysmorphic disorder. Arch Gen Psychiatry. 1999;56:1033–9.
58. Ipser J, Sander C, Stein D. Pharmacotherapy and psychotherapy for body dysmorphic disorder. Cochrane Database Syst Rev. 2009;1:CD005332. https://doi.org/10.1002/14651858.CD005332.pub2.
59. Uzun O, Ozdemir B. Aripiprazole as an augmentation agent in treatment-resistant body dysmorphic disorder. Clin Drug Investig. 2010;30:707–10.
60. Nakaaki S, Murata Y, Furukawa TA. Effect of olanzapine augmentation of paroxetine therapy in patients with severe body dysmorphic disorder. Psychiatry Clin Neurosci. 2008;62:370.
61. Phillips KA. Pharmacologic treatment of body dysmorphic disorder: review of the evidence and a recommended treatment approach. CNS Spectr. 2002;7:453–63.
62. Grace SA, Labuschagne I, Castle DJ, Rossell SL. Intranasal oxytocin alters amygdala-temporal resting-state functional connectivity in body dysmorphic disorder: a double-blind placebo-controlled randomized trial. Psychoneuroendocrinology. 2019;107:179–86.
63. Castle D, Beilharz F, Phillips KA, Brakoulias V, Drummond LM, Hollander E, et al. Body dysmorphic disorder : a treatment synthesis and consensus on behalf of the international college of obsessive-compulsive Spectrum disorders and the obsessive-compulsive and related disorders network of the European college of Neuropsychopharmacology. Int Clin Psychopharmacol. 2021;36:61–75.
64. Mahato RS, San Gabriel MCPS, Longshore CT, Schnur DB. A case of treatment-resistant depression and body dysmorphic disorder: the role of electro-convulsive therapy revisited. Innov. Clin Neurosci. 2016;13(7-8):37–40.
65. Nicewicz HR, Boutrouille JF. Body dysmorphic disorder. StatPearls; 2020. Available from https://www.ncbi.nlm.nih.gov/books/NBK555901/. Accessed 30 Jan 2021

Chapter 13
DLQI in Females: Important Disorders with Low DLQI

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13.1 Quality-of-Life Instruments in Dermatology

Skin diseases, especially chronic disorders like psoriasis, vitiligo and hidradenitis can cause significant psychosocial impact on patients' lives affecting their day-to-day activities and social functioning. The quantification of the impact of various skin disorders on the quality of life (QoL) of patients has been made possible due to the development of various dermatology specific QoL measurement instruments like Dermatology Life Quality Index (DLQI) and Skindex-29. Over the past two decades, a multitude of various age-specific (Children's Dermatology Life Quality Index [CDLQI], Infants' and Toddlers' Dermatology Quality of Life [InToDermQoL]) and disease-specific instruments (Cardiff Acne Disability Index [CADI], Acne-Specific Quality of Life Questionnaire [Acne-QoL], Skin Cancer Index [SCI] and Psoriasis Disability Index [PDI]) have also been developed [1]. Besides measurement of the impact of disease on patient QoL, these instruments are also used to measure the effectiveness of various treatment modalities in improving the patient outcomes and have become an integral part of various studies and clinical trials. Of the various QoL measurement instruments, the DLQI is the most commonly used in various studies and trials. In this chapter, we shall present an overview of the most commonly used QoL index—the DLQI and its importance in regard to female dermatoses and describe the various skin disorders having significant impact on the QoL in women.

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13.2 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI), developed by Finlay and Khan in 1998, is the most widely established dermatological life quality instrument [2]. It comprises of a self—administered questionnaire consisting of 10 questions which covers the impact of the disease across various parameters—symptoms, patient perception, relationships, leisure, work and adverse effects of treatment. Individual items on the questionnaire are scored on a 4 point scale (0–3) and a final total is calculated by the addition of the individual scores (0–30). A higher total score represents a greater impairment of the patients' quality of life. With the advantages of being easy to administer, extensively validated and having short completion time, it is used extensively in clinical trials, registries and guidelines, and has been translated to 99 different languages [3]. Banding system for the DQLI scores has been suggested to provide better interpretation of the scores. However the DLQI is not without flaws. Rasch analysis of DLQI scores have demonstrated a lack of unidimensionality and bias among the individual items in the instrument with regard to age, gender and nationality [4, 5].

13.3 Dermatology Life Quality Index (DLQI) in Women

Though initial studies by Finlay and Khan do not show significant differences in the mean DLQI in men and women, DLQI scores, several cross-sectional studies of various dermatoses have shown significant differences in DLQI between men and women [6–8]. Explanations provided include higher importance placed on physical appearance, societal and cultural pressure and maladaptive symptoms about appearance [9]. There exist subjective differences between how men and women perceive skin disease and also its impact on personal relationships, social interactions, work productivity and ultimately their overall quality of life.

In this chapter we shall discuss in brief, various dermatoses with major impact on quality of life in women.

13.3.1 Psoriasis

Psoriasis is a chronic inflammatory skin disease which usually manifests as erythematous scaly plaques that can involve any skin surface, typically having a predilection for the elbows, knees, lower back and the scalp. 20–30% of patients with psoriasis also develop psoriatic arthritis [10]. Besides psoriatic arthritis, psoriasis is also associated with an increased risk of other diseases such as metabolic syndrome, malignancies, cardiovascular complications and inflammatory bowel disease [11].

Psoriasis can occur at any age and has a bimodal onset. A systematic review of epidemiological studies on psoriasis suggests that the bimodal onset of psoriasis occurs slightly earlier in women (ages 18–29 and 50–59) compared to men (ages 30–39 and 60–79) [12].

Hormonal factors modulate psoriasis leading to fluctuation of disease activity in women with psoriasis especially during puberty, pregnancy and menopause [13]. Besides this, pregnancy and lactation also pose unique challenges with regard to disease management in women.

Psoriasis has significant adverse impact on the patients' QoL comparable to that caused by major illnesses like myocardial infarction, diabetes and hypertension [14]. A Czech study on gender specific differences in patients taking biologics showed that women had higher DLQI scores along with significantly higher prevalence of depression [15]. Pollo et al. in Brazil showed that female sex was associated with higher anxiety and depression scores [16]. A study by José et al. has shown women with psoriasis having higher DLQI and anxiety depression scores [17]. Beata et al. studied the levels of illness acceptance in psoriasis and showed that the level of illness acceptance among men was significantly higher than among women [18]. Women also experienced greater feeling of discrimination compared to men with both genders having similar skin involvement [19]. Women with psoriasis also tend to have higher levels of sexual dysfunction especially with the presence of genital lesions [20].

13.3.1.1 Psoriasis in Pregnancy

The initial onset of psoriasis is usually between the second and fourth decades coinciding with the peak reproductive period. In majority of women, psoriasis ameliorates during pregnancy however there is a proportion of patients who experience worsening [21]. Review of observational studies do not reveal any association between psoriasis and adverse pregnancy outcomes [22]. When managing psoriasis in pregnancy, it is important to balance the potential risks of psoriasis treatments with the risk of disease flare. Psoriasis has myriad treatment options including topical medications (emollients, corticosteroids, vitamin D analogues like calcipotriol, anthralin, tacrolimus, salicylic acid, tazarotene and coal tar), phototherapy, oral systemic drugs and biologics. Emollients are safe without any major adverse effects [23]. Topical steroids are considered safe for use in pregnancy and mild to moderate potency agents are preferred as studies suggest that potent to very potent agents may be associated with increased risk of low birth weight especially with large cumulative exposures [24]. Coal tar, anthralin and tazarotene have mutagenic properties and are to be avoided during pregnancy [25]. Systemic absorption of topical tacrolimus is minimal and is considered safe when used sparingly for smaller surface area [26]. Phototherapy with ultraviolet B (narrowband and broadband) is safe in pregnancy and can be initiated as a first line treatment in moderate to severe cases when topical treatments may be inadequate. Phototherapy with psoralen UVA is contraindicated due to the mutagenic nature of psoralen.

Traditional systemic agents like methotrexate and acitretin are classified as Class X as per FDA and are contraindicated in pregnancy due to their teratogenic effects. Cyclosporine can be considered as a treatment option for psoriasis in pregnancy however it is advisable to use the lowest possible dose for the shortest possible duration [27]. Although cyclosporine crosses the placental barrier, it has not been reported to have teratogenic effects. However, there are reports of its association with prematurity and low birth weight. Data regarding the safety of apremilast during pregnancy is lacking and is currently contraindicated in pregnancy.

13.3.1.2 Biologic Agents

With the rise in the use of biologics, data regarding their safety during pregnancy are also increasing. Risk of teratogenicity, effects on the development of the fetal immune system, maternal and fetal immunosuppression are factors to be considered before initiation of biologics in pregnancy. TNF-alpha inhibitors are now widely used for various autoimmune conditions and much of the available safety data is from their use in the treatment of rheumatological and gastrointestinal diseases. No significant differences were found in pregnancy outcomes between the normal population and patients using TNF-alpha inhibitors—etanercept, infliximab and adalimumab. These drugs are currently under pregnancy category B. One major concern with the use of these drugs is the risk of fetal immunosuppression. These antibodies can persist up to 6 months after delivery in infants and can cause increased susceptibility to infections. In such infants, it is recommended to delay the use of live vaccines until 6 months to 1 year of age. Certolizumab-pegol is a TNF-alpha inhibitor that has minimal placental transfer and current data does not show any adverse outcomes when compared to general population. Certolizumab-pegol currently appears to be safe for use in pregnancy when required. IL-23 inhibitors (ustekinumab) have been reported to be associated with a higher risk of spontaneous abortions and are contraindicated. IL-17 inhibitors can be transferred through the placenta. Current data suggests that the outcomes of pregnancy with exposure to secukinumab and ixekizumab are similar to that seen in the general population [23]. However, given the limited data available, it is advised to avoid these drugs in pregnancy at present.

13.3.2 Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic inflammatory disease that manifests as painful nodules, abscesses, sinuses and scars predominantly over the intertriginous regions. The prevalence of hidradenitis suppurativa varies from 0.0005 to 4.1% with a high female preponderance of 3:1 in North American and European population [28]. The presentation, clinical features, diagnosis and treatment of hidradenitis suppurativa have been discussed in detail in Chap. 7.

In women, studies show that the symptoms of hidradenitis suppurativa flareup in the perimenstrual period particularly in the premenstrual period [29]. A survey of patients with Hidradenitis suppurativa reported that in more than 50% of hidradenitis suppurativa patients undergoing LSCS, new lesions developed in the C-section scar.

13.3.2.1 Hidradenitis Suppurativa and Quality of Life in Women

Hidradenitis suppurativa can cause profound impairment in patients' quality of life in terms of both physical (pain, malodorous discharge) and psychosocial aspects (shame, embarrassment, distress, psychiatric comorbidities). Studies in Finnish and Polish populations have shown that women with hidradenitis suppurativa tend to score higher on DLQI compared to men [30, 31]. Hidradenitis suppurativa also has an adverse impact on female sexual health and female patients with hidradenitis suppurativa tend to experience significant distress [32].

13.3.3 Autoimmune Blistering Disorders

Autoimmune blistering disorders (AIBD) refer to a group of bullous dermatoses caused by circulating autoantibodies targeting either intraepidermal or dermoepidermal adhesion molecules. Quality of life in women with AIBD tends to be affected more than that in men owing to various factors. Management of these disorders in women during pregnancy and lactation is also challenging.

Pemphigus is a rare group of IgG4 mediated autoimmune blistering disorders affecting the skin and mucous membranes. The underlying pathogenesis is the development of autoantibodies against cellular adhesion molecules found in the desmosomes—Desmogleins 1 and 3, leading to loss of intercellular adhesion—acantholysis leading to blister formation. Clinically it is characterized by the development of flaccid blisters and erosions over the skin and mucous membranes. Pemphigus comprises of three major types—pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Pemphigus vulgaris is the most common type accounting for 70% of the total pemphigus cases followed by pemphigus foliaceus. Less common variants are pemphigus vegetans, pemphigus erythematosus, pemphigus herpetiformis and drug-induced pemphigus.

Reviews of the epidemiological studies of pemphigus group have shown increased female preponderance especially in pemphigus vulgaris [33–35]. Tunisian pemphigus foliaceus is also reported to have high female predominance [34, 35].

The pemphigoid group of disorders is characterized by the presence of antibodies against the proteins of the dermoepidermal junction. Bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA diseases and epidermolysis bullosa acquisita are included in this group.

Bullous pemphigoid is the most common autoimmune subepidermal blistering dermatoses and caused by antibodies against components of hemidesmosomes—BP180 and BP230. Bullous pemphigoid has also been shown to have a female preponderance with the incidence being greater in women till the age of 75 following which it becomes reversed [36, 37]. Mucous membrane pemphigoid and epidermolysis bullosa acquisita are also shown to have a female predominance [35].

Autoimmune blistering disorders can cause significant physical and psychosocial impairment. The chronic nature of these disorders, the need for long-term immunosuppressive treatment along with its side effects and the relapsing nature of the disease add significantly to this burden. Majority of the available literature is focused on pemphigus and bullous pemphigoid. Studies by Paradisi et al. in pemphigus have shown that women experience greater reduction in quality of life [38, 39]. The presence of oral lesions in pemphigus can cause severe physical impairment in women as they score higher in pain and functional limitation domains in Chronic Oral Mucosal Diseases Questionnaire [40]. Tabolli et al. (2014) discovered that QOL of females was reduced compared to males even during periods of quiescent disease [41].

13.3.3.1 Pregnancy and AIBD

AIBD during pregnancy can be challenging for dermatologists. Among the various entities in this group of diseases, pemphigus vulgaris and pemphigoid gestationis are especially important with regard to pregnancy. Pregnancy has been reported to exacerbate or induce onset of pemphigus vulgaris [42, 43].

Topical corticosteroid and topical calcineurin inhibitors can also be used as first line in mild or localized disease in both pemphigus and pemphigoid gestationis. However they are subject to the same limitations discussed in the earlier section on psoriasis [44].

Azathioprine and cyclosporine have been used for the treatment of pemphigus in pregnancy. Mycophenolate mofetil, cyclophosphamide and methotrexate are teratogenic and are contraindicated in pregnancy [45].

In most cases systemic corticosteroids are used as the first line treatment for pemphigus in pregnancy and form the mainstay of treatment in combination with steroid sparing agents like azathioprine and intravenous immunoglobulin (IVIg). Systemic corticosteroids are also used as first line treatment for pemphigoid gestationis.

Rituximab is an anti-CD20 monoclonal antibody which depletes B-cells and is used in the treatment of pemphigus. Though majority of the data on rituximab does not show increased incidence of congenital abnormalities, it has been reported to be associated with prematurity and spontaneous abortions. Rituximab can cross the placental barrier, thereby posing the risk of fetal immunosuppression due to B-cell depletion. Kushner et al. have recommended planning a pregnancy at least 12 months after the last infusion of rituximab [45]. However Lake et al. and Vassallo et al. suggest that the use of rituximab prior to conception can induce remission alleviating

the need for immunosuppressive agents during pregnancy [46, 47]. Plasmapheresis is considered to be safe in pregnancy and has been used for the treatment of refractory cases of pemphigus and also as monotherapy for pemphigus gestationis.

13.3.4 Vitiligo

Vitiligo is caused by destruction of melanocytes resulting in circumscribed depigmented macules. Vitiligo can significantly affect the quality of life especially when it occurs on the exposed areas of the body. Several studies using the DLQI have shown that vitiligo is associated with poorer quality of life in women when compared with men [48]. Women with vitiligo are also more likely to experience stigmatization [49]. Vitiligo is poorly understood in several parts of the world and is thought to be a contagious disease [50]. Women in such circumstances may find themselves isolated by society and can encounter difficulties with regard to education, employment and marriage. In such cultures, vitiligo can also pose threats to stability of marriage and relationship, with studies showing that married women face more discrimination compared to married men [51, 52]. Women with vitiligo also tend to be at higher risk for depression and anxiety [53]. Studies have reported increased sexual dysfunction in women with genital vitiligo [54].

Thus, vitiligo causes substantial disease burden as reflected by QoL impairment especially in women. In the management of vitiligo, dermatologists should take into consideration the impact of vitiligo on self-esteem and quality of life. Besides arrest of disease progression and repigmentation, interventions must also be provided to address the psychological needs of patients with vitiligo.

13.3.5 Acne Vulgaris

Acne vulgaris is one of the most common conditions encountered in dermatology practice. Acne can have a substantial impact on the quality of life and self-esteem and has been associated with a higher risk of depression, decreased social interaction, anxiety and suicidal ideation [55]. Unblemished facial skin in women is vital for attractiveness in many cultures and acne being one of the major causes for facial blemishes can have profound psychological impact on women [56]. Several studies have shown that women with acne experience higher emotional stress, lower self-esteem, reduced body satisfaction and sense of uselessness [57, 58]. Acne also begins in the adolescent ages and can have a huge impact on future psychosocial development in women. Adolescent girls and women with acne have been found to be at higher risk for depression and anxiety [59, 60]. The psychosocial burden of acne can be very severe, especially in women. Treatment of acne should be holistic and the psychological aspects of the disease should be actively managed in order to improve the patients' quality of life.

13.3.6 Alopecia

The term "alopecia" means partial or complete absence of hair from the sites of the body where it usually grows. Alopecia can be caused by a wide variety of causes and is classified into either scarring or non-scarring. Further details regarding various forms on alopecia and their management are elaborated in Chap. 9. Though alopecia may not be life threatening and is mainly a cosmetic concern in many cases, its impact on the patients' quality of life can be substantial. Over the ages, regardless of time period, cultures or ethnicity, healthy hair has been usually associated with beauty and youth, becoming an integral part of a person's identity. Though patterned hair loss in men has been accepted as a part of natural process, it is not the case for women. In women, hair symbolizes femininity and self-confidence and even a minimal loss of hair can be distressing and can have serious effect on their quality of life. This may be because women, compared to men tend to be more sensitive towards the perception of hair, possibly as a result of cultural and societal influences [61]. Androgenetic alopecia (female pattern hair loss—FPHL) is the most common cause of alopecia in women [62]. In women, the degree of impairment of quality of life by FPHL has been reported to be equivalent to that caused by diseases like psoriasis.

Several studies have investigated the effect of alopecia on quality of life. Zhuang et al. in their study on effectiveness of topical Minoxidil in women with FPHL, reported that patients having more severe FPHL had higher DLQI scores demonstrating that FPHL has high impact on quality of life. In a study by Cash et al. androgenetic alopecia was found to be significantly more distressing for women when compared to men and was associated with a negative body image [63]. Women with FPHL were reported to experience lower self-esteem and more severe psychosocial disorder, which were attributed to their hair loss when compared to women with non-apparent skin conditions [64].

Alopecia areata is a common form of non-scarring alopecia. Analysis of the National Alopecia Areata Registry showed that female gender was one of the risk factors associated with poor quality of life [65]. Women with alopecia areata are reported to experience more frustration and embarrassment along with a sense of loss [66]. Alopecia areata is also associated with a decrease in the quality of sexual life in women [66]. The prevalence of depression and anxiety has also been reported to be higher in women with alopecia areata.

Alopecia experienced during chemotherapy can be especially traumatic for women and has been reported as one of the three most distressing adverse events in women [67, 68]. Chemotherapy-induced alopecia was reported to be associated with negative body image and decreased psychosocial well-being in women treated for breast cancer, with a subset of the patients considering loss of hair to be more distressing than the loss of a breast [68, 69].

The burden of alopecia on quality of life, whether it be scarring or non-scarring forms, tends to be much more devastating in women. The psychological impact of hair loss forms a significant part of its morbidity, especially in women. Prompt recognition of the cause and early initiation of treatment along with integration of psychological support mechanisms and counselling are vital to reduce the burden of the disease.

13.3.7 Hirsutism

Hirsutism is defined as the abnormal and excessive growth of terminal hair in a male pattern in females. Hirsutism occurs in 5–15% percentage of females in the reproductive age group and is most commonly due to underlying polycystic ovarian syndrome (PCOS). The etiology, pathogenesis, clinical features and management of hirsutism have been discussed in detail in Chap. 9. Regardless of the specific cause, hirsutism can be devastating to the affected woman and can cause significant mental trauma and anguish. In an evaluation of hirsute women, Ekback et al. reported that most of these hirsute women experienced low self-esteem and limitation of social interaction due to their self-perceived ugliness and negative body image [70]. In patients with PCOS, the hirsutism and other symptoms occur just after puberty and can have a significant negative impact on further psychological development. Besides the psychosocial impact due to perception of disease by patient and society, the time and effort spent attending to the hair and physical appearance also compounds the burden. Several studies have evaluated the impact of hirsutism with majority of the studies being done in patients with PCOS [71]. Several reports have suggested hirsutism to be the most distressing symptom in PCOS [72–74]. Others suggest obesity and infertility to be the most significant. This may be because of the fact that many of these studies are population based and are influenced by the local culture and societal perception. Hirsutism has been linked to increased levels of anxiety and depression. A Swedish study evaluating the association between hair growth, anxiety and depression reported that higher levels of hairiness were associated with reduced quality of life, anxiety and depression [75]. Hahn et al. reported that hirsutism along with obesity decreased sexual satisfaction in PCOS patients [76].

Pasch et al. reported a difference in the perception of hirsutism between the clinician and the patients, with the patients viewing their symptoms to be more severe [77]. As self-perception is associated with quality of life, the clinical severity of hirsutism may not be representative of the true extent of its negative impact. Thus treatment for hirsutism needs to be tailored based on patient's distress and perception rather than clinical grading. Interventional studies with lasers have demonstrated improvement in the quality of life with hair reduction. However, the regrowth of hair after treatment may reverse this benefit and thus patients need to be adequately counselled.

13.4 Conclusion

Most skin diseases have a significant impact on the quality of life of the affected individual; this is more valid in women, particularly, in certain dermatoses. Here, we have briefly discussed the impact of skin diseases on quality of life, the instruments for measuring quality of life, the relevance of DLQI as an instrument, the dermatoses where DLQI is affected and the special considerations these have in women.

References

1. Chernyshov PV. The evolution of quality of life assessment and use in dermatology. Dermatology. 2019;235(3):167–74.
2. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6. https://doi.org/10.1111/j.1365-2230.1994.tb01167.x.
3. Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The dermatology life quality index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008;159(5):997–1035.
4. Twiss J, Meads DM, Preston EP, Crawford SR, McKenna SP. Can we rely on the dermatology life quality index as a measure of the impact of psoriasis or atopic dermatitis? J Investig Dermatol. 2012;132(1):76–84.
5. Nijsten T, Meads DM, de Korte J, Sampogna F, Gelfand JM, Ongenae K, et al. Cross-cultural inequivalence of dermatology-specific health-related quality of life instruments in psoriasis patients. J Investig Dermatol. 2007;127(10):2315–22.
6. Bidaki R, Majidi N, Moghadam Ahmadi A, Bakhshi H, Sadr Mohammadi R, Mostafavi S-A, et al. Vitiligo and social acceptance. Clin Cosmet Investig Dermatol. 2018;11:383–6.
7. Nicholas MN, Gooderham MJ. Atopic dermatitis, depression, and suicidality. J Cutan Med Surg. 2017;21(3):237–42.
8. Łakuta P, Marcinkiewicz K, Bergler-Czop B, Brzezińska-Wcisło L. How does stigma affect people with psoriasis? Postepy Dermatol Alergol. 2017;34(1):36–41.
9. Zhang X-J, Wang A-P, Shi T-Y, Zhang J, Xu H, Wang D-Q, et al. The psychosocial adaptation of patients with skin disease: a scoping review. BMC Public Health. 2019;19(1):1404.
10. Alinaghi F, Calov M, Kristensen LE, Gladman DD, Coates LC, Jullien D, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol. 2019;80(1):251–65.
11. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases. Part I. Epidemiology. J Am Acad Dermatol. 2017;76(3):377–90.
12. Iskandar IYK, Parisi R, Griffiths CEM, Ashcroft DM. Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender*. Br J Dermatol. 2021;184(2):243–58.
13. Ceovic R, Mance M, Bukvic Mokos Z, Svetec M, Kostovic K, Stulhofer Buzina D. Psoriasis: female skin changes in various hormonal stages throughout life—puberty, pregnancy, and menopause. Biomed Res Int. 2013;2013:e571912. https://doi.org/10.1155/2013/571912.
14. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41(3):401–7.
15. Martina K, Jorga F, Petra C, Tomas D, Iva L, Petr A, et al. Demographic data, comorbidities, quality of life, and survival probability of biologic therapy associated with sex-specific differences in psoriasis in the Czech Republic. Dermatol Ther. 2021;34:e14849.

16. Pollo CF, Miot HA, Matos TD, de Souza JM, MFS J, LDB M, et al. Prevalence and factors associated with depression and anxiety in patients with psoriasis. J Clin Nurs. 2020;30(3–4):572–80.
17. Martínez-Ortega JM, Nogueras P, Muñoz-Negro JE, Gutiérrez-Rojas L, González-Domenech P, Gurpegui M. Quality of life, anxiety and depressive symptoms in patients with psoriasis: a case-control study. J Psychosom Res. 2019;124:109780.
18. Kowalewska B, Cybulski M, Jankowiak B, Krajewska-Kułak E. Acceptance of illness, satisfaction with life, sense of stigmatization, and quality of life among people with psoriasis: a cross-sectional study. Dermatol Ther (Heidelb). 2020;10(3):413–30.
19. Schmid-Ott G, Künsebeck H-W, Jäger B, Sittig U, Hofste N, Ott R, et al. Significance of the stigmatization experience of psoriasis patients: a 1-year follow-up of the illness and its psychosocial consequences in men and women. Acta Derm Venereol. 2005;85(1):27–32.
20. Kurizky PS, Martins GA, Carneiro JN, Gomes CM, da Mota LMH. Evaluation of the occurrence of sexual dysfunction and general quality of life in female patients with psoriasis. An Bras Dermatol. 2018;93(6):801–6.
21. Ruiz V, Manubens E, Puig L. Psoriasis in pregnancy: a review (I). Actas Dermosifiliogr. 2014;105(8):734–43.
22. Bobotsis R, Gulliver WP, Monaghan K, Lynde C, Fleming P. Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies. Br J Dermatol. 2016;175(3):464–72.
23. Ferreira C, Azevedo A, Nogueira M, Torres T. Management of psoriasis in pregnancy—a review of the evidence to date. Drugs Context. 2020;9:2019.
24. Chi C-C, Wang S-H, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. Cochrane Database Syst Rev. 2015;10:CD007346.
25. Gottlieb AB, Ryan C, Murase JE. Clinical considerations for the management of psoriasis in women. Int J Womens Dermatol. 2019;5(3):141–50.
26. Rademaker M, Agnew K, Andrews M, Armour K, Baker C, Foley P, et al. Psoriasis in those planning a family, pregnant or breast-feeding. The Australasian psoriasis collaboration. Australas J Dermatol. 2018;59(2):86–100.
27. Kaushik SB, Lebwohl MG. Psoriasis: which therapy for which patient: psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2019;80(1):27–40.
28. Ingram JR. The epidemiology of hidradenitis suppurativa*. Br J Dermatol. 2020;183(6):990–8.
29. Collier EK, Price KN, Grogan TR, Naik HB, Shi VY, Hsiao JL. Characterizing perimenstrual flares of hidradenitis suppurativa. Int J Womens Dermatol. 2020;6(5):372–6. https://doi.org/10.1016/j.ijwd.2020.09.002.
30. Kluger N, Ranta M, Serlachius M. The burden of hidradenitis suppurativa in a cohort of patients in southern Finland: a pilot study. Skin Appendage Disord. 2017;3(1):20–7.
31. Krajewski PK, Matusiak Ł, von Stebut E, Schultheis M, Kirschner U, Nikolakis G, et al. Quality-of-life impairment among patients with hidradenitis suppurativa: a cross-sectional study of 1795 patients. Life (Basel). 2021;11(1):34.
32. Alavi A, Farzanfar D, Rogalska T, Lowes MA, Chavoshi S. Quality of life and sexual health in patients with hidradenitis suppurativa. Int J Womens Dermatol. 2018;4(2):74–9.
33. Porro AM, Seque CA, Ferreira MCC, MMS E. Pemphigus vulgaris. An Bras Dermatol. 2019;94(3):264–78.
34. Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. Immunol Res. 2018;66(2):255–70.
35. Zhao CY, Murrell DF. Autoimmune blistering diseases in females: a review. Int J Womens Dermatol. 2015;1(1):4–12.
36. Kridin K, Ludwig RJ. The growing incidence of bullous pemphigoid: overview and potential explanations. Front Med. 2018;5:220. https://doi.org/10.3389/fmed.2018.00220.
37. Jain SV, Murrell DF. Psychosocial impact of inherited and autoimmune blistering diseases. Int J Womens Dermatol. 2018;4(1):49–53.
38. Paradisi A, Sampogna F, Di Pietro C, Cianchini G, Didona B, Ferri R, et al. Quality-of-life assessment in patients with pemphigus using a minimum set of evaluation tools. J Am Acad Dermatol. 2009;60(2):261–9.

39. Paradisi A, Cianchini G, Lupi F, Pietro CD, Sampogna F, Didona B, et al. Quality of life in patients with pemphigus receiving adjuvant therapy. Clin Exp Dermatol. 2012;37(6):626–30.
40. Rajan B, Ahmed J, Shenoy N, Denny C, Ongole R, Binnal A. Assessment of quality of life in patients with chronic oral mucosal diseases: a questionnaire-based study. Perm J. 2021;18(1):e123. https://www.thepermanentejournal.org/issues/2014/winter/5600-oral-mucosal-diseases.html.
41. Tabolli S, Pagliarello C, Paradisi A, Cianchini G, Giannantoni P, Abeni D. Burden of disease during quiescent periods in patients with pemphigus. Br J Dermatol. 2014;170(5):1087–91.
42. Feliciani C, Genovese G, D'astolto R, Pontini P, Marzano AV. Autoimmune bullous diseases during pregnancy: insight into pathogenetic mechanisms and clinical features. G Ital Dermatol Venereol. 2019;154(3):256–62.
43. Patsatsi A, Marinovic B, Murrell D. Autoimmune bullous diseases during pregnancy: solving common and uncommon issues. Int J Womens Dermatol. 2019;5(3):166–70.
44. Genovese G, Derlino F, Berti E, Marzano AV. Treatment of autoimmune bullous diseases during pregnancy and lactation: a review focusing on pemphigus and pemphigoid gestationis. Front Pharmacol. 2020;11:583354.
45. Kushner CJ, Concha JSS, Werth VP. Treatment of autoimmune bullous disorders in pregnancy. Am J Clin Dermatol. 2018;19(3):391–403.
46. Lake EP, Huang Y-H, Aronson IK. Rituximab treatment of pemphigus in women of childbearing age: experience with two patients. J Dermatol Treat. 2017;28(8):751–2.
47. Vassallo C, Grassi S, Tagliabue E, Piccolo A, Brazzelli V. Pregnancy outcome after rituximab treatment before conception in patients affected by severe pemphigus vulgaris/superficialis. J Eur Acad Dermatol Venereol. 2017;31(7):e331–3.
48. Grimes PE, Miller MM. Vitiligo: patient stories, self-esteem, and the psychological burden of disease. Int J Womens Dermatol. 2018;4(1):32–7.
49. Thompson AR, Clarke SA, Newell RJ, Gawkrodger DJ. Vitiligo linked to stigmatization in British South Asian women: a qualitative study of the experiences of living with vitiligo. Br J Dermatol. 2010;163(3):481–6.
50. Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: a comprehensive overview part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011;65(3):473–91.
51. Sangma LN, Nath J, Bhagabati D. Quality of life and psychological morbidity in vitiligo patients: a study in a teaching hospital from north-East India. Indian J Dermatol. 2015;60(2):142–6.
52. Wang K-Y, Wang K-H, Zhang Z-P. Health-related quality of life and marital quality of vitiligo patients in China. J Eur Acad Dermatol Venereol. 2011;25(4):429–35.
53. Hamidizadeh N, Ranjbar S, Ghanizadeh A, Parvizi MM, Jafari P, Handjani F. Evaluating prevalence of depression, anxiety and hopelessness in patients with vitiligo on an Iranian population. Health Qual Life Outcomes. 2020;18(1):20.
54. Borimnejad L, Parsa Yekta Z, Nikbakht-Nasrabadi A, Firooz A. Quality of life with vitiligo: comparison of male and female muslim patients in Iran. Gend Med. 2006;3(2):124–30.
55. Gallitano SM, Berson DS. How acne bumps cause the blues: the influence of acne vulgaris on self-esteem. Int J Womens Dermatol. 2018;4(1):12–7.
56. Balkrishnan R, McMichael AJ, Hu JY, Camacho FT, Shew KR, Bouloc A, et al. Correlates of health-related quality of life in women with severe facial blemishes. Int J Dermatol. 2006;45(2):111–5.
57. Do JE, Cho S-M, In S-I, Lim K-Y, Lee S, Lee E-S. Psychosocial aspects of acne vulgaris: a community-based study with Korean adolescents. Ann Dermatol. 2009;21(2):125–9.
58. Hassan J, Grogan S, Clark-Carter D, Richards H, Yates VM. The individual health burden of acne: appearance-related distress in male and female adolescents and adults with back, chest and facial acne. J Health Psychol. 2009;14(8):1105–18.
59. Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in adolescents. Int J Dermatol. 2000;39(5):354–7.

60. Haroon MZ, Alam A, Ullah I, Ali R, Taimur MF, Raza K. Quality of life and depression among young patients suffering from acne. J Ayub Med Coll Abbottabad. 2019;31(3):436–40.
61. Robbins C, Mirmirani P, Messenger AG, Birch MP, Youngquist RS, Tamura M, et al. What women want—quantifying the perception of hair amount: an analysis of hair diameter and density changes with age in Caucasian women. Br J Dermatol. 2012;167(2):324–32.
62. Sinclair R, Patel M, Dawson TL, Yazdabadi A, Yip L, Perez A, et al. Hair loss in women: medical and cosmetic approaches to increase scalp hair fullness. Br J Dermatol. 2011;165(Suppl 3):12–8.
63. Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: comparisons with balding men and with female control subjects. J Am Acad Dermatol. 1993;29(4):568–75.
64. van der Donk J, Passchier J, Knegt-Junk C, van der Wegen-Keijser MH, Nieboer C, Stolz E, et al. Psychological characteristics of women with androgenetic alopecia: a controlled study. Br J Dermatol. 1991;125(3):248–52.
65. Shi Q, Duvic M, Osei JS, Hordinsky MK, Norris DA, Price VH, et al. Health-related quality of life (HRQoL) in alopecia areata patients—a secondary analysis of the National Alopecia Areata Registry Data. J Investig Dermatol Symp Proc. 2013;16(1):S49–50.
66. Li SJ, Huang KP, Joyce C, Mostaghimi A. The impact of alopecia areata on sexual quality of life. Int J Trichol. 2018;10(6):271–4.
67. Boland V, Brady A-M, Drury A. The physical, psychological and social experiences of alopecia among women receiving chemotherapy: an integrative literature review. Eur J Oncol Nurs. 2020;49:101840.
68. Choi EK, Kim I-R, Chang O, Kang D, Nam S-J, Lee JE, et al. Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. Psychooncology. 2014;23(10):1103–10.
69. Browall M, Gaston-Johansson F, Danielson E. Postmenopausal women with breast cancer: their experiences of the chemotherapy treatment period. Cancer Nurs. 2006;29(1):34–42.
70. Ekback M, Wijma K, Benzein E. "It is always on my mind": women's experiences of their bodies when living with hirsutism. Health Care Women Int. 2009;30(5):358–72.
71. Amiri M, Bidhendi Yarandi R, Nahidi F, Tohidi M, Ramezani TF. The relationship between clinical and biochemical characteristics and quality of life in patients with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2019;90(1):129–37.
72. Khomami MB, Tehrani FR, Hashemi S, Farahmand M, Azizi F. Of PCOS symptoms, hirsutism has the most significant impact on the quality of life of Iranian women. PLoS One. 2015;10(4):e0123608.
73. Açmaz G, Albayrak E, Acmaz B, Başer M, Soyak M, Zararsız G, et al. Level of anxiety, depression, self-esteem, social anxiety, and quality of life among the women with polycystic ovary syndrome. Sci World J. 2013;2013:851815.
74. Behboodi Moghadam Z, Fereidooni B, Saffari M, Montazeri A. Polycystic ovary syndrome and its impact on Iranian women's quality of life: a population-based study. BMC Womens Health. 2018;18:164.
75. Ekbäck MP, Lindberg M, Benzein E, Årestedt K. Health-related quality of life, depression and anxiety correlate with the degree of hirsutism. Dermatology. 2013;227(3):278–84.
76. Hahn S, Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, et al. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. Eur J Endocrinol. 2005;153(6):853–60.
77. Pasch L, He SY, Huddleston H, Cedars MI, Beshay A, Zane LT, et al. Clinician vs self-ratings of hirsutism in patients with polycystic ovarian syndrome: associations with quality of life and depression. JAMA Dermatol. 2016;152(7):783.

Chapter 14
Hair Disorders in Females

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14.1 Anatomy and Physiology of Hair

The hair follicle is divided into two regions, the upper part consisting of infundibulum and isthmus and the lower part comprising hair bulb and suprabulbar region. Every hair follicle undergoes three phases in its life cycle called anagen (growing phase), catagen (transition phase) and telogen (resting phase). The anagen, catagen and telogen hair comprise 84%, 2% and 14%, respectively, of the total scalp hair [1]. Hair disorders occur due to perturbations in the life cycle of hair or defect in the anatomy and physiology of hair.

14.2 Classification of Hair Disorders in Females

Hair disorders in females are divided into four groups: hair loss (cicatricial/noncicatricial), hair gain (hirsutism/hypertrichosis), hair shaft disorders (with increased fragility/without fragility) and hair pigmentation abnormalities [2] (Fig. 14.1). These disorders can be congenital, autoimmune, infectious or genetic.

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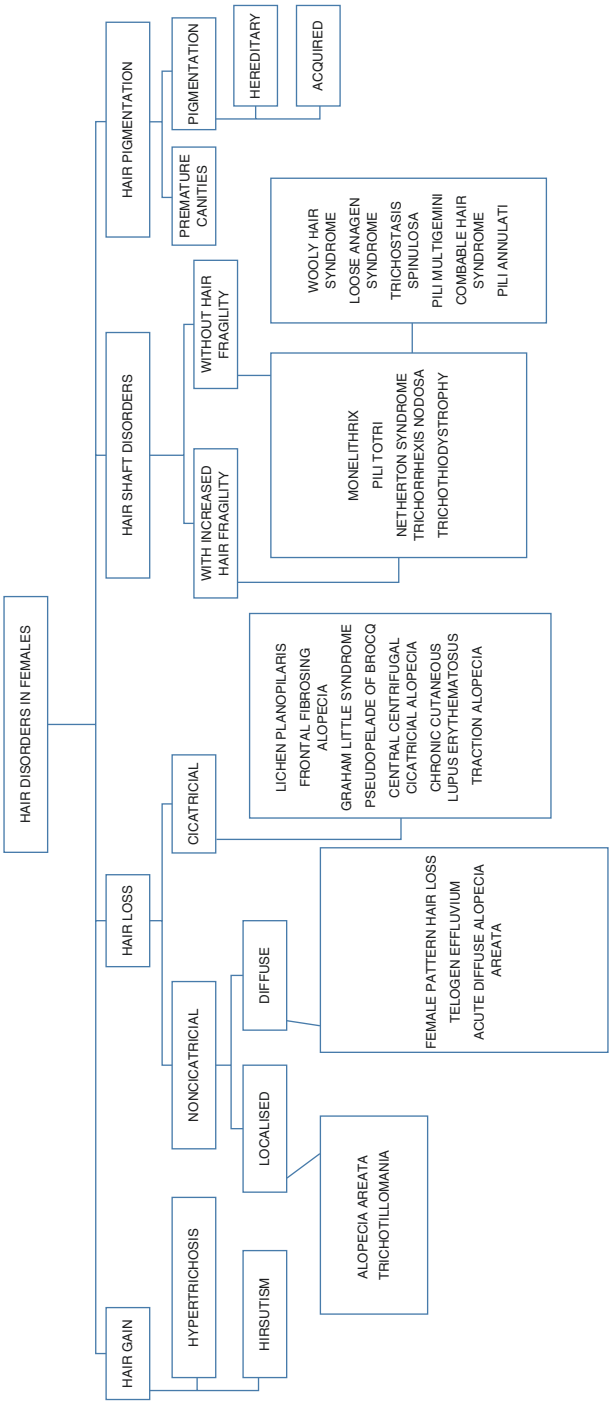

Fig. 14.1 Classification of hair disorders in females

These disorders are discussed in the following sections.

14.2.1 Female Pattern Hair Loss

Female pattern hair loss (FPHL) is the most common type of hair loss in females [3]. Earlier the patterned hair loss in both females and males were collectively called androgenetic alopecia (AGA); however, as there is identification of nonandrogenetic mechanism in its pathogenesis so now the term AGA is limited to patterned hair loss in males and patterned hair loss in females is called female patterned hair loss.

14.2.1.1 Epidemiology

FPHL starts at puberty in females; however, the prevalence increases with age. Twelve percent of women are affected by age 29 years, 25% by age 49 years, 41% by 69 years and >50% have some element of by 79 years in one study [2]. FPHL is commonly seen in Caucasians and has a lower prevalence in Asians.

14.2.1.2 Pathogenesis

The etiopathogenesis of FPHL is complex with multiple factors such as genetics, inflammation, hormones and environment playing a role in it. The pathomechanism behind FPHL is the stimulation of androgen receptors on the dermal papillae of terminal hair follicles by dihydrotestosterone, which leads to miniaturization of the terminal follicle to vellus hair follicle. These pseudo vellus hair follicles have arrector pili muscle attached and angiofibrotic streamers which distinguish them from true vellus hair. There is variation in the size of the hair follicles but the total no of hair follicles remain the same in affected patients. FPHL is more confined to frontal regions and vertex and spares the occipital region because the number of the androgen receptors and DHT enzyme in the hair follicles are more in the frontal region than the occipital region. The severity, prevalence and age of onset of patterned hair loss is less in females as compared to males due to the lower level of 5 alpha-reductase and androgen receptors and increased aromatase content in frontal hair in females. Apart from hormonal factors, various genetic factors also play a contributory role in the development of FPHL. Genes on the X chromosome locus containing the androgen receptor and ectodysplasin A2 receptor have been found to have a role in the early onset FPHL [4]. An Australian Genome-wide association study shows the association of the aromatase gene in the FPHL [5]. Several environmental factors like psychological stress, hypertension diabetes mellitus, smoking, multiple marriages, higher income and little physical activity ae associated with FPHL.

14.2.1.3 Clinical Features

Females can present at initial stages with increased shedding of hair, thinning of hair on the crown or both. Initial cases of FPHL with increased hair shedding are difficult to diagnose. Trichodynia may be associated with FPHL.

There are three different patterns of FPHL:

1. Diffuse thinning of the crown region with preservation of the frontal hairline: there are two scales used for this pattern: the commonly used 3-point Ludwig scale [6] and the 5-point Sinclair scale [7].

Grade	Description
I	Minimal hair thinning on crown which can be camouflaged by hair styling
II	Decreased volume and widening of central partition (more than Grade I)
III	Full baldness in areas of Grade I and II with see through appearance on top of scalp

2. Thinning and widening of the central part of the scalp with breach of frontal hairline, described as the Christmas tree pattern [8]—using the Olsen scale (Figs. 14.2 and 14.3).

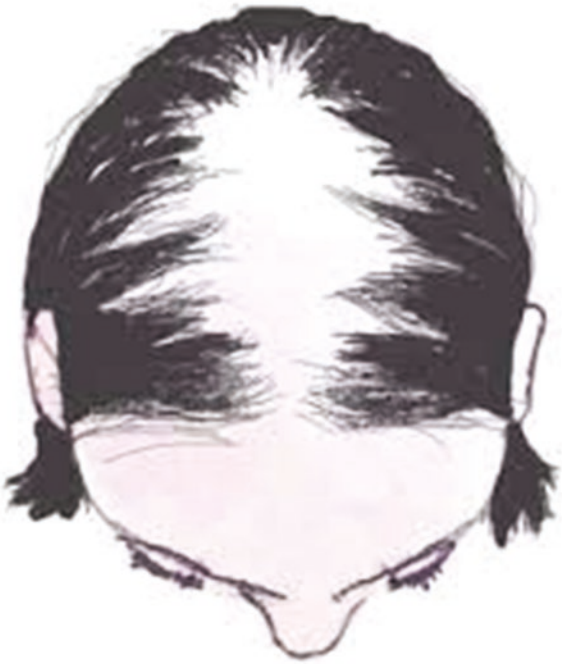

Fig. 14.2 Christmas tree pattern in FPHL

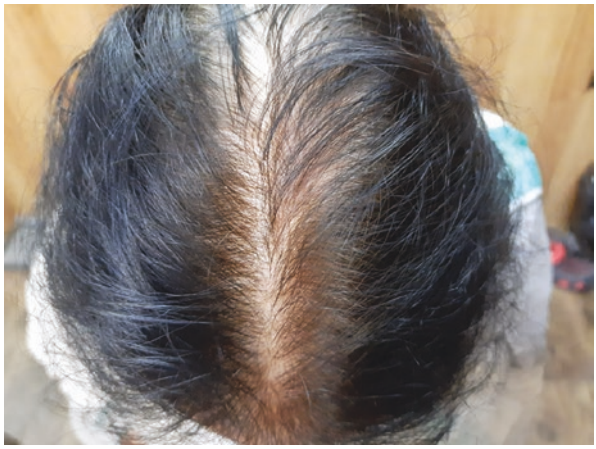

Fig. 14.3 Christmas tree pattern in FPHL

3. Thinning associated with bi-temporal recession; similar to male pattern baldness and classified by the Hamilton–Norwood scale [9].

All these patterns spare the occipital region. However, in some women, the hair thinning can be more diffuse, involving the parietal and occipital areas of the scalp with a pattern of diffuse alopecia.

14.2.1.4 Associations

FPHL has been found to be associated with early cardiovascular disease risk and hypertension due to higher levels of C-reactive protein, higher aldosterone, D-dimers and insulin levels in women [10, 11]. FPHL has been shown to compromise body image and strongly affect self-esteem of patients. In a study, it was found that 88% of females felt FPHL affected their daily life [12].

14.2.1.5 Investigations

The diagnosis of FPHL is usually indicated from a history of a decrease in the girth of the ponytail. Bedside tests like the hair pull test are used to support the diagnosis of FPHL. In hair pull test, 60 hair are held with the thumb and index and middle fingers and pulled upwards and outwards—if more than 10% of the same can be removed, then it is considered to be positive. Hair pull test is positive only in active cases and will be positive in affected regions only unlike telogen effluvium where it would be positive globally. Trichogram can also be used. Dermoscopy can contribute to the diagnosis of FPHL, especially in the early stages of the disease. Histopathology is the most reliable test to differentiate from chronic telogen effluvium Trichoscopic features and histopathological findings helpful in differentiating are given in Table 14.1.

Table 14.1 Diagnostic features of various types of alopecia encountered in female patients

Disease	Clinical features	Trichoscopy	Histopathological findings
Androgenic alopecia	Diffuse thinning on the crown central widening	Hair diameter variability of 20% and terminal hair infundibulum decreased to 1 or 2	Miniaturized hair follicles Terminal to vellus hair ratio <4:1
Telogen effluvium	Sudden onset diffuse shedding of scalp Trichodynia (20%)	Absence of hair fiber variability with large number of regrowing hair	Increased telogen hair >15% Suggestive >25% Diagnostic
Alopecia areata	Well-defined patches of noncicatricial alopecia on scalp, beard	Exclamation mark hair, yellow dots (most common and sensitive, broken hair, black dots and short vellus hair (suggestive of activity and most specific)	*Acute phase*—perifollicular inflammatory infiltrate (*swarm of bees appearance*). The inflammatory infiltrate consists of activated T lymphocytes, macrophages and Langerhans cells. Hair follicles do not progress beyond anagen III–IV *Subacute phase*—Decreased anagen and increased catagen and telogen hair *Chronic phase*—Follicular miniaturization with variable inflammatory infiltrate. Terminal to vellus hair ratio is decreased to 1:1 in contrast to 7:1
Lichen planopilaris	Asymptomatic or present with hair shedding, itching, pain or burning in the scalp Later—develop patches of scarring alopecia with violaceous pigmentation on the surface	Early stage—violaceous background with peripilar scaling at the proximal end of the hair (Figs. 14.4 and 14.5) late stage—shows fibrotic white dot, acquired pili torti, loss of follicular openings, white areas, honeycomb pigmentation, milky red areas and hair tufts	Early stage-band like inflammatory infiltrate and basal cell vacuolation at isthmus and infundibulum Late stage—perifollicular fibrosis with hourglass configuration DIF will show positive staining for colloid bodies, IgM, IgA or C3; linear bands of fibrin or fibrinogen at DEJ

Table 14.1 (continued)

Disease	Clinical features	Trichoscopy	Histopathological findings
Frontal fibrosing alopecia	Progressive recession of frontotemporal line with perifollicular erythema and follicular hyperkeratosis in postmenopausal females	Same as LPP	Same as LPP
Graham little syndrome	Triad of follicular plugins followed by scarring alopecia in the scalp Follicular plugging and noncicatricial alopecia in the axilla and pubis Keratosis pilaris other body sites	Same as LPP	Same as LPP
Discoid lupus erythematosus	Erythematous plaque with follicular plugging which develop scarring alopecia Face and ears can be involved	Follicular keratotic plugs bordered by tortuous blood vessels appearing as red spiders in yellow dots	Early—interface dermatitis with perivascular and peri appendageal inflammatory infiltrate, mucin deposition and basement membrane thickening DIF shows linear deposition of IgG, IgM and C3 at basement membrane zone
Traction alopecia	Early stages—there is perifollicular erythema, papules and pustules in the frontal and temporoparietal areas Scarring alopecia at sites of tight buns, ponytails, tight braids with fringe sign [13] Fringe sign—a strip of thin hair at the distal end of the patch (Fig. 14.6) [13]	Reduced hair density, absent hair follicles, hair casts, absent hair with brown outlined follicular openings	Increased catagen/telogen count Pigment casts Trichomalacia

(continued)

Table 14.1 (continued)

Disease	Clinical features	Trichoscopy	Histopathological findings
Trichotillomania	Bizarre or angular shaped patches of ill-defined hair loss with broken hair of varying length involving the frontoparietal region of the scalp, contralateral to the dominant hand (Fig. 14.7) Public hair, body hair or facial hair may be affected	Broken hair at different lengths, longitudinal split ends of hair, irregular coiled hair, follicular microhemorrhages and amorphous hair residue. I hair (modified black spots due to remnants of hair shafts arising from broken pulled hair) [14] Flame hair (proximal hair residue that remains after pulling anagen hair) Tulip hair (short hair with dark tulip-shaped ends) V sign (frayed hair) and yellow dots [15]	Numerous empty canals, trichomalacia, incomplete disrupted follicular anatomy clefts in the hair matrix, intraepithelial and perifollicular hemorrhages and intrafollicular pigment casts Hamburger within a bun sign [16]—vertically oriented split of hair shafts and proteinaceous material and erythrocytes are present in the split. Most of the follicles are in catagen with very few in telogen
Central centrifugal cicatricial alopecia/hot comb alopecia	Progressive focus of cicatricial alopecia starting on vertex and then spreading outwards Inflammation at periphery and centre—smooth, shiny and noninflamed with hair present in scarred areas Itching, pain and burning may be present	Peripilar gray/white halo that is a (specific and sensitive dermatoscopic sign) Honeycomb-pigmented network that represents the hyperpigmented rete ridges and the hypomelanotic dermal papillae Hair shaft variability white patches (follicular dropout and scarring) perifollicular erythema, concentric white perifollicular and interfollicular scales, black dots interfollicular-pigmented asterisk-like or stellate brown macules	Premature degeneration of IRS resulting in outward migration of hair shaft through the ORS at level of isthmus Lamellar fibroplasia, dense lymphocytic inflammation surrounding the follicle Follicular destruction and fibrous tract formation

Table 14.1 (continued)

Disease	Clinical features	Trichoscopy	Histopathological findings
Pseudopelade of Brocq	Irregularly defined and confluent patches of scarring alopecia	Lack of follicular ostia	Early stage—sparse or moderate lymphocytic infiltrate around the infundibulum and the absence of sebaceous glands are pathologic hallmarks Late the follicular epithelium becomes more and more atrophic and follicles are often surrounded by concentric lamellar fibroplasias until finally the follicle is replaced by fibrous tracts

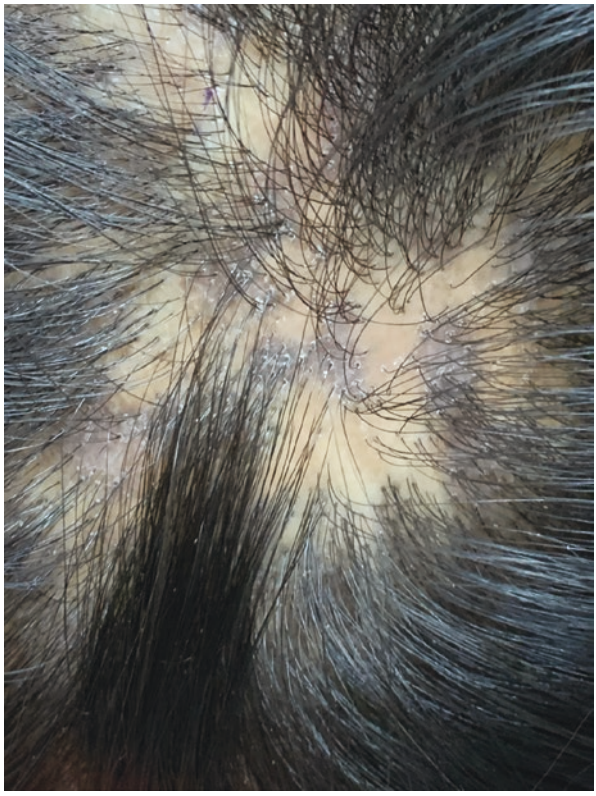

Fig. 14.4 Clinical picture of LPP with violaceous pigmentation, perifollicular scaling and scarring alopecia

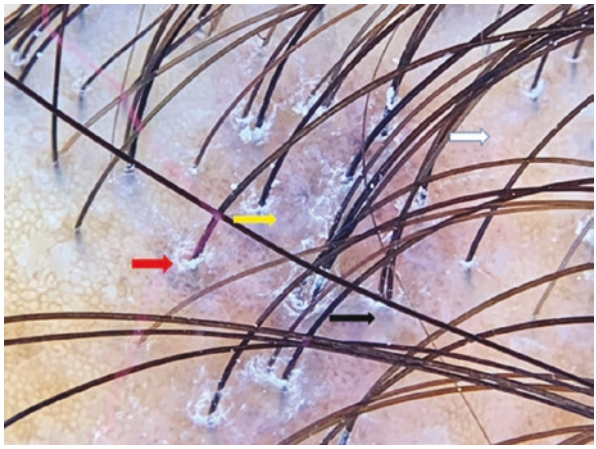

Fig. 14.5 Trichoscopic findings in LPP absence of follicular openings (white arrow); perifollicular scaling (red arrow); white structure less cicatricial areas (yellow arrow); perifollicular erythema (black arrow)

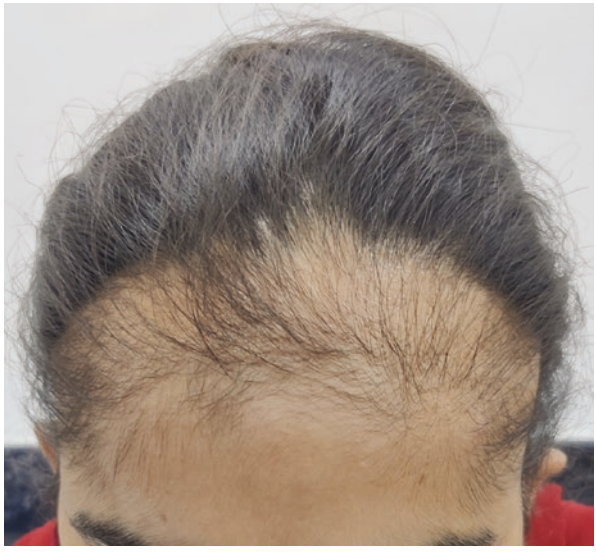

Fig. 14.6 Traction alopecia in a Sikh female with fringe sign

Rakowska et al. proposed major and minor dermoscopic criteria for the diagnosis of FPHL [17]. Major criteria include (1) more than 4 yellow dots in 4 images in the frontal area; (2) lower average hair thickness in the frontal area compared with the occiput; and (3) more than 10% of thin hairs (<0.03 mm) in the frontal area. Minor criteria include (1) increased frontal to the occipital ratio of single-hair pilosebaceous units; (2) vellus hairs; and (3) perifollicular discoloration. The diagnosis of FPHL is made when two major criteria or one major plus two minor criteria are present.

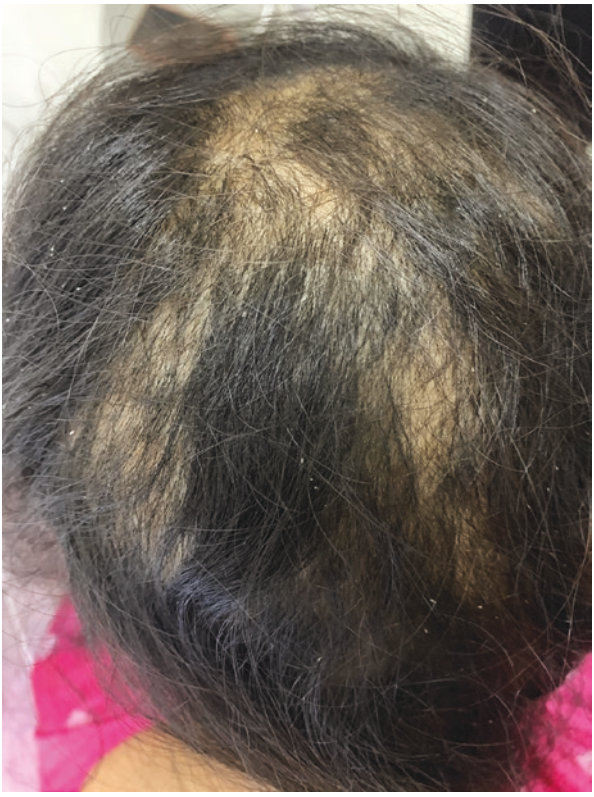

Fig. 14.7 Trichotillomania (scarring hair loss with hair broken off at irregular lengths with coincidental pediculosis capitis)

Hemogram, ferritin and thyroid function tests should be done in all patients with FPHL to rule out concomitant telogen effluvium due to iron deficiency disorder or a thyroid disorder. FPHL has been found to be associated with hyperandrogenism. Tests to rule out hyperandrogenism need to be done in patients with irregular menses, hoarse voice, hirsutism, loss of libido and clitoromegaly.

14.2.1.6 Treatment

Treatment of FPHL involves counselling the patient about its tendency for lifelong progression, with rates of progression being extremely variable, and ensuring compliance to treatment.

Topical minoxidil is the most commonly used drug for the management of FPHL. Minoxidil gets converted into minoxidil sulphate by the enzyme sulfotransferase present in the outer root sheath, leading to the opening of ATP-sensitive potassium channels which increase calcium entry into the hair follicle and inhibit

the epidermal growth factor (EGF)-induced inhibition of hair growth. Also, it increases the expression of hepatocyte growth factor (HGF) mRNA, increasing duration of the anagen growth phase. Minoxidil 2% lotion and 5% foam are FDA-approved treatments for FPHL. One mL of minoxidil is to be applied on the dry scalp twice a day. Patients should be counselled regarding the possibility of initial hair fall at 4–6 weeks due to early telogen release. Effect starts to appear at 4 months and the maximal response is noticed at 1 year. Side effects like irritation and hair growth on the face are the common side effects. Hypertrichosis is seen in 4% of the females and is reversible, reducing in 4–5 months. Contact dermatitis due to propylene glycol is also known to occur due to minoxidil. Minoxidil is contraindicated in pregnant and lactating females.

Other topical therapies include melatonin 0.1%, topical ketoconazole and topical prostaglandins analogue with varying results.

Women who respond poorly to monotherapy or who have signs of hyperandrogenism can also be given systemic medications. 5 Alpha-reductase inhibitors like finasteride and dutasteride have been tried in FPHL with varying efficacy. They are not FDA-approved for use in women and contraindicated in pregnant women and during lactation. Large scale studies on its efficacy for FPHL are limited. Finasteride can be given at dose of 2.5–5 mg with varying results.

Spironolactone is a synthetic steroid which acts by blocking androgen receptors and weakly inhibits androgen biosynthesis. It is given in doses of 50–300 mg/day. It is the most commonly used anti-androgen for the treatment of FPHL and hirsutism. Side effects include breast tenderness, menstrual irregularities and postmenopausal bleeding. The rise in BP and serum potassium can be seen in patients with renal failure.

Cyproterone acetate is an androgen receptor blocker. It also decreases the androgen synthesis and decreased uptake of androgen. It has been tried in doses of 50–100 mg/day for the first 10 days of each menstrual cycle. The side effects of cyproterone acetate are weight gain, breast tenderness, nausea and loss of libido.

Flutamide is a nonsteroidal anti-androgen which acts by inhibiting androgen uptake and inhibiting the nuclear binding of androgen within the target tissue.

Low-dose oral minoxidil is not often used in treatment of FPHL. In a randomized controlled trial, topical 0.75% adenosine containing lotion was found to increase the growth of anagen hair and thick hair in patients with FPHL [18].

Hair transplantation is usually not required but has been tried in FPHL and is successful in patients with limited hair loss and retain good hair density at donor sites. Camouflage and wigs are an easy alternative. Camouflage involves adding small fibers held in place electrostatically or dyeing the scalp the same color as the hair to create the illusion of thick hair. Wigs can be worn over the top of the existing hair and hairpieces can be interwoven with existing hair. Wig hair is made of acrylic fiber which withstands wear and tear or natural fiber which looks better, is easier to style and is long-lasting but more expensive.

14.2.2 Telogen Effluvium

Telogen effluvium is the second most common cause of hair loss in females. It is characterized by sudden onset diffuse shedding of approximately 100–1000 hair per day.

14.2.2.1 Etiopathogenesis

Telogen effluvium is caused by an abnormality in the normal hair cycle, which is triggered by numerous factors. Precipitating factors for telogen effluvium include stress, trauma, post Covid-19, anorexia nervosa, pregnancy, drugs, thyroid diseases, nutritional deficiency and acute febrile illness. There is a disbalance of TH1/TH2 cytokine balance during stress leading to change in hair parameters [19]. Also there is an inflammation of the small papillary or peripapillary vessels due to circulating immune complexes in patients with telogen effluvium secondary to SLE or post febrile illness [20]. It occurs 2–6 weeks after the onset of high fever, and usually lasts for at least 6 weeks. In about one-third of the cases, no triggering agent is found. The cause for the same is the sudden premature conversion of all anagen hair follicles into telogen hair leading to shedding of hair, after 3 months of the precipitating event. Headington [21] has described five functional types of telogen effluvium.

Immediate anagen release—Sudden damage of anagen hair due to chemotherapeutic drugs leading to shedding of hair.

Delayed anagen release—It is seen in telogen gravidarum. During pregnancy, there are high levels of estrogen which maintain the hair in anagen phase but at delivery, anagen hair turns into telogen, and after 2–4 months telogen hair is shed. It lasts for 2 months or may be longer. It is seen in 20% of women and not necessarily in all deliveries, but almost always after first delivery. This may be due to the stress-induced arrest of mitosis which is maximum during first delivery.

Short anagen syndrome—This is seen in androgenic alopecia where there is shortening in duration of anagen phase and telogen effluvium precedes visible balding of the scalp.

Immediate telogen release—This is seen after minoxidil therapy. Minoxidil stimulates exogen hair to release before development of anagen phase, hence after minoxidil therapy hair loss in noticed after 4–6 weeks.

Delayed telogen release—It occurs in animals with synchronous hair cycles during shedding of winter coats. It occurs due to prolonged telogen phase followed by transition to anagen phase.

However, there is a new classification given by Rebora et al. [22] to explain the pathogenesis of telogen effluvium.

14.2.2.1.1 Premature Teloptosis

It is similar to Headington's immediate telogen release. The effects seen during treatment with salicylic acid, retinoids and minoxidil can be explained by premature teloptosis. Retinoids cause the disruption of desmosomes and hemidesmosomes leading to detachment of keratinocyte and shedding. The shedding of hair after 4–6 weeks of minoxidil is due to the sudden release of telogen hair. It also supports the seasonal correlation of telogen effluvium with autumn. The UV radiation in previous summers caused cadherin disruption and shedding in autumn 2–3 months later.

14.2.2.1.2 Collective Teloptosis

It clubs Headington's delayed anagen and telogen release. It is used to describe the mechanism for hair loss seen in neonates, postpartum TE and hair loss due to non-cytostatic drugs. The occipital hair in neonates is in the telogen phase at delivery; hence, teloptosis (hair shedding) occurs 3 months after delivery, thus being responsible for transient neonatal hair loss. Estrogen, minoxidil and finasteride cause collective teloptosis on treatment cessation.

14.2.2.1.3 Premature Entry into Telogen Phase

This type may be equivalent to Headington's immediate anagen release. Here there is an anagen arrest usually due to an antimitotic insult. The hair loss depends on the duration, intensity of insult, the phase of the hair cycle during which insult took place and the preexisting hair disorder like Androgenetic alopecia. If the insult takes place during the anagen phase (I–V) the hair shed would be dystrophic. If the hair is in the near end of anagen phase (anagen VI), the hair will enter the telogen phase and will be shed as telogen hair after 3 months. If the insult is massive and lasts long enough, both the dystrophic and telogen type of hair loss will occur. It explains the hair loss due to chemotherapeutic drugs, nutritional insufficiencies and lymphocyte toxicity (autoimmune telogen effluvium). Autoimmune telogen effluvium is associated with thyroid diseases, Sjogren disease, inflammatory bowel disease and autoimmune atrophic gastritis.

14.2.2.2 Bedside Tests

The hair pull test in these patients is positive, with more than 10% of the hair being extracted from any part of the scalp. Hair trichogram shows more than 25% of the hair are in the telogen stage in acute phase.

14.2.2.3 Investigations

Investigations like hemogram, thyroid function tests, serum ferritin, vitamin B12 and vitamin D3 levels should be done to rule out the etiology of telogen effluvium. Histopathology of acute forms is nonspecific but in chronic telogen effluvium, only an increased telogen hair is detected.

Telogen effluvium may be acute or chronic when its duration exceeds 6 months.

14.2.2.3.1 Acute Telogen Effluvium

Acute TE is described as an acute-onset scalp hair loss occurring 2–3 months after a triggering event. The functional mechanism of shedding in majority of these cases is immediate anagen release. Majority of cases usually remit within a few months.

14.2.2.3.2 Chronic Telogen Effluvium (CTE)

CTE was described by David A. Whiting in 1996 [23]. It is idiopathic and seen in females aged 30–60 years. Patients present with sudden-onset diffuse shedding of hair enough to cause chunks of hair seen in the bathroom, brushes and combs. It is chronic with intermittent episodes of improvement. Hair pull test is positive. Hair wash test in which the total number of telogen hair and vellus hair shed is counted after shampooing has been found to be useful in differentiating CTE with FPHL. FPHL shows more than 10% of vellus hair (<3 cm) [23]. Various differentiating features between FPHL and CTE are given in Table 14.2.

Trichodynia has been found to be associated in 20% of patients. It occurs in sites where hairs are actually shedding and it may be regarded as a sign of severity of the disorder and of the possibility that TE may continue further, often more than 3 months.

Table 14.2 Differentiating features between FPHL and chronic TE [24, 25]

	FPHL	Chronic TE
Distribution	Central portion of scalp and preserved frontal hairline	Generalised
Onset	Gradual	Abrupt
Appearance	Hair thinning with wide midline part	Diffuse thinning
Hair shedding	Minimal	Prominent
Hair pull test	Usually negative (positive in active patients at frontal region	Positive at all sites
Other history	Family history +	H/O previous major illness or stress
Scalp biopsy	T:V ≤4	T:V ≥7
Hair wash test	Vellus hair >10%	Vellus hair <10%

14.2.2.4 Chronic Diffuse Telogen Hair Loss

It refers to telogen hair shedding, longer than 6 months, secondary to a variety of organic causes. Prominent causes include thyroid disorders, profound iron deficiency anemia, acrodermatitis enteropathica, malnutrition and drug induced.

The treatment for the acute telogen effluvium is the removal of the underlying cause. To find the cause it must be remembered that a lag of 3 months is present and patients may come when the cause of TE ceases to be active. Topical corticosteroids have been tried in patients with autoimmune telogen effluvium. There is no proven role of vitamins or supplements for any form of telogen effluvium. A treatment of CTE warrants ruling out other causes of CDTHL, including AGA, drug-induced hair loss, hypo- and hyperthyroidism, and chronic diseases. The treatment options for CTE are not many. Topical treatment which have effect on hair cycle can be tried.

14.2.3 Hirsutism

Hirsutism is defined as the growth of terminal hair in females in androgen-dependent areas. It is characterized by the growth of coarse pigmented long hair on the face, chest, abdomen, back and thighs. There are various causes for the same as mentioned in Table 14.2.

14.2.3.1 Severity Score

The severity of hirsutism is graded on the basis of modified Ferriman–Gallwey scoring (mFG) system. Each body site is scored on the basis of the severity of hair growth and all the scores are added to get the final score. mFG <8 is normal and >8 is considered hirsutism. mFG score 8–15 is considered mild hirsutism and score >15 is considered moderate to severe hirsutism.

14.2.3.2 **Investigations** (Table 14.3)

In women with locally excessive hair growth with mFG <8, androgen levels need not be measured [27]. However, in women with mFG >8; If sexual hair growth is moderate to severe or there is clinical evidence suggestive of hyperandrogenic disorder, early morning serum total and free testosterone should be tested. Menstrual irregularity, infertility, galactorrhea, central obesity, acanthosis nigricans, clitoromegaly and sudden onset or rapid progression of hirsutism are indicative of a hyperandrogenic disorder. Further investigations corresponding to the etiology should be done. If total testosterone is >200 ng/dL, the patient is evaluated for tumoral hirsutism, ovarian hyperthecosis and HAIR-AN syndrome.

Table 14.3 Causes of hirsutism with clinical features and investigations [26]

Cause	Clinical features	Investigations
Constitutional		
Familial	Facial with prolongation of preauricular implantation line	Normal
SAHA syndrome	Hirsutism (central or peripheral) Acne Intense seborrhea FPHL Oligomenorrhea or polymenorrhea	Mild increase in DHEAS or test testosterone normal
Endocrine organ based		
Adrenal hirsutism		
Congenital adrenal hyperplasia (21 α hydroxylase deficiency), cushing syndrome, adrenal tumors	Central hirsutism, virilization	↑ 17-OH progesterone ↑ DHEAS ↑↑ ACTH
Ovarian hirsutism		
PCOS, ovarian hyperthecosis syndrome, ovarian tumors	Lateral hirsutism, acne, seborrhea, obesity, menstrual disorders	↑ Free testosterone ↓ SHBG ↑ Estrone
Pituitary hirsutism		
Prolactin secreting pituitary adenoma, psychogenic drugs ectopic hormone production (small cell lung cancer; carcinoid tumor)	Amenorrhea, galactorrhea, FPHL, acne, seborrhea, both central and lateral hirsutism	↑ Prolactin, ↑↑ ACTH (in SCC lung and carcinoid tumor)
Drugs		
Anabolic steroids	Hirsutism on lateral aspects of the face and back	Elevated parent drug or metabolite in blood, urine or hair

14.2.3.3 Treatment

Treatment of hirsutism includes temporary modalities of hair epilating like waxing, sugaring, tweezers, plucking. Hair depilatory creams are thioglycolates which disrupt the disulphide bond in the hair, hence dissolving the hair. Side effects of the depilatory creams are sulphurous odor and irritant dermatitis.

Eflornithine cream irreversibly inhibits ornithine decarboxylase, which catalyzes the rate-limiting step for follicular polyamine synthesis. Effect starts to appear at 6–8 weeks. Permanent hair reduction is defined as attaining at least 30% reduction of terminal hair and sustaining this reduction for a period longer than complete growth cycle of hair follicles (4–12 months), depending on the body site.

Photo-epilation and electrolysis of hair follicle are the permanent methods of hair removal. Photo-epilation is preferred for women whose unwanted hair is auburn, black, brown and electrolysis for white or blonde hair. Various lasers like alexandrite, diode and ruby laser and Nd:YAG and IPL sources emitting

wavelengths between 500–1200 nm are available for permanent hair reduction. Precooling and paracooling is required during hair removal laser. Side effects of lasers are erythema, hyperpigmentation, burn and paradoxical hypertrichosis. Paradoxical hypertrichosis is mostly seen in patients with the Mediterranean or Middle Eastern background on the neck and face. Women with hyperandrogenism are at higher risk. Electrolysis involves electric current passing through fine wire electrodes, which is manually inserted sequentially into individual hair follicles. There are two techniques of electrolysis, the galvanic electrolysis technique and thermolysis technique which use direct current and alternating current respectively to target hair follicle. In women with hirsutism despite cosmetic hair removal methods, pharmacological therapy is desired. Women who are not seeking fertility should be started on oral contraceptive pills. OCP reduces hyperandrogenism by suppression of LH secretion, increasing SHBG by stimulating its hepatic production, and decreasing binding of androgen to its receptor. OCP with lower androgenicity progestins like desogestrel and gestodene and androgen receptor antagonists like drospirenone and cyproterone acetate are efficacious drugs. Antiandrogens like spironolactone dose of 50–300 mg/day, finasteride 2–2.5 mg/day and flutamide 25–300 mg/day are added to OCPs if there is no response to OCPs after 6 months of treatment. Due to their teratogenic potential, anti-androgens are not indicated in females with childbearing potential. However, in women who are not sexually active, have undergone permanent sterilization or are on long-acting reversible contraception, either OCPs or anti-androgen can be initiated as initial treatment.

14.2.4 Alopecia Areata

Alopecia areata is an autoimmune condition characterized by acute onset of well-defined patches of noncicatricial hair loss on the scalp, beard and eyebrows.

14.2.4.1 Epidemiology

With a lifetime prevalence of 2%, it is found in 0.1–0.2% of the population at a given time [28, 29]. All the ethnic groups and both the genders are equally affected. 70–80% of cases occur before the age of 40 years with around 48% of patients having the onset of disease in the first to the second decade [30].

14.2.4.2 Predisposing Factors

AA has a genetic predisposition for certain MHC classes like HLA DQB1*0301 and HLA DRB1*1104. A family history of AA is found to be present in 10–42% of patients. Genes encoding natural killer cell receptor D ligands and downstream effectors of JAK pathway influence AA susceptibility.

14.2.4.3 Pathogenesis

AA results from breakdown in immune privilege with assault on the follicle at the level of the bulb by CD8 lymphocytes. The peribulbar lymphocytic infiltrate induces hair follicle keratinocytes to undergo apoptosis that results in inhibition of cell division within the hair matrix and shaft formation.

14.2.4.4 Clinical Features

Patients present with well defined, smooth, round to irregular patches of hair loss (Figs. 14.8 and 14.9). Towards the periphery of the area of active hair loss, small 3–4 mm exclamation mark hair is seen. These are dystrophic hair with fractured tips due to inhibition of cell division of hair matrix at the level of hair bulb. If there is severe inhibition of cell division, there may be fracture of the hair shaft before emergence from the scalp, which are called black dots. White hair are often spared and hair are frequently white when they regrow.

Fig. 14.8 Patchy alopecia areata in a female

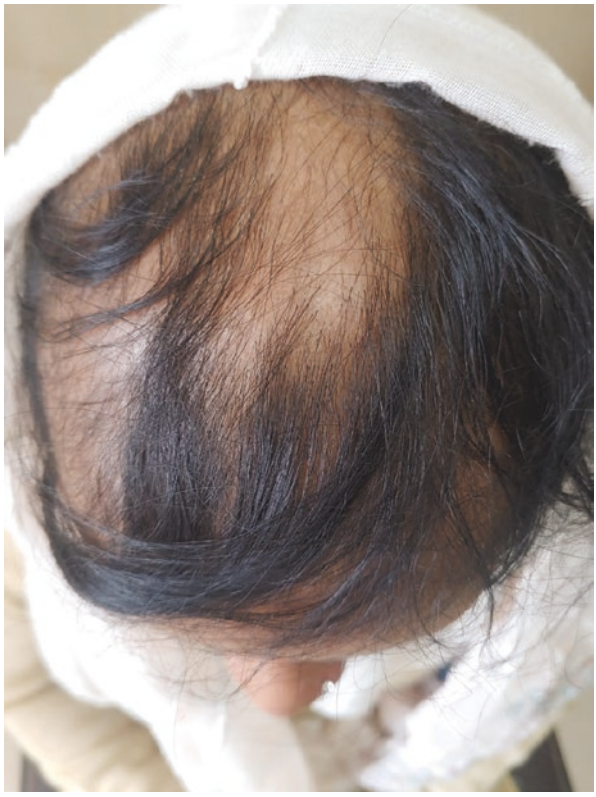

Fig. 14.9 Multiple patches of alopecia areata in a female

Marie Antoinette Syndrome/Thomas More Syndrome are conditions in which the scalp hair suddenly turns white. This condition is actually an acute episode of diffuse AA in which there is sudden whitening of hair due to preferential loss of pigmented hair. This condition has been named after Marie Antoinette, a French queen, whose hair allegedly turned white the night before her last walk to the guillotine during French revolution. Similarly Thomas More's hair turned white overnight in the Tower of London before his execution.

14.2.4.5 Variants of AA

There are different types of AA on the basis of severity, pattern and extent.

Based on extent

- Patchy (Figs. 14.8 and 14.9).
- Alopecia totalis (AT, whole scalp).
- Alopecia universalis (AU, all body hair affected).

Based on morphology

- Ophiasis—It is the pattern in which the hair loss occurs in the shape of a wave at the circumference of the head.
- Sisaipho—(ophiasis inversus) frontotemporoparietal region is affected with alopecia and occipital band being normal.
- Reticular—AA in a net-like pattern.
- Perinevoid (around nevi) and linear are two other unusual variants of AA.
- Acute diffuse and total alopecia—Sato Kwawamura et al. described this sudden-onset inflammatory non-cicatricial alopecia which has marked female predominance and is characterized by diffuse hair shedding without typical patches.

Based on prognosis (Ikeda's classification)

- Ikeda type I (no disease association)—It accounts for 80% of the cases, presents with single patches of alopecia in age between 20 and 40 years with single patch lasting less than 6 months and infrequent development to AT in less than 10% cases.
- Ikeda type II (associated with atopic disease)—accounts for 10% of the cases, presents with multiple patches of alopecia, reticular alopecia or ophiasis, present before 20 years of age with each patch last for more than 1 year and frequent development to AT in 75% cases.
- Ikeda type II-(prehypertensive type)—accounts for 5% of the cases. It presents with the reticular type of alopecia areata, usually in young adults from families with arterial hypertension. They develop into alopecia totalis in 40% of the cases.
- Ikeda type IV (associated with autoimmune endocrinopathy)—accounts for 5% of the cases. It affects people aged more than 40 years and has a chronic course.

Nail involvement has been found to be present in 2–44% of AA cases, with children more affected (40%) than adults (20%). Findings are geometrical nail pitting, sandpaper-like trachyonychia, punctate leukonychia, red lunula, thinning, Beau's line and onychomadesis. The nail changes may persist after the resolution of alopecia areata as 20 nail dystrophy. The nail changes may precede the onset of alopecia areata when it is termed as alopecia areata unguium.

14.2.4.6 Associations

Various conditions have been found associated with alopecia areata. Autoimmune diseases like autoimmune thyroid disease, vitiligo, pernicious anemia, celiac disease and lupus erythematosus have been found to be associated with alopecia areata. The risk of atopic dermatitis was high in children less than 10 years. AA is rarely associated with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome. It occurs due to mutation in the AIRE gene. It is characterized by the presence of two out of these disorders: Addison's disease, mucocutaneous candidiasis and hypoparathyroidism. Other features that can be

seen in APECED syndrome are chronic atrophic gastritis with pernicious anemia, hypogonadism, alopecia areata, autoimmune hepatitis and vitiligo. AA has also been found to be seen in patients on anti-TNF-alpha therapy. It has also been found to be associated with psychiatric disorders like major depression, generalized anxiety disorder, social phobia and paranoid disorder.

14.2.4.7 Investigations

Dermoscopy of alopecia areata is very characteristic (Fig. 14.10). Histopathology can also be done in doubtful cases.

14.2.4.8 Differential Diagnosis

The differential diagnosis of alopecia areata is patchy hair loss in syphilis and lupus erythematosus. Hence antinuclear antibody test and rapid plasma reagin test should be done in patients where other clinical findings support these diagnoses. Tinea capitis (black dot) and trichotillomania are other differential diagnoses of AA.

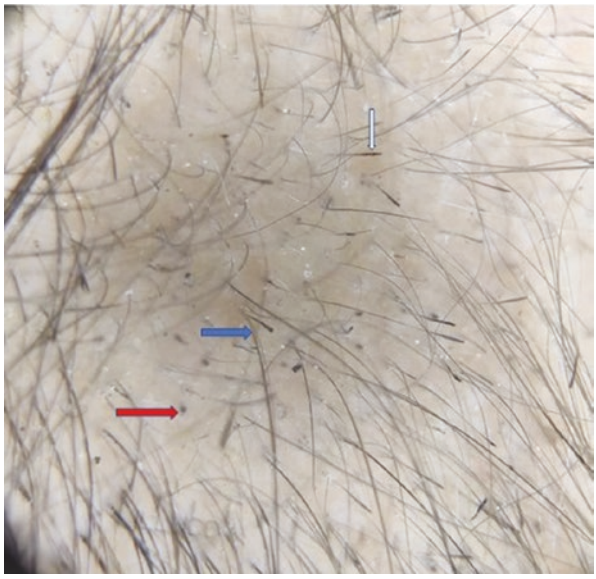

Fig. 14.10 Trichoscopic findings in alopecia areata—black dot (red arrow), tulip hair (blue arrow), exclamation hair (white arrow)

14.2.4.9 Treatment

Management of alopecia areata is based on the age group of the patient and surface area involved. Various topical agents like topical minoxidil, topical corticosteroids, calcineurin inhibitors and contact immunotherapy are used to manage alopecia areata.

Intralesional corticosteroid (ILC) in the concentration of 2.5 mg/mL (eyebrow and beard) and 5–10 mg/mL (scalp) given by jet injector or insulin syringe at 4–6 weeks interval is the best modality for patches in adults if the SALT score is less than 30%. The response to intralesional corticosteroids develops at 4–8 weeks. The intralesional steroids are given for a maximum of 6 months. If there is no response at 6 months, insufficiency of steroid receptors is considered. ILC are not to be used in children less than 6 years while in adolescents, ILC or topical corticosteroids can be used.

Topical corticosteroids can be prescribed as first-line topical treatment (alone or in combination) to treat scalp, eyebrow, or beard AA, mostly employed in young children.

In scalp AA, a potent topical corticosteroid should be applied daily for at least 6–12 weeks and, at most, 3–6 months.

Topical calcineurin inhibitors can be applied to treat scalp, eyebrow, or beard AA but should not be considered the first-line topical treatment, alone or in combination, for beard AA.

Topical prostaglandin analogues (e.g., bimatoprost or latanoprost) can be prescribed as first-line topical treatment (alone or in combination) to treat eyelash AA. It can be prescribed in conjunction with other topical or systemic agents, but it does not need to be used for all patients with AA.

Acute and widespread AA (>30%) are best treated with systemic corticosteroid therapy. Sharma proposed 300 mg oral prednisolone pulses at 4 weeks interval for 4 doses or till hair growth is observed [31]. Betamethasone oral pulse in the dose of 5 mg/kg on two consecutive days for a total duration of 12 weeks is found to be effective in alopecia areata [32]. Intravenous methylprednisolone at dose 500 mg once or 250 mg twice a day on three consecutive days every month has been found to be effective in extensive AA.

Topical immunotherapy with allergic contact sensitizers like diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester (SABDE) has been effective in AA. These drugs modulate the T cell-mediated mechanisms responsible for AA and counteract the proinflammatory cytokines such as TNF-alpha, IL-10 and TGF-beta. SABDE is more effective than DPCP and has fewer side effects. However, DPCP is more stable in acetone and cheaper than SABDE. Dinitrochlorobenzene is mutagenic hence not commonly used. The extent of hair loss before therapy is the most

important predictor before effective treatment for DPCP. The remission rates with DPCP for multilocular AA were 43.8%, subtotal AA and ophiasis 33.3% and AT/AU 21.4%. Poor compliance, cumbersome to use, side effects, high cost and poor accessibility are major drawbacks of contact immunotherapy limiting its use.

Various immunosuppressive drugs like cyclosporine, methotrexate have been tried in reducing the activity of alopecia areata. Cyclosporine inhibits the activation of helper T cells pathogenic in AA and found to have regrowth at second to fourth week at a dose of 6 mg/kg/day for 12 weeks [33].

Newer drugs including JAK-STAT inhibitors like Tofacitinib and Ruxolitinib have been found to be effective in AA. In a study of 13 adolescents treated with tofacitinib, 9 patients had a significant hair growth of 93% at 6.5 months [34]. Intralesional PRP has also been tried in alopecia areata and found to increase hair growth [35]. The treatment algorithm for the management of alopecia areata is given in Fig. 14.10 [36].

14.2.4.10 Prognosis

Severe alopecia (AT/AU), presence of nail disease, young age at disease onset, presence of family history of alopecia areata, atopy, association with other autoimmune disease, ophiasis, and disease duration of more than 1 year suggest poor prognosis of disease. Spontaneous remission is seen in 30–50% patchy AA within the first 6–12 months of disease onset and 66% of patients show complete regrowth of hair within 5 years. The risk of relapse is 85% after 20 years. However, only 22.5% of AT will go into partial remission and 2.5% will go into complete remission. Five to ten percent of patchy AA progresses to AT/AU.

14.2.5 Lichen Planopilaris

Lichen planopilaris is among the most commonly diagnosed causes of scarring alopecia.

14.2.5.1 Epidemiology

It is seen commonly in the third–fourth decade of life. LPP is more common in females than males, with a ratio varying from 1:8 to 9:1.

14.2.5.2 Pathogenesis

It is an autoimmune disease in which T lymphocytes target the follicular antigen with the destruction of hair follicle stem cells. Recent studies suggested the role of PPAR —Gamma in the destruction of the pilosebaceous unit [37]. PPAR-gamma is decreased in LPP which leads to aberrant lipid metabolism in sebaceous gland leading to accumulation of toxic lipids which develop an inflammatory response and further scarring.

14.2.5.3 Clinical Features

Patients presents with patches of cicatricial alopecia (see Table 14.1). Cutaneous lesions of LP can be seen in 40% of the patients.

14.2.5.4 Investigations

See Table 14.1.

14.2.5.5 Treatment

Treatment options include findings based on case series or studies. *Ultrapotent Topical and intralesional steroids* are first-line therapy for active LPP. It is used twice daily for the first month, followed by a once-daily application for 3 months then every other day for 3 more months [38]. *Systemic steroids* at a dose of 1 mg/kg/day for 15 days tapered over 4 months is the second-line treatment in active cases but it has a high relapse rate of 80%. The can be used as monotherapy or in association with other topical and or systemic therapies. In extensive involvement, systemic steroids hydroxychloroquine, methotrexate and cyclosporine have been shown to be effective in Lichen planopilaris. Hydroxychloroquine 200 mg twice daily is the first-line systemic agent which may be switched to cyclosporine if manifestations continue after 3–4 months. In a RCT hydroxychloroquine 400 mg daily versus methotrexate at a dose of 15 mg weekly administered for 6 months in refractory LPP, there was a higher efficacy of Methotrexate over at 6 months than HCQ [39]. There was an improvement in perifollicular erythema, perifollicular scaling and follicular keratosis. The response rate to monotherapy to HCQ is 51% while methotrexate is 87.5%. In a retrospective study, mycophenolate mofetil at a dose of 0.5 mg twice weekly for 4 weeks and then 1 g twice daily for at least 20 weeks showed a complete response in 5 patients with 85% reduction in lichen planopilaris area index score [40]. Other agents tried in LPP are *pioglitazone*, *griseofulvin*, *oral tetracyclines*, *retinoids* and *thalidomide* with varying success.

There are two main clinical variants, viz. frontal fibrosing alopecia and Graham Little–Piccardi–Lasseur syndrome. *Frontal fibrosing alopecia* is seen in postmenopausal females. There can be eyebrow involvement in 73% and body hair has been found to be lost in 25% of patients. Topical steroids, calcineurin inhibitors, doxycycline, finasteride hydroxychloroquine, mycophenolate mofetil and UVB have also been used with disappointing results.

14.3 Hair Loss in Lupus Erythematosus

Lupus erythematosus (LE) is an important cause of hair loss in females. Hair loss is seen in about 50% of patients of SLE at some point in time. The hair loss in lupus can be specific (in which interface dermatitis is seen). This includes acute, subacute, discoid, tumid lupus erythematosus. Acute LE is characterized by patchy type of alopecia. Subacute LE manifests as polycyclic, annular or psoriasiform plaques with thick adherent scale resulting in patchy hair loss. Noninflammatory patches of alopecia are seen in tumid LE. Discoid LE in early stage is characterized by well-defined patches of alopecia with erythematous to violaceous surface follicular pugging, telangiectasia and scaling may be present. In late stages, dyspigmentation, follicular plugging and atrophic scarring is seen. DLE accounts for 30–40% of scarring alopecia [41]. DLE affects the scalp in 30–50% of patients and out of that 60% of the patients develop permanent and reversible hair loss. The age of onset is 20–40 years and is more prevalent in African American. Treatment of DLE includes photoprotection, broad-spectrum sunscreen, topical steroids lotion and topical calcineurin inhibitors. Systemic agents like hydroxychloroquine, chloroquine, acitretin, clofazimine and rituximab have also been tried. A patchy type of alopecia is seen in 14–50% of the patients of LE (Fig. 14.11) [42]. They can occur before, during or after the diagnosis of SLE. These patches have some degree of erythema and dermoscopic may show hypopigmentation and vessel changes. HPE shows atrophy of epidermis, hyperkeratosis, interface dermatitis and pigment incontinence. It responds to immunosuppressive therapy of LE.

Lupus nonspecific alopecia includes lupus hair and alopecia areata. Lupus hair are dry, fragile short hair on the frontal hairline seen in 5–30% of women with active phase of lupus and improves after LE flare subside. These occur as postulated due to hair shaft breakage and retarded hair growth. AA in SLE may show deep dermal mucin in histopathology and it has an unpredictable course. Telogen effluvium and anagen effluvium is also seen in lupus. Anagen effluvium occurs approximately 7 days. It may occur due to drugs like cyclophosphamide or methotrexate used in LE and flares of LE can cause rapidly dividing matrix cells to shut down during the active phase.

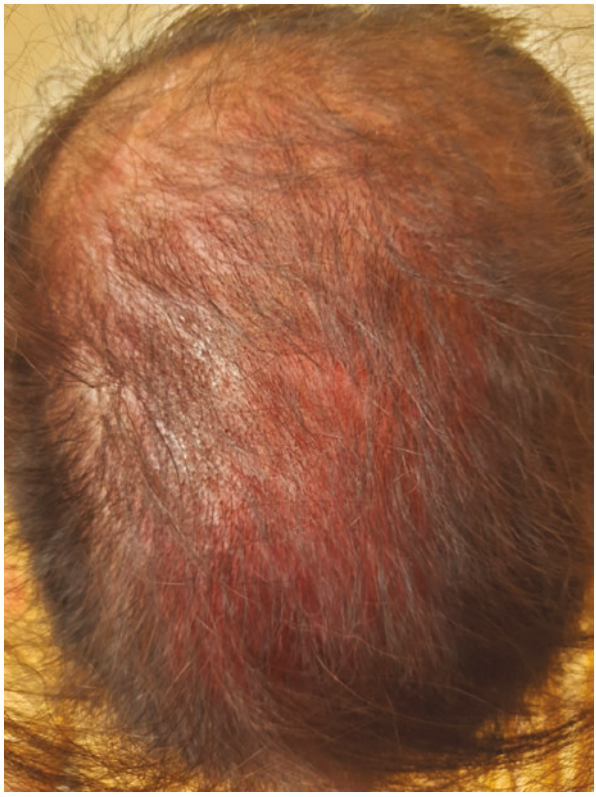

Fig. 14.11 Patchy alopecia in a patient of systemic lupus erythematosus

14.3.1 Pseudopelade of Brocq

Pseudopelade of Brocq is an idiopathic, chronic, slowly progressive patchy cicatricial alopecia.

14.3.1.1 Epidemiology

It is seen in women over 40 years of age.

14.3.1.2 Etiopathogenesis

The etiology and pathogenesis is not known.

14.3.1.3 Clinical Features and Investigations

See Table 14.1.

14.3.1.4 Diagnostic Criteria

Braun-Falco (1986) proposed the following clinical and histological criteria.

Clinical criteria
- Irregular and confluent patches of hair loss.
- Moderate atrophy (late stage).
- Mild redness around hair follicles (early stage).
- Female predominance (3:1).
- A long course of more than 2 years.
- Slow progression.
- Spontaneous termination possible.

Histological criteria
- No marked inflammation.
- No widespread scarring.
- No significant plugging of hair follicles.
- No sebaceous glands.
- Normal epidermis.
- Fibrotic streamers in dermis.

Immunohistochemistry
- Negative.

14.3.1.5 Prognosis

The course is the variable and alopecia is irreversible.

14.3.1.6 Treatment

No treatment stopped the progression. Autografting from nonscarred areas and surgical expansion can be done in severe cases.

14.3.2 Trichotillomania

Trichotillomania is characterized by a repetitive compulsive habit of pulling one's hair. Trichotillomania is listed in the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-V) as an obsessive-compulsive and related disorders.

14.3.2.1 Diagnostic Criteria for Trichotillomania

1. The individual pulls their hair out on a recurrent basis, which results in hair loss.
2. Repeated attempts have been made to reduce or stop the hair pulling altogether.
3. The hair pulling causes significant distress or impairment in areas of occupational, social or other regions of functioning.
4. The hair pulling cannot be better attributed to another medical condition.
5. The hair pulling cannot be better explained as a symptom of another mental disorder.

14.3.2.2 Epidemiology

It is more commonly seen in adolescent females with the female:male ratio being 7:1. In childhood, young males are more commonly affected. It is a habit similar to thumb-sucking and nail-biting in children.

14.3.2.3 Clinical Features

The skin overlying the scalp is normal and hair is never completely lost within [1] the affected area, unlike alopecia areata (Table 14.1).

14.3.2.4 Investigations (Table 14.1)

Sometimes patients rarely present with Rapunzel syndrome. These patients present with nausea, abdominal pain, vomiting, obstruction with a hairball (trichobezoar) and intestinal perforation. Patients with insight should be referred to a psychiatrist or clinical psychologist.

Treatment of trichotillomania involves counselling, aimed at habit reversal along with pharmacotherapy using clomipramine or selective serotonin receptor inhibitors.

14.3.3 Traction Alopecia

14.3.3.1 Epidemiology and Pathogenesis

Traction alopecia is common in women of African origin due to curved hair follicle and cultural hairdressing practices prevalent there. The axial symmetry and helical shape give rise to geometric points of weakness making African hair more prone to breaking and tight hairstyles add the mechanical trauma to the hair shaft. Tight buns, ponytail hair extension and tight braids are highest risk hairstyles. Chemical relaxation of the hair through interruption of the disulphide bonds weakens the hair

shaft adds to a higher predisposition to TA. The mechanical damage induces inflammatory response which presents as perifollicular erythema with pustules and or papules in areas of friction. Chronic and repeated traction causes follicular damage and hair loss.

14.3.3.2 Clinical Features and Investigations

See Table 14.1.

14.3.3.3 Treatment

The main treatment is the relief of traction by loosening traumatic hairstyles, avoiding chemical and thermal treatment. Initial treatment includes the use of topical and intralesional corticosteroids and oral and topical antibiotics as anti-inflammatory agents. Minoxidil has also been tried in late stages. In advanced cases with scarring hair transplantation with techniques like punch grafting with rotation flaps, micro (1–2 follicular unit grafts) and mini (3–4 follicular unit grafts) grafting have been documented [43, 44].

14.3.4 Central Centrifugal Cicatricial Alopecia

14.3.4.1 Epidemiology

Central centrifugal cicatricial alopecia, also called hot comb alopecia, is seen commonly in women of African ethnicity. The female to male ratio is 3.

14.3.4.2 Pathogenesis

The condition has a multifactorial etiology involving both genetic and environmental causes. The traumatic hair practices in the African women predispose to this condition. It is called follicular degeneration syndrome due to premature degeneration of the inner root sheath.

14.3.4.3 Clinical Features and Investigations

See Table 14.1.

14.3.4.4 Treatment

Patients are advised to do minimal hair styling and grooming. Potent topical steroids may arrest progression and doxycycline or minocycline is useful in inflammatory cases with pustules. Minoxidil has been tried in these patients due to its similarity with FPHL.

14.4 Hair Shaft Disorders

Some hair shaft disorders present with increased hair breakage due to increased hair fragility. Monilethrix is a condition in which scalp hair is beaded along with follicular keratoses on the nape of neck and occiput. In Pili Torti hair is flattened and at irregular intervals completely rotated through 180° around their long axis. Netherton syndrome is an autosomal recessive disorder characterized by a triad of ichthyosis linearis circumflexa, atopy and trichorrhexis invaginata. Trichorrhexis invaginata involves the invagination of the distal part of the hair into the proximal portion appearing as bamboo hair. Trichorrhexis nodosa occurs in response to the hair shaft injury. It is an extreme form of withering. It occurs due to hairdressing procedures, shampooing, brushing. Congenital metabolic diseases like argininosuccinic aciduria, biotinidase deficiency and trichohepato-enteric syndrome can develop trichorrhexis nodosa. Trichothiodystrophy is characterized by hair shaft abnormalities due to decreased sulphur content along with lamellar ichthyosis, nail dystrophy and mental retardation and skin fragility. Polarizing light microscopy shows tiger tail appearance due to alternating dark and light bands.

Hair shaft disorders without increased fragility include pili annulati, uncombable hair syndrome, loose anagen hair syndrome, trichostasis spinulosa and Pili multigemini. Pili annulati is a normal incidental finding characterized by alternate dark and light bands due to split in the hair cortex. Woolly hair is tightly coiled hair associated with twists and grooves. They are common in Africans, found to be associated with congenital disorders like Naxos syndrome and Carvajal syndrome. Woolly hair nevus can present as can be localized patch of woolly hair along with congenital melanocytic nevus. Uncombable hair syndrome presents at 6 months to 12 years of age with silver coloured hair with a disorderly appearance. On light microscopy, the shaft has a three-dimensional aspect hence known as Pili trianguli et canaliculi. It is found to be associated with Neurofibromatosis and valproate therapy. Loose anagen syndrome is prevalent in children of 2–6 years of age, more commonly seen in females. It may present with decreased hair density, unruly hair or increased hair shedding. It occurs due to premature keratinization of the inner root sheath. Hair pull test is positive with Trichogram showing floppy sock appearance due to roughened cuticle, misshapen anagen bulbs and long tapered twisted

hair. It may resolve spontaneously. Minoxidil has been tried in many cases with variable results. Trichostasis spinulosa presents as vellus telogen hair on the face, trunk, limbs, interscapular area and found to be associated with the application of minoxidil and steroids, syringoma, epidermal inclusion cyst and chronic renal failure. Pili multigemini is when multiple hairs arise from multiple follicular structures but single pilosebaceous canal. It is associated with cleidocranial dysostosis.

14.5 Premature Canities

Premature canities means premature whitening of hair as a result of the ageing process. The age cutoff for premature canities is 25, 30 and 35 years in Caucasians, Asians and Africans, respectively [45]. There is early depletion of melanocyte reservoirs in the hair bulb; however, the nonmelanised melanocytes are still there in outer root sheath. Genetic syndrome-like Werner and Rothmund Thompson syndrome, nutritional disorders like kwashiorkor, autoimmune like pernicious anemia, atopy and thyroid disorders can lead to premature canities. The beard and moustache are the first to grey followed by scalp or body hair. On the scalp, temples are affected first followed by the crown and later to occur. Treatment includes camouflage, calcium pantothenate, PABA, PUVA-sol, melitane, topical prostaglandin analogues and antioxidants.

14.6 Pigmentary Disorders

Hereditary diseases like albinism, Waardenburg syndrome and piebaldism have whitening of hair. Vogt Koyanagi Harada syndrome and Allezendrani syndrome are the acquired causes of poliosis (localized patches of white hair). Drugs like chloroquine and hydroxychloroquine cause bleaching of the hair. Dithranol and chrysarobin stain light-coloured hair brown. Imatinib causes premature greying and skin hypopigmentation, and prostaglandin analogues cause darkening of eyelashes and iris. Nutritional deficiencies like copper deficiency in Menkes kinky hair syndrome cause achromotrichia. Intermittent protein transmission leads to the flag sign of kwashiorkor (*signe de la bandera*). Various metabolic disorders like phenylketonuria, homocystinuria and porphyria can cause altered hair pigmentation. The high concentration of copper in tap water or swimming pools can cause green color hairs. A yellowish staining of hair can be seen in heavy smokers and patients with exposure to picric acid dithranol.

References

1. Thiers BH, Galbraith GMP. Alopecia areata. In: Theirs BH, Dobson RL, editors. Pathogenesis of skin diseases. New York: Churchill Livingstone; 1986. p. 57–64.
2. Birch MP, Lalla SC, Messenger AG. Female pattern hair loss. Clin Exp Dermatol. 2002;27:383–8.
3. Fabbrocini G, Cantelli M, Masarà A, Annunziata MC, Marasca C, Cacciapuoti S. Female pattern hair loss: a clinical, pathophysiologic, and therapeutic review. Int J Women's Dermatol. 2018;4:203–11.
4. Redler S, Brockschmidt FF, Tazi-Ahnini R, Drichel D, Birch MP, Dobson K, et al. Investigation of the male pattern baldness major genetic susceptibility loci AR/EDA2R and 20p11 in female pattern hair loss. Br J Dermatol. 2012;166:1314–8.
5. Yip L, Zaloumis S, Irwin D, Severi G, Hopper J, Giles G, et al. Gene-wide association study between the aromatase gene (CYP19A1) and female pattern hair loss. Br J Dermatol. 2009;161:289–94.
6. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol. 1977;97:247–54.
7. Sinclair R, Jolley D, Mallari R, Magee J. The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. J Am Acad Dermatol. 2004;51:189–99.
8. Olsen EA. Current and novel methods for assessing efficacy of hair growth promoters in pattern hair loss. J Am Acad Dermatol. 2003;48:253–62.
9. Hamilton JB. Patterned loss of hair in man; types and incidence. Ann N Y Acad Sci. 1951;53:708–28.
10. Arias-Santiago S, Gutiérrez-Salmerón MT, Castellote-Caballero L, Buendía-Eisman A, Naranjo-Sintes R. Androgenetic alopecia and cardiovascular risk factors in men and women: a comparative study. J Am Acad Dermatol. 2010;63:420–9.
11. Arias-Santiago S, Gutiérrez-Salmerón MT, Buendía-Eisman A, Girón-Prieto MS, Naranjo-Sintes R. Hypertension and aldosterone levels in women with early-onset androgenetic alopecia. Br J Dermatol. 2010;162(4):786–9.
12. Van Der Donk J, Hunfeld JA, Passchier J, Knegt-Junk KJ, Nieboer C. Quality of life and maladjustment associated with hair loss in women with alopecia androgenetica. Soc Sci Med. 1982;1994(38):159–63.
13. Kumalo NP. The "fringe sign" for public education on traction alopecia. Dermatol Online J. 2012;18(9):16.
14. Malakar S, Mehta PR. "I hair": a prognostic marker in alopecia areata and trichotillomania. Indian J Dermatol. 2017;62:658.
15. Rakowska A, Maj M, Zadurska M, Czuwara J, Warszawik-Henzel O, Olszewska M, Rudnicka L. Trichoscopy of focal alopecia in children-new trichoscopic findings: hair bulbs arranged radially along hair-bearing margins in aplasia cutis congenita. Skin Appendage Disord. 2016;2(1–2):1–6.
16. Royer M, Sperling L. Splitting hairs: the "hamburger sign" in trichotillomania. J Cutan Pathol. 2006;33(Suppl 2):63–4.
17. Rakowska A, Slowinska M, Kowalska-Oledzka E, Olszewska M, Rudnicka L. Dermoscopy in female androgenic alopecia: method standardization and diagnostic criteria. Int J Trichol. 2009;1:123–30.
18. Oura H, Iino M, Nakazawa Y, Tajima M, Ideta R, Nakaya Y, et al. Adenosine increases anagen hair growth and thick hairs in Japanese women with female pattern hair loss: a pilot, double-blind, randomized, placebo-controlled trial. J Dermatol. 2008;35:763–7.

19. Peters EMJ, Müller Y, Snaga W, Fliege H, Reißhauer A, Schmidt-Rose T, et al. Hair and stress: a pilot study of hair and cytokine balance alteration in healthy young women under major exam stress. PLoS One. 2017;12:e0175904.
20. Cesena A. Relatione dell'origine et successi della terra di Varese descritta dal r.p. Antonio Cesena l'anno 1558. Liguria: Accademia Lunigianese di Scienze Giovanni Capellini; 1993. p. 113.
21. Headington JT. Telogen effluvium. New concepts and review. Arch Dermatol. 1993;129:356–63.
22. Rebora A. Proposing a simpler classification of telogen effluvium. Skin Appendage Disord. 2016;2:35–8.
23. Whiting DA. Chronic telogen effluvium: increased scalp hair shedding in middle-aged women. J Am Acad Dermatol. 1996;35:899–906.
24. Shrivastava SB. Diffuse hair loss in an adult female: approach to diagnosis and management. Indian J Dermatol Venereol Leprol. 2009;75(1):20–7.
25. Rebora A, Guarrera M, Baldari M, Vecchio F. Distinguishing androgenetic alopecia from chronic telogen effluvium when associated in the same patient: a simple noninvasive method. Arch Dermatol. 2005;141(10):1243–5.
26. Camacho FM. Hypertrichosis and hirsutism. Chapter 70. In: Bolognia JL, Schaffer JV, Cerroni L, editors. Dermatology. 4th ed. Amsterdam: Elsevier; 2018. p. 1188–202.
27. Martin KA, Anderson RR, Chang RJ, Ehrmann DA, Lobo RA, Murad MH, Pugeat MM, Rosenfield RL. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol. 2018;103(4):1233–57.
28. Safavi K. Prevalence of alopecia areata in the first National Health and Nutrition Examination Survey. Arch Dermatol. 1992;128:702.
29. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc. 1995;70:628–33.
30. Kyriakis KP, Paltatzidou K, Kosma E, Sofouri E, Tadros A, Rachioti E. Alopecia areata prevalence by gender and age. J Eur Acad Dermatol Venereol JEADV. 2009;23:572–3.
31. Sharma VK. Pulsed administration of corticosteroids in the treatment of alopecia areata. Int J Dermatol. 1996;35(2):133–6.
32. Agarwal A, Nath J, Barua KN. Twice weekly 5 mg betamethasone oral pulse therapy in the treatment of alopecia areata. J Eur Acad Dermatol Venereol JEADV. 2006;20:1375–6.
33. Açıkgöz G, Çalışkan E, Tunca M, Yeniay Y, Akar A. The effect of oral cyclosporine in the treatment of severe alopecia areata. Cutan Ocular Toxicol. 2014;33(3):247–52.
34. Craiglow BG, Liu LY, King BA. Tofacitinib for the treatment of alopecia areata and variants in adolescents. J Am Acad Dermatol. 2017;76:29–32.
35. Trink A, Sorbellini E, Bezzola P, Rodella L, Rezzani R, Ramot Y, et al. A randomized, double-blind, placebo—and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata. Br J Dermatol. 2013;169:690–4.
36. Trüeb RM. The difficult hair loss patient: guide to successful management of alopecia and related conditions. Cham: Springer; 2015.
37. Harries MJ, Paus R. Scarring alopecia and the PPAR-γ connection. J Investig Dermatol. 2009;129:1066–70.
38. Assouly P, Reygagne P. Lichen planopilaris: update on diagnosis and treatment. Semin Cutan Med Surg. 2009;28(1):3–10.
39. Naeini FF, Saber M, Asilian A, Hosseini SM. Clinical efficacy and safety of methotrexate versus hydroxychloroquine in preventing lichen planopilaris progress: a randomized clinical trial. Int J Prev Med. 2017;8:37.
40. Cho BK, Sah D, Chwalek J, Roseborough I, Ochoa B, Chiang C, et al. Efficacy and safety of mycophenolate mofetil for lichen planopilaris. J Am Acad Dermatol. 2010;62:393–7.
41. Fabbri P, Amato L, Chiarini C, Moretti S, Massi D. Scarring alopecia in discoid lupus erythematosus: a clinical, histopathologic and immunopathologic study. Lupus. 2004;13:455–62.

42. Ye Y, Zhao Y, Gong Y, Zhang X, Caulloo S, Zhang B, et al. Non-scarring patchy alopecia in patients with systemic lupus erythematosus differs from that of alopecia areata. Lupus. 2013;22:1439–45.
43. Earles RM. Surgical correction of traumatic alopecia marginalis or traction alopecia in black women. J Dermatol Surg Oncol. 1986;12:78–82.
44. Özçelik D. Extensive traction alopecia attributable to ponytail hairstyle and its treatment with hair transplantation. Aesthet Plast Surg. 2005;29(4):325–7.
45. Sehrawat M, Sinha S, Meena N, Sharma PK. Biology of hair pigmentation and its role in premature canities. Pigment Int. 2017;4(1):7.

Chapter 15
Nail Diseases in Women

Soni Nanda, Chander Grover, and Sonal Bansal

15.1 Introduction

Nail in humans have always been an important tool protecting the terminal phalanx against injury, improving manual dexterity and enabling picking up small objects. At the same time, they have been considered to be a marker of social status and the overall health and hygiene of an individual. Females have a natural inclination toward beautification of their bodies; this includes adornment of their nails. Throughout history, women have been recorded to enhance their beauty with nail cosmetics. The use of nail cosmetics dates back to 5000 BC, when women in India, China, and Egypt used henna to dye their fingernails [1, 2]. Henna is still used in some cultures to adorn nails (Fig. 15.1).

The nail in women is proposed to be constitutionally different from those in men. There is a higher risk of nail fragility in women, which could be assumed to be a result of the women being more conscious of any cosmetic impairment in their nails and seeking redressal for that. However, other factors are also probably involved. There is an age-related decrease in lipid content of the nail plate which is more common and more severe in women [3]. It is possible that nails in women are constitutionally more fragile [4, 5] as intercellular keratinocyte bridges are weaker as compared to men, and are further weakened with age. However, there is no difference with respect to the content of major trace elements [6]. A larger number of women are engaged in household chores as compared to men, and this predisposes

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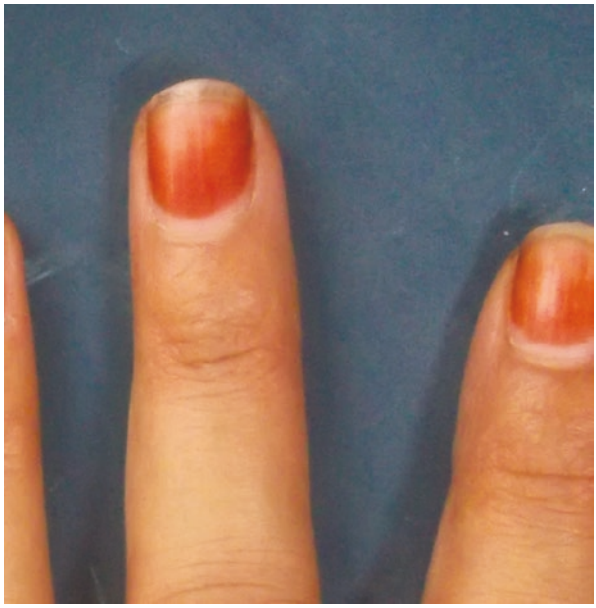

Fig. 15.1 Henna applied on finger nails by a middle-aged woman. Note the proximal curved border of exogenous pigment

them to development brittleness, as compared to men [7]. Another important aspect of nail health in women is proportionately higher occupational risk of nail health issues as compared to men, due to the commoner involvement in household work. This includes excessive exposure to water, harsh soaps and detergents which compromises the structure and function of nails, making them more prone to certain infections and disorders like brittle nails and paronychia.

It is widely believed that a healthy nail should ideally have a shiny surface, with a pink nail bed and a white free margin that extends well beyond the nail bed. There should be a dorsal slight curve both transversally and distal to proximal [8]. The cuticle and nail folds should be well attached to the nail plate, leaving no crevices or ragged edges [9]. It is this standard of beauty that most women aspire for, especially as the nails are a very visible part of the body. Nail hygiene is also an important aspect of personal grooming, which most women try to attain to perfection. It is also an important part of hand hygiene, which all of us are trying to ensure diligently. Healthy grooming habits include cutting fingernails straight across and slightly rounding the free edges. However, an overzealous self-cleaning of nails (using files or various sharp instruments), excessive cutting or filing, or salon cleansing during procedures like manicure/pedicure, can lead to increased chances of ingrown nails or infections (due to undue manipulation of cuticle or use of unsterile instruments). As these procedures are more commonly resorted to by women, such issues are also more commonly seen in them.

Modern day nail cosmetics include a wide range of products ranging from onycho-cosmeceuticals to nail polishes, acrylics, silks, gels, and extensions. It is a global, multibillion-dollar industry, the primary consumers of which are women. In

2018, nail cosmetics became an $8.36 billion industry in the USA [10]. Globally, the retail market for nail polish increased from $3 billion in 2007 to $45 billion in 2012 [11]. It is estimated that 85–90% of women worldwide use nail care product [12]. The above figures are a clear reflection of the increasing use of nail care products. However, these products come with a risk of adverse effects and associated nail issues, which are correspondingly on the rise.

It is clear that the esthetic appearance of nails is important to women; thus awareness regarding how to maintain a healthy nail, safe practices for the use of nail cosmetics, and an early identification and treatment of nail disorders should help women use nail cosmetics and maintain functional nails throughout their lives. This chapter aims to discuss these issues in detail. We first discuss the use of nail cosmetics and nail beautification techniques. This is followed by the various issues which may be associated or are found with a higher frequency in women. The management of these conditions is also discussed in detail.

15.2 Physiologic Nail Changes in Women

Various age-related nail changes are known in women and may often be confused with pathological conditions requiring medical attention. The etiology is unclear but may be due to an impaired blood flow to the nail unit. A complete review of symptoms and, if warranted, screening laboratory studies for thyroid, kidney, and liver function should be reassuringly normal. Throughout the normal aging process, nails become more brittle and the rate of growth slows [13]. From the age of 25 years onward, nail growth rate is known to decrease by 0.5% each year [14]. Aging nail may appear pale, dull, or opaque [15]. Their calcium content is increased while iron content is decreased. Texture wise, the nail plate becomes more friable with fissuring, splitting, and longitudinal striations [16]. Neapolitan nails describe an age-related nail discoloration resulting in nails which are opaque distally, normal pink centrally, and white proximally [17]. Brittle nails also increase with age, affecting 19% of patients aged <60 years and 35% of the population aged >60 years [18]. Postmenopausal women are particularly predisposed to nail brittleness as discussed previously (Fig. 15.2) [13].

Importantly, the risk of nail disorders like onychomycosis, paronychia, and onycholysis increases with age [15]. This may be related to a decrease in nail growth rate with age [13]. Other factors may include gait abnormalities, or changes in anatomy (e.g., hallux valgus), which predispose toenails to trauma, which is a risk factor for progression of tinea pedis to tinea unguium.

Malnutrition is known to have a negative effect on nail growth. A severe nail dystrophy is observed in kwashiorkor. Soft, brittle, often fissured nails can be seen in cachexia and bulimia [19–21]. In severe vitamin B12 deficiency in dark-skinned people, multiple longitudinal pigmented bands may occur. Genetically determined nail consistency does not show any influence with any particular food, even the so-called organic or biologic.

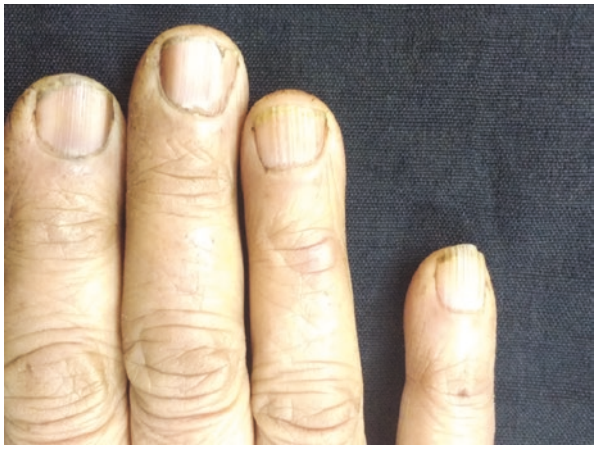

Fig. 15.2 Increased longitudinal ridging in a postmenopausal woman—a physiological change

15.3 Nail Cosmetics and Women

Women wear nail cosmetics to enhance the esthetic appearance of their nails. Ironically, nail cosmetics may themselves lead to substantial and sometimes permanent nail changes, worsening their aesthetic appearance. An awareness of these potential complications may help avoid or at least expeditiously diagnose and treat them.

The common cosmetic procedures being done on nails include manicures/pedicures including nail cleansing and application of nail polish; or the use of artificial nails including gel nails and acrylic nails.

15.3.1 Manicure and Pedicure

These are common salon procedures, routinely done by many women almost on a monthly basis. A manicure or a pedicure is defined as cleaning, shaping, and sometimes augmenting of fingernails or toenails by the application of a nail lacquer or other nail enhancement. It also involves the smoothening or filing of any calluses, especially on soles [22]. Steps of a manicure/pedicure and their implications, especially in this COVID era, are summarized in Table 15.1 [25].

Thus, it can be seen that a fairly simple and routine procedure has the potential to sometimes irreversibly damage the cosmesis of the nail unit, or cause chronic infections with a long recovery period. At the same time, adverse consequences can be easily prevented with attention to detail and following proper procedure.

Table 15.1 Steps of a manicure/pedicure

Stepwise process	Details of the steps	Possible adverse effects	Precautions or remarks
Soaking in warm, soapy water	Soaking to remove any debris from under the nails and to soften the nails and cuticles	Pedicure tubs in which hands and feet are soaked have been reported to cause *Mycobacterium fortuitum* infections from a nail salon in California [23]	Avoid excessive soaking Clean and sterilize tubs regularly
Removal of nail paint	Existing nail paint, if any, is then removed with products which are mostly acetone based	Excessive dryness because of acetone	Use of acetone-free products or use of moisturizer afterward
Filing/ trimming	Trimmed and filed to a desired shape (rounded or pointed)—the ideal shape is a central, delicate arc without any sharp corners, so as to create the illusion of a long, slender finger [22]	Onychoschizia or lamellar nail splitting Transmission of fungal and viral infections from one nail to another and from one person to another Overzealous shaping and cutting can predispose to hang nails, nail plate fractures, and ingrown nails [24]	Distal filing is preferred over clipping of nails Do preferably with a disposable filer for reduction of transmission of infections Preferably shape with a very slight curve with corners left untouched
Scraping	Foot scraper or a pumice stone is then used to buff the rough skin of palms and soles and any thick calluses are layered off	Over vigorous scraping can sometimes lead to scratches which can get infected	Scraping should be done softly and never vigorously
Softening of cuticles	By either applying a chemical cuticle remover (an alkaline substance like 0.4% sodium or potassium hydroxide) or applying a moisturizer. Once soft and malleable, the cuticles are pushed proximally and/or clipped away with a metal or wood implement	This is the most damaging step in the whole procedure as it predisposes the nail folds to subsequent environmental insults and secondary infections	Avoid pushing or trimming cuticle at all
Buffing of the nail plate	Buffing is done to smoothen any ridges and to improve adhesion of nail lacquer or other nail enhancements to be applied subsequently	Thinning of the nail plate, which in turn can lead to frequent breakage and risk of infections	Overaggressive buffing should be avoided

15.3.2 Nail Polish and Removers

The commonest nail cosmetic available in the market is the humble nail polish, variously known as nail paint, nail enamel and nail lacquer. It serves the primary purpose of nail beautification due to various colors and finishes available [26]. However,

at the same time, it offers mechanical protection to the nail plate, improves its water binding capacity, and fills in fractures and camouflages the nail ridges effectively.

Revlon® was the first company to start manufacturing nail polishes. They were first manufactured as a by-product of automobile painting industry where a film-forming polymer was dissolved in a volatile organic solvent to form an opaque lacquer. The commonest practice among nail polish manufacturers is to dissolve nitrocellulose in butyl-acetate or ethyl acetate. The film that is created by the nail polish is oxygen permeable as against artificial nail prostheses which are oxygen impermeable [9].

Nevertheless, certain adverse reactions are known to be associated with nail polish usage. These include the following.

1. *Allergic dermatitis*: Patients allergic to nail varnish often develop dermatitis at sites distant from the fingers. It is seen in 1–3% of cases, and often presents with unilateral eyelid dermatitis or linear areas of dermatitis on the face and neck caused by habitual rubbing of these areas with freshly painted fingernails. Rarely, generalized eczema or involvement of the genitalia may also be seen. The most common allergen implicated in nail polish allergy is 7% thermoplastic resin TSFR (toluene sulfonamide formaldehyde resin) which is the commonest adhesive used in nail polishes. Hypoallergenic nail polishes have alkyl polyester resins instead. An increasing recognition of this frequent sensitizer has led to the current availability of many tosylamide/formaldehyde resin–free nail polishes and thus a reduction in patch-test positivity to this allergen over the years [27].
2. *Color changes*: A prolonged use of nail polish can lead to yellow/red discoloration of the nail plate which fades over a fortnight after removal. The proximal end of such a discoloration is parallel to the proximal nail fold, thus confirming its exogenous origin. It is advisable to have nail polish–free days to keep the nails healthy and free of this complication.
3. Nail polish removers (acetone based) cause excessive dryness and brittleness of the nail plates. Nails can develop surface keratin granulations due to the use of nail polishes and nail removers (Fig. 15.3). This condition simulates superficial white onychomycosis. It commonly happens when old nail polish is not removed before applying a fresh coat.
4. The use of nail polish (for longer than 4 days) has been documented to harbor microorganisms [28] (especially if it is chipped) (Fig. 15.4). This fact is of immense importance in certain professions like health-care workers and food handlers, who are at higher risk of transmitting these organisms.

Any discussion about nail polishes cannot be complete without discussing nail polish removers. They are used for uniformly removing nail polish from the nail plate for examining the nail or before a fresh coat can be applied. The following types are commercially available.

1. *Acetone-based* nail-polish removers are the most commonly available ones. However, they have been reported to cause irritant dermatitis and an excessive use can also lead to brittleness of nails.

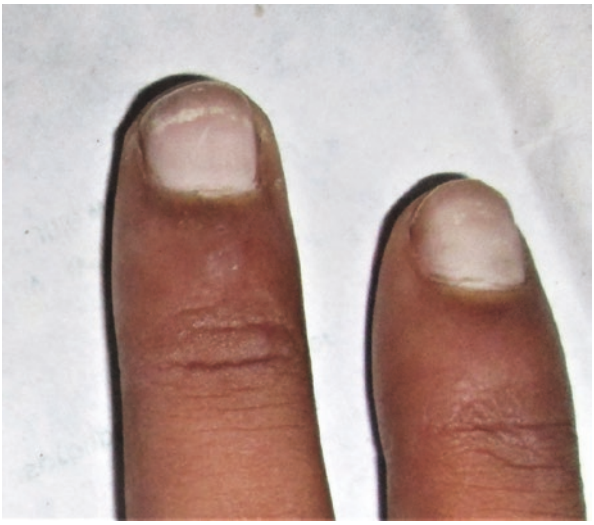

Fig. 15.3 Nail discoloration and keratin granulation seen after removal of nail paint after a long time

Fig. 15.4 Chipping of the nail paint within 3–4 days. This is a sanctuary site for various microorganisms

2. *Acetone-free* nail-polish removers contain ethyl acetate, butyl acetate, or ethyl lactate. Nail polish remover pads containing gammabutyrolactone are also available and are safe and convenient to use. Rarely, they get converted to GHB (gamma-hydroxybutyrate) which can result in systemic toxicity.

15.3.3 Sculptured/Artificial Nails

Sculptured nails are applied as acrylic or gel nails, both of which contain acrylates [29]. These sculptured/artificial nails are designed to give a more shiny and lustrous appearance to the nail plate. However, they are associated with unique adverse effects as well. Artificial nails are more likely to get colonized with Gram-negative

bacilli and yeast as compared to natural nails hence these have an increased probability of transmitting infections as well [30–33]. Also, it is more difficult to clean artificial nails compared to normal nails resulting in the larger number of residual bacterial under the artificial nails. Outbreaks of various infective diseases due to artificial nails, for example, infections by *Candida albicans* and *Pseudomonas aeruginosa*, have been reported [32, 33].

15.3.3.1 Gel Nails

Gel nails refers to an ultraviolet light–curable nail lacquer. They are being used for over three decades to improve the appearance of nails by imparting luster and shine to the nail plate (Fig. 15.5a, b). They also enable nail polish to stay for a longer duration. Unlike standard nail polish, gel nails require photocuring (fixing). They have gained popularity because they are long-lasting, resistant to chipping and scratching, and are easy to apply.

Shellac® (CND, San Diego, CA) and OPI gel polishes® are examples of commercially available gel nail polish. They contain photoinitiators that are photocured with either a UV (typical wavelength of 340–380 nm) [34]; or a light-emitting diode (LED) lamp, and some are formulated to be used with either type of lamp. LED lamps accomplish photocuring more quickly because they emit a narrower spectrum of light. However, UV lamps are less expensive and are therefore more routinely used in the photocuring process.

Gel nail, though a very commonly done cosmetic procedure at nail salons, has not been utilized adequately by the dermatologists. As a matter of fact, they have been mostly shunned by us because of various reported side effects [35–37]. However, most of the reported side effects are technique dependent and can be avoided by careful application and removal.

Gel nails are an excellent tool for camouflaging superficial nail abnormalities. They improve the patient satisfaction manifold when combined with medical treatment in conditions like nail lichen planus or psoriasis where medical treatment takes

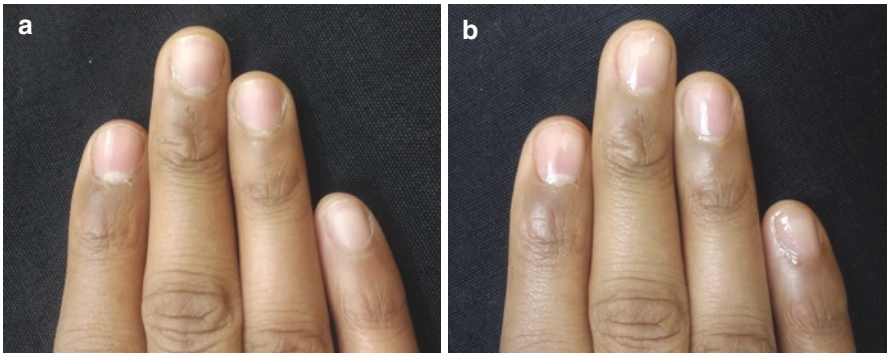

Fig. 15.5 (**a**, **b**) Gel nails imparting shine and luster to multiple nails in a patient with weathered nails and hang nails

a long time for effects to show. Gel nails are also useful for conditions like brittle nails and also for breaking the habit of nail biting. These have also been found useful by professionals like guitarist who experience damaged nails due to occupational reasons; or for improving cosmetic appearance of nails with irreversible damage, like pterygium. Gel nails are also a good option for self-limiting conditions like trachyonychia where patient is excessively concerned about the appearance of nails.

We have experience with using gel nails in various conditions like trachyonychia, nail pitting, onychorrhexis, onychoschizia, Beau's lines, nail psoriasis, nail lichen planus (including pterygium), and brittle nails with gratifying results. It seems that the use of gel nails on cosmetically disfigured nails is even more rewarding than over apparently normal nails as in most cases the rate of growth of diseased nails is slower, making gel nail last longer. For diseased nails, the nail plate is already rough; hence, minimal, if any, buffing is required. Last but not least, it is a lot easier to manage patient's expectations as any improvement in their nail condition is very gratifying to them. Nevertheless, gel nails have their own limitations like limited applicability in infectious conditions like onychomycosis, paronychia, etc. They should also be avoided in case of melanonychia (to prevent masking of changes) or in cases with known allergy to acetone or any component of gel.

Gel nails is a commonly done professional nail salon procedure, but kits are also available online for home use. Such at-home gel polish kits, using UV light, can pose a significant health threat as the usage is unregulated, and users are untrained [38]. The duration of contact with irritants found in nail cosmetics is found to be increased for consumers who use these nail kits [39]. A 2016 study of 65 consumers who developed side effects from at-home gel polish kits found that the most common complaint was painful, pruritic periungual eczematous dermatitis. Other side effects included onycholysis, lesions under the nail plate, and weak or brittle nails [40]. Thus, they are best done under supervision. Their removal through acetone wraps may potentially dry and weaken the nail plate. Patients on photosensitizing oral medications, such as tetracyclines, may experience photo-onycholysis when exposed to UV radiation required to cure the polymer. A newly recognized complication of UV light—cured polish is the formation of pterygium inversum unguium (PIU) which is the adherence of the hyponychium to the nail plate. It is responsible for morbidity and pain especially during cutting or filing of the nails [41]. Cervantes et al. reported a case series of 17 patients who all developed PIU after 2–5 years of gel polish application. In 9 of these 17 patients, both LED and UV-A light had been used. Of the remaining 8 patients, 5 had used only LED light and 3 did not know or could not recall which type of light they used. All but 2 patients had resolution within a few weeks of switching from gel to normal nail polish. Patients and providers should be educated about this potential complication so they can recognize it early and stop gel manicures immediately, thereby hopefully leading to resolution of PIU.

The UV light lamps used for curing nail cosmetics use UV-A to photocure, harden, and dry the nail cosmetic. UV-A radiation is a known carcinogen. As these lights are available for home use, consumers may be unaware of the potential risk of carcinogenesis. It has been estimated that the time of exposure to UV lamps during usual photocuring ranges from 3 to 5 min, repeated every 2–4 weeks [39]. Another

study by MacFarlane and Alonso concluded that the amount of UV-A exposure from UV nail lamp is as damaging as spending an additional 1.5–2.7 min in sunlight each day for 2 weeks [42]. They also reported on two female users of UV lamps who developed squamous cell carcinoma on their hands in the absence of a personal or family history of skin cancer. Even other studies have found that the risk of developing skin cancer with these lamps is low. Nonetheless, the current recommendation by the Skin Cancer Foundation is to avoid the use of UV lamps. If patients are going to use photocured polishes, then the use of a broad-spectrum sunscreen or nitrile gloves on the rest of the hand, before exposure is recommended [39]. Lastly, it is important to discuss that the use of nail adornments obscures the nail unit features for a long time, and therefore may lead to a delay in the diagnosis of malignancies.

Acrylic nails are a result of spontaneous polymerization of acrylate or methacrylate monomers [43]. A uniform thin layer of acrylic nail product is applied quickly to the nail plate which hardens on air exposure.

Acrylic nails, after setting, provide a transparent and robust canvas for further nail adornment. They last long and can be removed easily. However, they require more care than natural fingernails. They need filling every 2–3 weeks where the loose acrylic is clipped from the distal nail edges. At the same time, new acrylic needs to be applied proximally to fill in the defect, else a lever arm gets created, predisposing the natural nail plate to traumatic onycholysis.

Over the years, acrylic nails are losing popularity as they look less natural, especially if applied incorrectly. The application process involves strong chemicals and fumes, which precludes its use in pregnancy. They also have a real potential to damage the nail bed after 2–4 months of continued use. The natural nail plate may become yellowed, dry, and thin. For those using acrylic nails, it is highly recommended that the natural nail should be allowed to grow and act as a support by resting them every 3 months. Acrylate-based nail products are also known inducers of ACD and distant dermatitis [37]. The signs of allergy to nail products include pruritic eczematous dermatitis of the fingers, hands, and wrists, although up to 10% of patients may experience dermatitis localized only to the face or neck [44]. Other reported side effects include dryness of nails, paronychia, brittleness, masking of underlying nail disorders, and reported cases of nonmelanoma skin cancer [42].

15.3.4 Nail Hardeners

Nail hardeners are another category of nail cosmetic product which are promoted for use in cases with brittle or fragile nails. They are proposed to improve the strength of nail plate. The active ingredient in nail hardeners is up to 5% formaldehyde mostly. They are also known to cause of allergic contact dermatitis, which can involve distant sites. In sensitized individuals, a concentration of formaldehyde as low as 0.006% can trigger ACD [45]. In them, products that contain formaldehyde should be completely avoided. Prolonged usage can lead to brittle nails (cross-link density rises and flexibility is reduced). Contact allergic dermatitis, onycholysis, and subungual hyperkeratosis can also occur.

15.3.5 Onychocosmeceuticals [46]

This category includes many commercially available preparations that claim to be useful for various nail disorders. These are mostly combinations of several vitamins, minerals, sulfur-containing amino acids or proteins, hormones, medicinal yeast, crushed egg shells, and even organic food. Their efficacy has not been proven in controlled trials and anecdotal evidence is equivocal with some patients reporting miraculous improvement, while most see no effect.

One of the best known onychocosmeceuticals is biotin, also known as vitamin B7. Its Recommended Daily Allowance (RDA) is 30 mcg. Earlier, a daily dose of 2.5–10 mg was recommended for hair and nail health, but recent studies show that this can lead to a reversible alteration of thyroid profile due to an interference with immunoassays, leading to falsely low or high thyroid hormone values. This interference has the potential to affect a wide range of analytes [47].

Other such drugs reportedly responsible for nail health include pyridoxine, ascorbic acid, thiamine, calcium D-pantothenate, medicinal yeast, L-cystine, keratin, and *p*-amino benzoic acid. Both an increase or decrease of vitamin A has been implicated in brittleness of nails. The role of vitamin E, sulfur-containing amino acids and proteins, fluorides, and calcium is role is not clear [48]. Supplementation with minor elements like iron [49], zinc, selenium, silica, and rhodanides without any manifest deficiency, has been reported to benefit nail health as evidenced by the fact that their deficiency may result in several nail disorders.

15.3.6 Nail Care Oils

Various oils are commercially promoted as nail care oils. These include products containing jojoba oil, bisabolol, panthenol, vitamins, and amino acids. Some of these are proposed to work by helping to hold humidity. In general, oils as well as creams and ointments make the nails more elastic, thus prevent nail splitting.

15.3.7 Risks to Salon Employees

A discussion of nail health in women would not be complete without a discussion of the health of nail salon workers. According to the Centers for Disease Control and Prevention [50], 96% of nail salon workers are women, and 63% of these women are minority workers. This vulnerable group is potentially exposed to numerous chemicals during a routine workday. Nail salon workers are exposed for much longer periods to these chemicals and are therefore more affected than consumers. Many publications have discussed the possible associations between nail cosmetic exposures and the respiratory, neurologic, and musculoskeletal health of these female workers [51–54].

A serious risk for these workers is allergic contact dermatitis. For the last 10 years, nail technicians have been the primary occupation experiencing acrylate allergy [44], which most frequently presents in this group as pulpitis and fissures. Acrylate allergy in nail salon workers may also present as onycholysis, onychodystrophy, subungual hyperkeratosis, paresthesiae, urticarial rash, and upper respiratory tract symptoms [38, 44].

To minimize the health risks to nail salon workers, it is recommended that nail cosmetic procedures, especially the application and removal of artificial nails should be done in a well-ventilated room. Salon workers should be encouraged to wear masks and pregnant women should not be engaged in these procedures.

15.4 Nail Disorders in Women

This section deals with nail disorders which are seen more commonly in women, or have special consequences in the female sex. These include brittle nails, paronychia, onycholysis, and so on.

15.4.1 Brittle Nails

Brittle nails (BN), better referred to as nail fragility, is a common problem affecting up to 20% of population especially women over 50 years of age [18]. The female-to-male ratio is 2:1. BN are characterized by increased fragility leading to splitting, flaking, and crumbling of the nail plate presenting clinically as excessive longitudinal ridging (onychorrhexis); horizontal lamellar splitting (onychoschizia); and irregularity of the free margin of the nail plate [15, 18] (Fig. 15.6). Normal nails have 18% water and when this content becomes less than 16% the nails lose elasticity and become brittle. A reduced sulfur content and iron content may also contribute to loss of flexibility of nails [55]. Disorders associated with defective keratin like trichothiodystrophy are also associated with BN. Also, patients having fine or thinner nails are more prone to brittleness.

Environmental triggers that exacerbate brittle nails include weather, with winters causing more brittleness due to less moisture content in cold air. Although water contact increases the water content of nail plate temporarily, it also makes the nail plate more pliable, dry, and brittle. Hence, women involved in household work end up having BN (Fig. 15.6). Exposure to chemicals (solvents, acids, alkalis, etc.), nail cosmetics (nail polish removers, nail hardeners, and cuticle removers), and nail procedures (artificial nails, nail adornments) increase the chances of getting BN (Fig. 15.7). Other factors which lead to BN include fungal infections and trauma including the mechanical microtrauma due to daily work and habit tic deformities like onychotillomania and onychophagia. BN are also associated with a number of dermatologic disorders like psoriasis, lichen planus, and alopecia areata; and with systemic disorders like endocrine disorders, metabolic diseases, infections, and nutritional deficiencies [56].

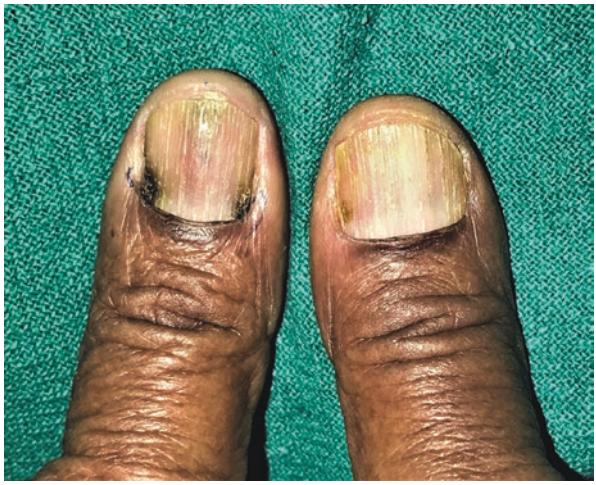

Fig. 15.6 Brittle nails in an elderly lady who engages in a lot of household work. Onychorrhexis, onychoschizia and irregular free margin can be seen. The left thumb nail shows evidence of pseudomonas paronychia

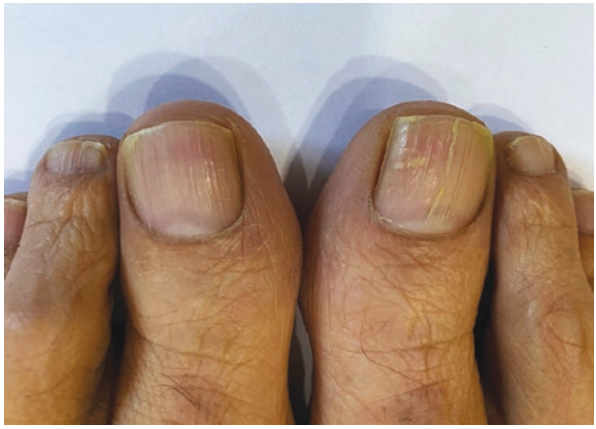

Fig. 15.7 Brittle nails involving toenails subsequent to repeated application and removal of nail paints

Table 15.2 Management principles for brittle nails

1.	Limit further trauma
2.	Gentle cleansing with a pH-balanced soap
3.	Use of moisturizing creams/ointments/oils
4.	Wearing gloves to avoid contact with irritants such as water and chemicals
5.	Avoiding filing the surface of the nail
6.	Limiting the use of frequent nail cosmetics
7.	Taking timely treatment for any underlying nail disorder
8.	Supplementation of any underlying deficiency

Management of brittle nails involves a multimodal approach with removal of causative factor being the most important (Table 15.2). Patients need to be educated about the basic principles of nail care [40, 48].

Other than this, the role of various supplements has been proposed for improving the strength of such nails. Oral supplementation with biotin (2.5–10 mg orally per day) has been used to improve the quality of nails, but the need for supplementation is unclear because biotin is synthetized to a great degree by intestinal bacteria [48]. A marked biotin deficiency is associated with poor nail quality. A study by Colombo et al. [57] documented a 25% increase in nail thickness in women who took biotin supplementation for 6–9 months. Another study by Hochman et al. [58] concluded that although biotin supplementation is not consistently effective among all patients, there is a trend toward being beneficial to nail health. There may be a role for biotin in nail health, but additional studies, including investigation of dosages and the effect of biotin on brittle nails, to improve the evidence base.

Empirical biotin administration, may not be without associated side effects. Food and Drug Administration has warned that it may interfere with laboratory testing (e.g., tests for troponin levels, thyroid-stimulating hormone, and parathyroid hormone) and lead to incorrect diagnoses [59]. However, this warning applies to high-dose biotin supplementation, and there may not be any need to discontinue biotin before laboratory testing for patients taking biotin at dermatologic doses of 5 mg per day [60].

Iron supplementation is reportedly effective if ferritin levels are below 10 ng/mL. Prolonged zinc supplementation in a dose of 20–30 mg/day may be useful for some patients. Cosmetic treatments like nail moisturizers, nail enamels, nail lacquers, and nail hardeners have found to be useful. In our personal experience we have found a single coat of gel nails to be a useful treatment for brittle nails [61].

15.4.2 Paronychia

Paronychia refers to an inflammation of the nail fold(s). It can be acute or chronic and may present in isolation or in association with an ingrown nail [62]. Both acute and chronic paronychia are commonly seen in women, presumably due to excessive exposure to water, detergents, and cosmetics.

Acute paronychia is characterized by a painful swelling with pus collection involving the nail fold(s) which is of <6 weeks duration. The common presentation is acute onset pain, edema, erythema, and tenderness along the lateral and/or PNFs commonly involving a single digit (Fig. 15.8). It is a very common hand infection with a female/male ration of 3:1 [63]. The most common inciting factor for acute paronychia is trauma to the nail unit, leading to a disruption of the protective tip barrier. It can often be a result of nail tic disorders like nail biting, ingrown nail, manicure/pedicure, household wet work, frequent hand washing, or retention of a foreign body associated with penetrating trauma [64]. Acute paronychia is a bacterial infection, with *Staphylococcus aureus* being the most commonly isolated infectious organism, which may even be acquired from contaminated nail grooming instruments [65, 66].

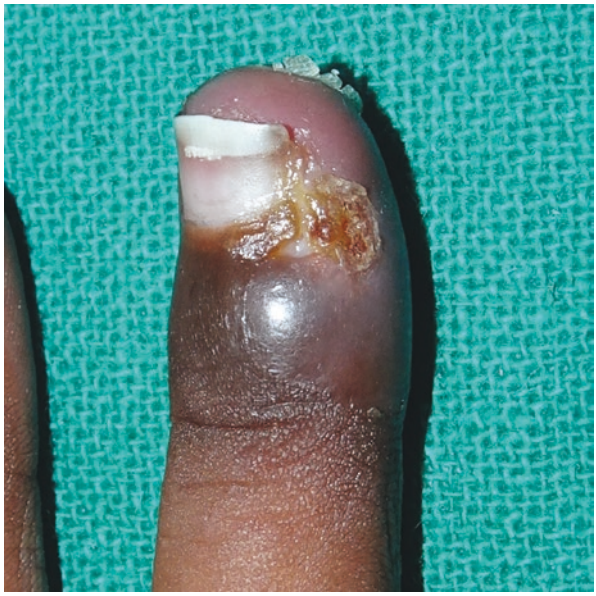

Fig. 15.8 Acute paronychia in a house maid. The nail also shows pseudoleukonychia involving the nail plate

Management involves nonsurgical methods like warm water soaks with Burrow's solution (aluminum acetate), vinegar, diluted povidone–iodine or chlorhexidine. Topical antibiotic and corticosteroid applications have been found to be useful in cases with minimal erythema. Systemic antibiotics like trimethoprim–sulfamethoxazole/cephalexin/amoxicillin and clavulanic acid or clindamycin are needed in cases where the infection has set in, with substantial erythema [65]. Surgical management is reserved for patients not responding to medical interventions and those with well-formed abscess.

Chronic paronychia (CP) refers to an inflammation and swelling of the nail folds, conventionally >6 weeks in duration. It is often accompanied with disruption or a loss of cuticle, which provides an easier access to environmental insults/organisms to enter the cul-de-sac under the proximal nail fold. It usually involves multiple nails and periodic exacerbations are seen. Proximal nail matrix may become raised and separated from underlying nail. Several nail changes like ridging, grooving, discoloration, beau's lines, and onychomadesis may be seen due to the associated nail matrix damage [67].

The pathogenesis of chronic paronychia is multifactorial because of an unchecked influx of pathogens and allergens. It is now considered to be a form of hand dermatitis due to exposure to environmental allergens with secondary colonization of the sulcus by Candida [68–70]. Common causes include occupational exposure to moisture and chemical irritants commonly seen in homemakers.

Management involves general measures like avoidance of wet work, limiting the contact with irritants like detergents by wearing vinyl gloves over cotton gloves while doing house hold work, and strictly avoiding manipulation of nail folds especially during grooming procedures like manicure/pedicure. Topical mid-potency

corticosteroid ointments for 2–4 weeks are the mainstay of medical management. Surgical management is reserved for severe, recalcitrant cases.

15.4.3 Onycholysis

Onycholysis is defined as a distal or distal–lateral separation of the nail plate from the underlying and/or lateral supporting structures (nail bed, hyponychium, lateral nail fold). When the separation begins proximally near the nail matrix, the process is called onychomadesis.

Clinically, the area of separation appears as a white or yellow nail plate due to air trapped beneath it. It may also be discolored due to accumulation of bacteria, most commonly Pseudomonas (green color due to pyocyanin) or yeast species like *Candida albicans* (Fig. 15.9).

Pathogenesis of onycholysis can be multifactorial and often unclear. It is known that a normal nail bed lacks a granular layer. Causes that disturb the normal formation of nail bed, like psoriasis or lichen planus, often lead to an appearance of a nail bed granular layer resulting in onycholysis. It can also result due to trauma, be it physical, irritation-induced, or allergic. Depending on the cause, onycholysis can be classified as primary (idiopathic) or secondary.

1. *Idiopathic (primary) onycholysis*—This refers to a painless separation of the nail plate from the nail bed, which occurs without an apparent cause (Fig. 15.9). Overzealous manicure, frequent wetting, and cosmetic solvents may often be the inciting factors, which can be found out on extensive probing. Often, minor trauma can precipitate this condition in patients keeping abnormally long nails.

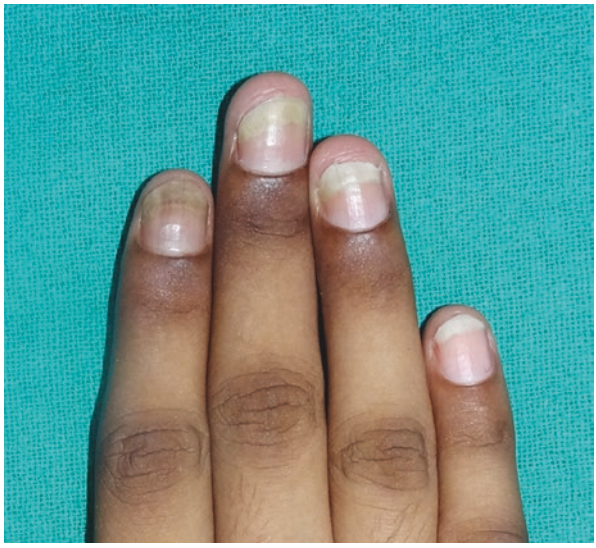

Fig. 15.9 Idiopathic onycholysis involving multiple nails in a housemaid

The affected nails tend to grow very quickly. The affected nails are mostly asymptomatic, though pain may occur if there is further separation due to trauma or if active infection supervenes. The condition is most commonly seen in women and many cases return to normal after a few months. The longer it lasts, the less likely is the nail to become reattached, due to keratinization of the exposed nail bed.

2. *Secondary onycholysis*—This type occurs associated with a well-defined cause. Onycholysis is either one of the nail manifestations or a major nail manifestation, in these disorders (Fig. 15.10). The salient etiologies associated with onycholysis are summarized in Table 15.3 [71].

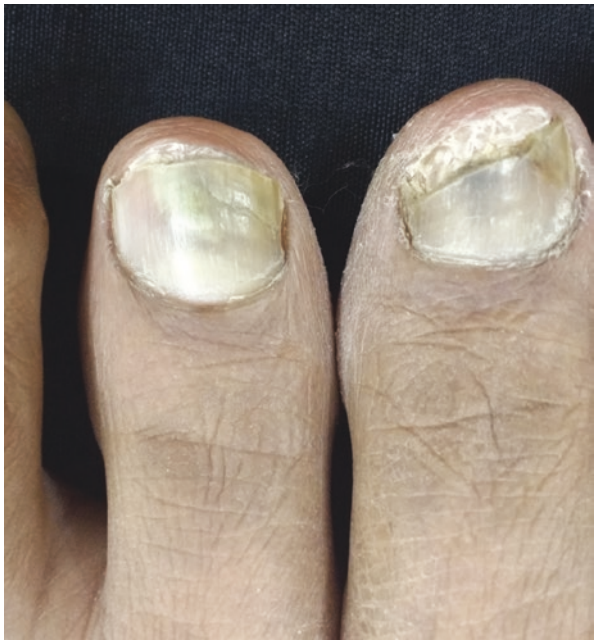

Fig. 15.10 Prominent distal onycholysis with subungual hyperkeratosis and discoloration in a patient with onychomycosis

Table 15.3 Various causes of secondary onycholysis

Dermatologic causes	Psoriasis, fungal infection, Reiter's syndrome, hyperhidrosis, pemphigus vulgaris, pellagra, leprosy, syphilis, occupational trauma, psoriatic arthritis
Drug-induced	Antibiotics—most commonly tetracyclines, chemotherapeutic agents, retinoids
Systemic causes	Thyroid diseases, yellow nail syndrome, shell nail syndrome, bronchogenic carcinoma, multiple myeloma, scleroderma, anemia, peripheral vascular diseases, and diabetes mellitus
Others	Nail cosmetics, pregnancy, hereditary

15.4.4 Nail Tic Disorders

Nail tic disorders, though common, are some of the most poorly understood, less researched, and often misdiagnosed disorders. These disorders are known to be more common in females; hence, they will be discussed here briefly. They include a spectrum of changes seen in patients with obsessive or repetitive behavior centered around the nail unit. Various disorders are detailed below.

1. *Onychophagia*/nail biting is defined as "putting one or more fingers in the mouth and biting on the nail with teeth" [72]. This behavior pattern usually starts in childhood or adolescence and may persist in adulthood. The condition is usually limited to the fingernails and there is no predilection to bite any one nail (Fig. 15.11) [73]. Acute paronychia is the most common complication associated, though most patients eventually develop chronic paronychia. The skin surrounding the nails may show erythema, inflammation, excoriations, hang nails, scarring, or even keloid formation in severe cases.
2. *Onychotillomania* is an autoaggressive disorder that results from recurrent picking and manicuring of the nails [74]. It leads to visual shortening, distortion nand, in severe cases, complete extraction of the nails [75]. Patients usually use their hands/nails to pick the affected nail, although anything accessible from scissors to knives to toothpicks may be used [76].
3. *Habit-tic deformity* (washboard nails) is caused by habitual external trauma to the nail matrix [77]. Although any nail can be affected, thumbnails are often the primary targets. Most patients report manipulating the proximal nail fold or periungual area with an adjacent fingernail, often subconsciously. Characteristic nail changes include a central depression and short transverse, parallel ridges running from the nail fold to the distal edge of the nail (Fig. 15.12). In severe cases, the cuticles may disappear, and the lunulae may hypertrophy.
4. *Onychotemnomania* refers to a tendency to cut nails extremely short, with scissors, blade, or knife, sometimes going as far as up to the proximal end [78]. This

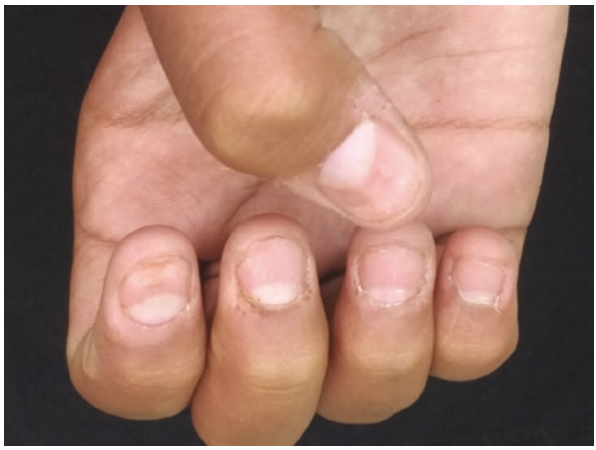

Fig. 15.11 Nails of a chronic nail biter. Onychophagia leads to shorter nails, exposed nail bed, larger lunulae, nail surface irregularities and nail fold excoriations with hang nails

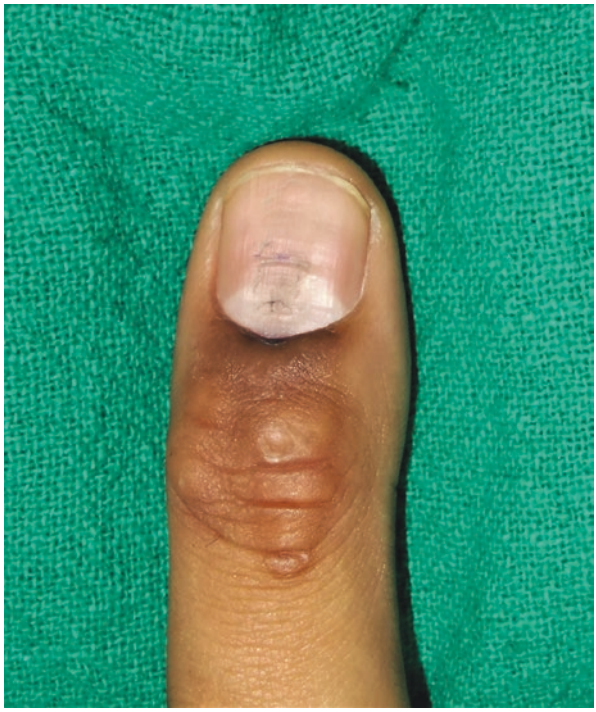

Fig. 15.12 Habit tic deformity involving the left thumb nail. The short transverse, multiple ridges over the nail plate a result of the repeated manipulation of the proximal nail fold as evidenced by its hyperpigmentation, thickening, and cuticle disruption

leads to extremely small nail plates with exposed distal nail beds. It is a severe variant of factitious nail disorder.

5. *Onychoteiromania* refers to extremely thin nails that crack or split easily with excessive filing or rubbing of the nail surface. Patients may even file the nail folds and in worse cases, the nail bed epithelium may be reached.
6. *Onychodaknomania* is extremely rare, frankly psychotic behavior biting of fingernails between the teeth [79], which is extremely painful it leads to irregular and deep depressions on the nail plate surface with punctate or striate leuk-onychia. This self-mutilation is often denied and warrants a thorough psychiatric evaluation. It may respond well to combination therapy with anti-psychotics and antidepressants.
7. *Bidet nails* or worn-down nail syndrome refers to a triangular defect in the nail plate with its base at the thinnest free edge of the nail. It is a self-inflicted defect acquired due to trauma of cleaning the nails against a hard surface. It classically involves the second, third, and fourth fingernails of the dominant hand. They may also be considered as a variant of onychoteiromania. *Lacquer nail*, described by Rigopoulos et al. [80], has significant overlap with worn down nail syndrome. It occurs as a result of excessive rubbing of the nail plate with nail filers provided with topical antifungal nail lacquers.
8. *Perionychotillomania* is the habit of picking and tearing the periungual skin, also known as perionychophagia. The presence of hangnails may be the initiating

factor. However, this habit itself leads to the development of hangnails, creating a vicious cycle of picking and tearing the periungual skin.

9. *Onycholysis semilunaris* is a common (but underrecognized) factitious nail disorder that primarily afflicts women. It presents with a sharp, distal, asymmetric but semilunar onycholysis without inflammation, affecting one or many nails, both in dominant and nondominant hand. It often results from vigorous manicure with hard brushes, or use of chemicals to clean the distal nail fold, leading to hyponychial injury, pushing the distal nail fold backward. At times, secondary bacterial colonization, especially by *Pseudomonas* may occur. Repeated cleaning and formation of biofilms sets up a vicious cycle of worsening onycholysis. Treatment is difficult as patients usually deny habitual cleaning and biofilms interfere nail plate attachment. It involves cutting the nails short to the point of attachment and keeping the exposed bed free of microbes by daily application of antibiotics for a long period.

15.4.5 Ingrown Nail

This is also known as lateral ingrowth of nail plate or *onychocryptosis*. It is common in women related to inappropriate/tight footwear; common use of heels; and excessive cutting and cleaning of the lateral nail plates. The condition commonly affects the great toenails (Fig. 15.13). In the initial stages, advice regarding appropriate footwear, proper cutting of nails and conservative measure like taping or strapping may help. However, with advancing inflammation, lateral nail fold hypertrophy or formation of granulation tissue (Fig. 15.13), the need for surgical intervention becomes unavoidable. The commonly used surgical method is partial lateral nail plate avulsion and lateral matricectomy.

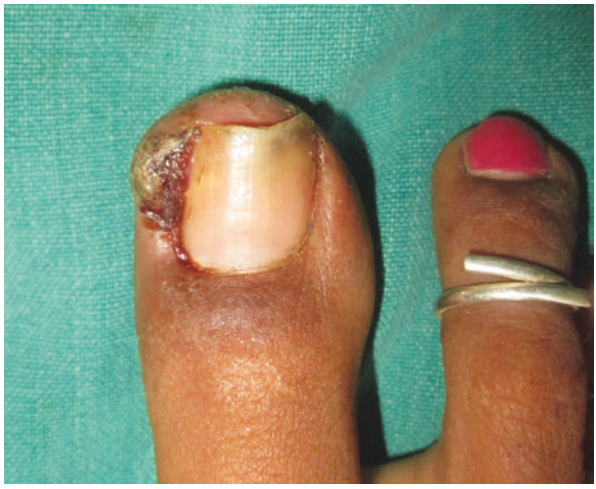

Fig. 15.13 Ingrown toe nail in a woman due to tight shoes and improper nail cutting

Retronychia refers to proximal ingrown nail and is being increasingly recognized to be a common entity on young women, again related to tight footwear or repeated microtrauma [81]. Patients present with proximal nail fold inflammation and elevation of the proximal nail plate which is often discolored and opaque. There is absence of distal nail growth signified by the patient's history of not needing to cut the nails. In extreme cases, granulation tissue may be formed over the proximal nail fold.

The pathogenesis involves proximal detachment of the nail plate which is then pushed upward inciting inflammation while a new nail plate grows beneath it, further pushing the old nail plate upward. It may result in multiple nail plates getting sandwiched beneath the old nail plate and the proximal nail fold. Definitive treatment involves total nail plate avulsion which relieves and reverts the nail fold inflammation. The new nail plate growth is often normal and recurrences are not seen.

15.4.6 Subungual and Periungual Warts

Warts (verrucae) due to Human Papilloma Virus (HPV) subtypes 1, 2, 4, 27 are the most common type of benign tumors affecting the nail unit. Infection is more commonly seen in nail biters, occupations involving wet work, and so on, hence more common in women [82]. This can be attributed to higher chances of trauma to skin barrier during household work or cosmetic procedures like manicure, pedicure, and artificial nails.

The incubation period is difficult to determine, but may range from few weeks to more than a year. The lesions appear as skin colored, rough papules initially arising in the proximal and lateral nail folds and hyponychium (Fig. 15.14). The diagnosis can be aided by dermoscopic examination which shows frog spawn appearance with whitish structureless areas and vessels or pink clods suggestive of thrombosed vessels, in the center [83].

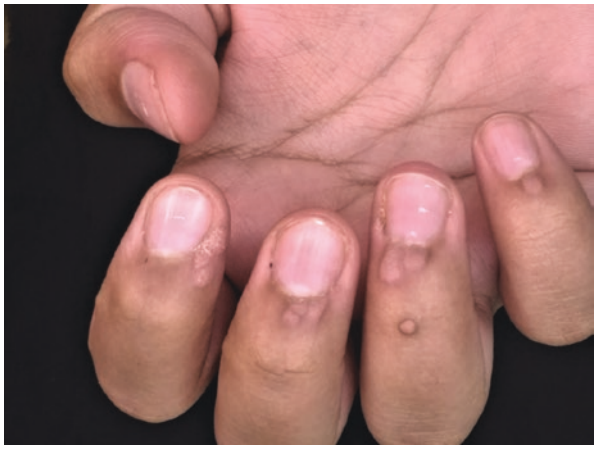

Fig. 15.14 Multiple periungual warts in a nail biter

Treatment for ungual warts is challenging as a large part of the lesion may be subungual, hence not approachable [84]. Topical therapies like keratolytic agents (salicylic acid, lactic acid, and trichloroacetic acid), virucidal agents (glutaraldehyde, cidofovir), and immunotherapy (imiquimod, contact sensitizers, and BCG) have been found to be useful. Intralesional therapies with cytotoxic drugs like bleomycin and fluorouracil are increasing becoming the favored treatment modality [85]. Systemic treatment in form of immunotherapy (cimetidine, levamisole, zinc, BCG, etc.), virucidal agents (cimetidine), and antiproliferative agents like acitretin is also useful in some cases. Electrocautery is not advocated in this area due to a higher risk of scarring. Fractional CO_2 laser and cryotherapy are recommended as second line treatment for periungual warts [86].

15.4.7 Onychomycosis

Onychomycosis is the most common nail infection, accounting for up to 50% of all nail dystrophies [87]. It is most commonly caused by dermatophytic fungi, specifically *Trichophyton rubrum*, but in some series up to 30–40% of onychomycosis may be due to nondermatophyte molds and yeast [88].

Transmission of fungal species to the nail unit is often a result of tinea pedis or mannum or through contact with contaminated objects like contaminated nail grooming instruments [89]. Cuticle abrasion, paronychia, and contact dermatitis can also facilitate entry for fungi. It was reported in a study that 67/68 women who developed a nail concern after removal of artificial nails were diagnosed to have onychomycosis [90]. Another study found the nail polish top coat to act as fomite and thus be a nidus for onychomycosis [89].

Treatment of onychomycosis requires prolonged oral antifungal therapy with the gold standard being oral terbinafine. The effects are better if combination therapy with topical, surgical or device-based measures are used as adjuvants. Prevention of onychomycosis includes gentle nail care, use of clean instruments during nail care, and early treatment of tinea pedis for toenails.

15.4.8 Nail Tumors

Women are equally predisposed as men to develop various nail unit tumors; however, glomus tumors are disproportionately commoner in women than men (up to four times). These are smooth muscle hamartomas arising from glomus bodies (specialized arteriovenous anastomoses for temperature regulation). They constitute 1–5% of soft tissue tumors of the hands and up to 75% of them are found in the subungual location [91]. These arise commonly in middle-aged women (30–50 years of age).

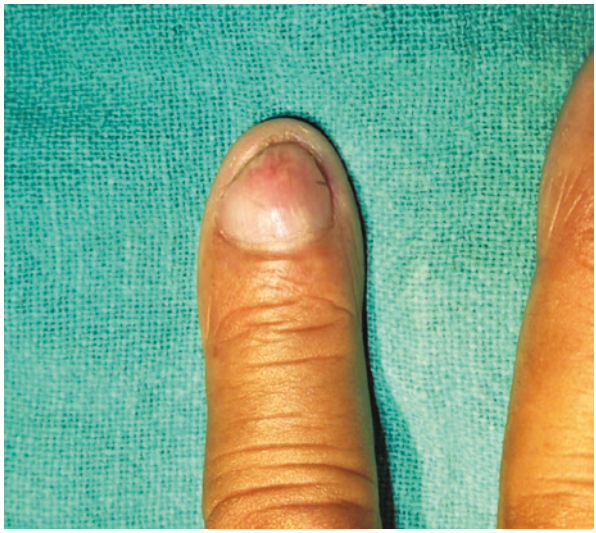

Fig. 15.15 Glomus tumor in 45-year-old lady involving the right index finger

Clinically, the lesions present as a painful nail accompanied with cold hypersensitivity, severe paroxysmal pain, and pin point pain confined to the affected nail site. The tumor is mostly subcentimetric in size, which may occasionally appear as a bluish or reddish subungual lesion (Fig. 15.15). There may be no visible changes in many cases, but the pain is characteristic. Other reported changes include longitudinal erythronychia, true or apparent leukonychia, distal splitting, fissuring, or elevation of nail plate [92]. Useful clinical tests for diagnosis include Love's pin test (pressure induced intense pin-point pain) and Hildreth's test (relief in pain because of transient ischemia induced by a blood pressure cuff). Cold test shows exacerbation of pain on placing an ice cube on nail. Onychoscopy can help in better delineation of the tumor location [92].

Diagnosis is often clinical but imaging techniques like plain X-ray (only larger lesions), ultrasound examination (nonspecific solid hypervascular hypoechoic mass) and high-resolution MRI (modality of choice) are helpful in preoperative diagnosis and planning surgical removal. Histopathology of the lesion is confirmatory showing branching vascular channels of varying sizes, surrounded and separated by nests and aggregates of glomus cells, which are monomorphic round cells with regular, round nuclei, and eosinophilic cytoplasm.

Surgical excision is the treatment of choice for these painful lesions, and can be done either translingually or through a lateral (lateroungual or laterodigital Keyser–Littler) approach. Nail deformity and recurrences are major concerns after surgery, which can be minimized by through preoperative evaluation and careful intraoperative removal while avoiding damage to the nail matrix and nail bed.

15.5 Conclusion

Nail health in women is important for their efficient daily functioning as well as their external appearance, emotional well-being, and cosmesis. The normal aging process as well as state of nutrition in women leads to nail changes that may impair the appearance as well as function of nails, if not promptly addressed. Maintaining healthy nails is based on the use of efficient and safe grooming practices. The plethora of nail cosmetics used is very attractive for women worldwide, but has the potential to compromise nail health. It is important for women and their health-care providers to be aware of such potential complications so that they can be avoided or at least diagnosed early and treated. In collaboration with her health-care provider, a woman should be able to maintain healthy, functional nails throughout her life.

References

1. Shafer L. Nail care: from ancient rites to new heights. 1993. https://www.nailsmag.com/392664/nail-care-fromancient-rites-to-new-heights. Accessed 22 Jul 2019.
2. Tsatalis JP, Rajabi-Estarabadi A, Tosti A. Speaking with your hands—the history of the manicure. JAMA Dermatol. 2018;154(5):595.
3. Brosche T, Dressler S, Platt D. Age-associated changes in integral cholesterol and cholesterol sulfate concentrations in human scalp hair and finger nail clippings. Aging Clin Exp Res. 2001;13(2):131–8.
4. Lubach D, Beckers P. Wet working conditions increase brittleness of nails, but do not cause it. Dermatology. 1992;185(2):120–2.
5. Helmdach M, Thielitz A, Röpke EM, Gollnick H. Age and sex variation in lipid composition of human fingernail plates. Skin Pharmacol Appl Skin Physiol. 2000;13(2):111–9.
6. Lubach D, Wurzinger R. Trace elements in samples of brittle and nonbrittle finger nails. Derm Beruf Umwelt. 1986;34(2):37–9.
7. Grover C. Nail fragility. In: Tosti A, editor. Nail disorders. Amsterdam: Elsevier; 2018. p. 113–28.
8. Madnani NA, Khan KJ. Nail cosmetics. Indian J Dermatol Venereol Leprol. 2012;78(3):309–17.
9. Draelos ZD. Cosmetic treatment of nails. Clin Dermatol. 2013;31(5):573–7.
10. Mazareanu E. Nail salons in the U.S.–Statistics and facts. 2019. https://www.statista.com/topics/4624/nailsalons-in-the-us/. Accessed 22 Jul 2019.
11. Sun C. Factors affecting female consumers' acceptability on nail polish [thesis]. Manhattan: Kansas State University; 2014.
12. Swan SH. Prenatal phthalate exposure and anogenital distance Goldstein Research. Global nail care industry: market trends, size, opportunity and forecast 2016–2024. 2018. https://www.goldsteinresearch.com/report/nail-care-market-global-industry-analysis. Accessed 1 Jul 2019.
13. Maddy AJ, Tosti A. Hair and nail diseases in the mature patient. Clin Dermatol. 2018;36(2):159–66.
14. Cohen PR, Scher RK. Geriatric nail disorders: diagnosis and treatment. J Am Acad Dermatol. 1992;26(4):521–31.
15. Singh G, Haneef NS, Uday A. Nail changes and disorders among the elderly. Indian J Dermatol Venereol Leprol. 2005;71(6):386–92.
16. Mehndiratta V, Suvarna S. Age related nail changes. In: Grover C, Relhan V, Nanda S, Bansal S, editors. NSI textbook of onychology. New Delhi: Evangel Publishing; 2021. p. 29–34.

17. Horan MA, Puxty JA, Fox RA. The white nails of old age (Neapolitan nails). J Am Geriatr Soc. 1982;30(12):734–7.
18. Lubach D, Cohrs W, Wurzinger R. Incidence of brittle nails. Dermatologica. 1986;172(3):144–7.
19. Daniel CR, Sams WM, Scher RK. Nails in systemic disease. Dermatol Clin. 1985;3:465–83.
20. Hediger C, Rost B, Itin P. Cutaneous manifestations in anorexia nervosa. Schweiz Med Wochenschr. 2000;130:565–75.
21. Ruymann FB. Juvenile polyps with cachexia. Report of an infant and comparison with Cronkhite—Canada syndrome in adults. Gastroenterology. 1969;57:431–8.
22. Lawry M, Rich P. The nail apparatus: a guide for basic and clinical science. Curr Probl Dermatol. 1999;11:202–4.
23. Vugia DJ, Jang Y, Zizek C, Ely J, Winthrop KL, Desmond E. Mycobacteria in nail salon Whirlpool Footbaths, California. Emerg Infect Dis. 2005;11(4):616–8.
24. Draelos ZD. Nail cosmetics. Medscape reference. In: Elston DM, editor. 2011. http://emedicine.medscape.com/article/1067468-overview#showall. Accessed 10 Feb 2012.
25. Jefferson J, Rich P. Update on nail cosmetics. Dermatol Ther. 2012;25(6):481–90.
26. Rich P. Nail cosmetics. Dermatol Clin. 2006;24:393–9.
27. DeKoven JG, Warshaw EM, Zug KA, Maibach HI, Belsito DV, Sasseville D. North American Contact Dermatitis Group patch test results: 2015–2016. Dermatitis. 2018;29(6):297–309.
28. Nanda S. Chapter 6: Basic nail care and hygiene. In: Grover C, Relhan V, Nanda S, Bansal S, editors. NSI textbook of onychology. New Delhi: Evangel Publishing; 2021.
29. Shellac vs Gel Nail. http://www.diffen.com/difference/Gel_Nails_vs_Shellac_Nails. Accessed 2 Feb 2021.
30. Pottinger J, Burns S, Manske C. Bacterial carriage by artificial versus natural nails. Am J Infect Control. 1989;17:340–4.
31. Hedderwick SA, McNeil SA, Lyons MJ, Kauffman CA. Pathogenic organisms associated with artificial fingernails worn by healthcare workers. Infect Control Hosp Epidemiol. 2000;21:505–9.
32. Moolenaar RL, Crutcher JM, San Joaquin VH, Sewell LV, Hutwagner LC, Carson LA, et al. A prolonged outbreak of *Pseudomonas aeruginosa* in a neonatal intensive care unit: did staff fingernails play a role in disease transmission? Infect Control Hosp Epidemiol. 2000;21:77–9.
33. Parry MF, Grant B, Yukna M, Adler Klein D, McLeod GX, Taddorio R, et al. Candida osteomyelitis and diskitis after spinal surgery: an outbreak that implicates artificial nail use. Clin Infect Dis. 2001;32:352–7.
34. Shihab N, Lim HW. Potential cutaneous carcinogenic risk of exposure to UV nail lamp: a review. Photodermatol Photoimmunol Photomed. 2018;34:362–5.
35. André J, Achten G. Onychomycosis. Int J Dermatol. 1987;26:481–90.
36. Holzberg M. Common nail disorders. Dermatol Clin. 2006;24:349–54.
37. Baran R, André J. Side effects of nail cosmetics. J Cosmet Dermatol. 2005;4:204–9.
38. Ortega ME, Pastor-Nieto MA, Mercader-Garcia P, Silvestre-Salvador JF. Allergic contact dermatitis caused by (meth)acrylates in long-lasting nail polish: are we facing a new epidermis in the beauty industry? Contact Dermat. 2017;77(6):360–6.
39. Wang JV, Korta DZ, Zachary CB. Gel manicures and ultraviolet A light: a call for patient education. Dermatol Online J. 2018;24(3):20.
40. Chang RM, Hare AQ, Rich P. Treating cosmetically induced nail problems. Dermatol Ther. 2007;20(1):54–9.
41. Cervantes J, Sanchez M, Eber AE, Perper M, Tosti A. Pterygium inversum unguis secondary to gel polish. J Eur Acad Dermatol Venereol. 2018;32(1):160–3.
42. MacFarlane D, Alonso CA. Occurrence of nonmelanoma skin cancers on the hands after UV nail light exposure. Arch Dermatol. 2009;145(4):447–9.
43. Dinani N, George S. Nail cosmetics: a dermatological perspective. Clin Exp Dermatol. 2019;44(6):599–605.
44. Gonçalo M, Pinho A, Agner T, Andersen KE, Bruze M, Diepgen T, et al. Allergic contact dermatitis caused by nail acrylates in Europe. An EECDRG study. Contact Dermat. 2018;78(4):254–60.

45. Mestach L, Goossens A. Allergic contact dermatitis and nail damage mimicking psoriasis caused by nail hardeners. Contact Dermat. 2016;74(2):112–4.
46. Haneke E. Onychocosmeceuticals. J Cosmet Dermatol. 2006;5(1):95–100.
47. Elston MS, Sehgal S, Du Toit S, Yarndley T, Conaglen JV. Factitious graves' disease due to biotin immunoassay interference—a case and review of the literature. J Clin Endocrinol Metab. 2016;101(9):3251–5.
48. Forslind B. Biophysical studies of the normal nail. Acta Dermato-Venereol. 1970;50:161–8.
49. Djaldetti M, Fishman P, Hart J. The iron content of fingernails in iron deficient patients. Clin Sci. 1987;72:669–72.
50. Centers for Disease Control and Prevention. Nail technicians' health and workplace exposure control. 2018. https://www.cdc.gov/niosh/topics/manicure/default.html. Accessed 1 Jul 2019.
51. Cogliano VJ, Grosse Y, Baan RA, Straif K, Secretan MB, El Ghissassi F. Meeting report: summary of IARC monographs on formaldehyde, 2-butoxyethanol, and 1-tertbutoxy-2-propanol. Environ Health Perspect. 2005;113(9):1205–8.
52. Quach T, Von Behren J, Goldberg D, Layefsky M, Reynolds P. Adverse birth outcomes and maternal complications in licensed cosmetologists and manicurists in California. Int Arch Occup Environ Health. 2015;88(7):823–33.
53. Swan SH. Prenatal phthalate exposure and anogenital distance in male infants. Environ Health Perspect. 2006;114(2):A88–9.
54. Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect. 2005;113:1056–61.
55. Klauder GV, Brown H. Sulphur content of hair and nails in abnormal states. Arch Derm Syphilol. 1935;34:568–79.
56. Arora P. Brittle nails. In: Grover C, Relhan V, Nanda S, Bansal S, editors. NSI textbook of onychology. New Delhi: Evangel Publishing; 2021. p. 420–9.
57. Colombo VE, Gerber F, Bronhofer M, Floersheim GL. Treatment of brittle fingernails and onychoschizia with biotin: scanning electron microscopy. J Am Acad Dermatol. 1990;23(6 Pt 1):1127–32.
58. Hochman LG, Scher RK, Meyerson MS. Brittle nails: response to daily biotin supplementation. Cutis. 1993;51(4):303–5.
59. John JJ, Lipner SR. Consumer perception of biotin supplementation. J Cutan Med Surg. 2019;23:613–6.
60. Piraccini B. Reassurance on the safety of biotin. G Italiano Di Derm E Venerol. 2018;153(6):877.
61. Nanda S, Grover C. Utility of gel nails in improving the appearance of cosmetically disfigured nails: experience with 25 cases. J Cutan Aesthet Surg. 2014;7(4):240–1.
62. Lomax A, Thornton J, Singh D. Toenail paronychia. Foot Ankle Surg. 2016;22:219–23.
63. Rockwell PG. Acute and chronic paronychia. Am Fam Physician. 2001;63(6):1113–6.
64. Shaffritz AB, Coppage GM. Acute and chronic paronychia of the hand. J Am Acad Orthop Surg. 2014;22(3):165–74.
65. Brook I. Paronychia: a mixed infection. Microbiology and management. J Hand Surg. 1993;18(3):358–9.
66. Relhan V, Bansal A. Paronychia. In: Grover C, Relhan V, Nanda S, Bansal S, editors. NSI textbook of onychology. New Delhi: Evangel Publishing; 2021. p. 389–97.
67. Relhan V, Goel K, Bansal S, et al. Management of chronic paronychia. Indian J Dermatol. 2014;59(1):15–20.
68. Habif TP. Clinical dermatology: a color guide to diagnosis and therapy. 4th ed. Edinburgh: Mosby; 2004. p. 871–2.
69. Hay RJ, Baran R, Morre MK, et al. Candida onychomycosis—an evaluation of role of *Candida* species in nail disease. Br J Dermatol. 1988;118:47–58.
70. Tosti A, Piraccini BM, Ghetti E, et al. Topical steroids versus systemic antifungal in the treatment of chronic paronychia: an open, randomized double-blind and double dummy study. J Am Acad Dermatol. 2002;47(1):73–6.

71. Jadhav VM, Mahajan PM, Mhaske CB. Nail pitting and onycholysis. Indian J Dermatol Venereol Leprol. 2009;75:631–3.
72. Teng EJ, Woods DW, Twohig MP, Marcks BA. Body-focused repetitive behavior problems. Prevalence in a nonreferred population and differences in perceived somatic activity. Behav Modif. 2002;26:340–60.
73. Ghanizadeh A. Nail biting; etiology, consequences and management. Iran J Med Sci. 2011;36:73–9.
74. Alkiewicz J. Uber onychotillomania. Dermatol Wochenschr. 1934;98:519–21.
75. Pacan P, Grzesiak M, Reich A, Kantorska-Janiec M, Szepietowski JC. Onychophagia and onychotillomania: prevalence, clinical picture and comorbidities. Acta Derm Venereol. 2014;94:67–71.
76. Grzesiak M, Pacan P, Reich A, Szepietowski JC. Onychotillomania in the course of depression: a case report. Acta Derm Venereol. 2014;94:745–6.
77. Samman PD. A traumatic nail dystrophy produced by a habit tic. Arch Dermatol. 1963;88:895–6.
78. Haneke E. Autoaggressive nail disorders. Dermatol Rev Mex. 2013;57:225–34.
79. Michopoulos I, Gournellis R, Papadopoulou M, Plachouras D, Vlahakos DV, Tournikioti K, et al. A case of autophagia: a man who was mutilating his fingers by biting them. J Nerv Ment Dis. 2012;200:183–5.
80. Rigopoulos D, Charissi C, Belyayeva-Karatza Y, Gregoriou S. Lacquer nail. J Eur Acad Dermatol Venereol. 2006;20:1153–4.
81. de Berker DA, Richert B, Duhard E, Piraccini BM, André J, Baran R. Retronychia: proximal ingrowing of the nail plate. J Am Acad Dermatol. 2008;58:978–83.
82. Herschthal J, Mc Leod MP, Zaiac M. Management of ungula warts. Dermatol Ther. 2012;25:545–50.
83. Moghaddas N. Periungual verrucae diagnosis and treatment. Clin Podiatr Med Surg. 2004;21:651–61.
84. Adalatkhan H, Khalilollahi H, Amini N, et al. Compared therapeutic efficacy between intralesional bleomycin and cryotherapy for common warts: a randomized clinical trial. Dermatol Online J. 2007;13:4.
85. Ischimen A, Aydemir EH, Goksugur N, et al. Intralesional 5-fluorouracil, lidocaine and epinephrine mixture for the treatment of verrucae: a prospective placebo controlled, single blind randomized study. J Eur Acad Dermatol Venereol. 2004;18:455–8.
86. Khurana A, Saxena S. Viral infections of the nail unit. In: Grover C, Relhan V, Nanda S, Bansal S, editors. NSI textbook of onychology. New Delhi: Evangel Publishing; 2021. p. 162–71.
87. Faergemann J, Baran R. Epidemiology, clinical presentation and diagnosis of onychomycosis. Br J Dermatol. 2003;149(Suppl. 65):1–4.
88. Lipner SR, Scher RK. Onychomycosis: clinical overview and diagnosis. J Am Acad Dermatol. 2019;80(4):835–51.
89. Klafke GB, da Silva RA, de Pellegrin KT, Xavier MO. Analysis of the role of nail polish in the transmission of onychomycosis. Bras Dermatol. 2018;93(6):930–1.
90. Shemer A, Trau H, Davidovici B, Grunwald MH, Amichai B. Onychomycosis due to artificial nails. Eur Acad Dermatol Venereol. 2008;22(8):998–1000.
91. Jayasree P, Grover C. Soft tissue tumors of the nail. In: Grover C, Relhan V, Nanda S, Bansal S, editors. NSI textbook of onychology. New Delhi: Evangel Publishing; 2021. p. 294–310.
92. Grover C, Jayasree P, Kaliyadan F. Clinical and onychoscopic characteristics of subungual glomus tumor: a cross-sectional study. Int J Dermatol. 2020;60(6):693–702. https://doi.org/10.1111/ijd.15358.

Chapter 16
Tropical Diseases in Women

Swetalina Pradhan, Abhisek Mishra, and Kananbala Sahu

16.1 Introduction

With debates, actions, and investments gathering steam around the world, the new year has brought a renewed vigour for the realization of the "Health for Everyone" agenda [1]. To fulfil this vision, the wellbeing of women must be positioned at the forefront of our discourse. Although substantial progress has been made in mitigating maternal mortality, adolescent reproductive health services, and high-quality contraception, the missing link is the tropical disease burden in highly populous portion of the world like South east Asia. To a significant degree, tropical diseases are poverty-borne ailments that are frequently ignored. In addition, some of tropical diseases can result in affecting the patient socially, economically, and psychologically. Studies suggest that these diseases are extremely troublesome for young women because of their effects on the chances of marriage, education, and self-esteem [2, 3].

Billions of people in the world are affected by these neglected tropical diseases. While caused by numerous etiological agents, due to their geographical distribution and their overlooked status, NTDs are classified as a separate category. It must be noted that, while the disease is curable in all its aspects, the challenge in its confrontation is not contained in the biological domain, but in the social and cultural sphere,

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which, after all, affects the world's poorest regions, a reality which demonstrates its relationship with social disparities. By categorizing NTD as a group can facilitate their control and care in a coordinated and integrated way [4–6].

WHO has estimated that half a billion of people are suffering from tropical diseases in developing countries which include schistosomiasis, trypanosomiasis, chagas disease, leishmaniasis, and leprosy.

The skin-related tropical diseases include tuberculosis, cutaneous leishmaniasis, post-kala-azar dermal leishmaniasis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis, scabies, and yaws [7–9].

16.2 Leprosy

16.2.1 Epidemiology

Leprosy is the earliest recognized human illness. As per literature around 600 BC, the first recorded documents from India had documented genuine leprosy cases. This neglected tropical disease is caused by Mycobacterium leprae. The current prevalence is estimated as 0.2/10,000 population globally as per World Health Organization. Globally, India accounts for 60 pc of all new cases reported annually, with approximately a million new cases between 2016 and 2020, according to the National Leprosy Eradication Programme (NLEP). In India, there are 44,877 new cases reported in 2019 which are females and it is highest in the world [10–13].

16.2.2 Leprosy Transmission

The incubation period may vary from months up to 5 years. The bacilli are transmitted from one individual to other through aerosol inhalation. The main route of transmission is the nasal mucosa [14–16]. Less commonly, transmission can occur by skin erosions [16, 17]. It can be also transmitted through blood, placenta, breast milk, and insect bites [18–20].

16.2.2.1 Role of Women in Leprosy Transmission

Female is closely associated with her children and all the family members. When female becomes an index in the family, chance of transmitting infection to other family members including her children is much more. The child of leprosy affected mother will transmit the infection to community once infected with lepra bacillus. Hence a female affected with leprosy not only increases the disease burden in the family but also in the community.

16.2.2.2 Leprosy Spectrum

Leprosy mainly affects the skin, the peripheral nerves, mucosa of the upper respiratory tract and the eyes. The most widely accepted Ridley and Jopling classification (1966) has divided leprosy into five groups: tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), mid-borderline leprosy (BB), borderline lepromatous leprosy (BL), and lepromatous leprosy (LL) [21]. Later, the leprosy was reclassified with the addition of pure neuritic leprosy and indeterminate leprosy. TT, BT, and indeterminate leprosy are considered PB leprosy, and BB, BL, and LL Hansen's are classified as MB leprosy. Pure neuritic leprosy can fall on both spectrums depending on the number of nerves involved and the bacillary load. The cellular immunity goes down as one moves from the tuberculoid pole to lepromatous pole. The number of skin lesions increase, and size of skin lesions gradually decreases from TT pole to LL pole. Asymmetrical distribution of skin lesions is found in tuberculoid pole and as one downgrades to lepromatous pole the lesions become symmetrically distributed. Due to good immunity, the nerve trunks are usually enlarged in tuberculoid forms of leprosy. Due to damage to the nerve trunks and feeder nerves along with the denervation of skin appendages in tuberculoid forms the skin lesions look dry because of absence of sweating with relative loss of hair on the affected areas [21].

Indeterminate leprosy is first sign in 20–80% leprosy patients and usually presents as hypopigmented patch with loss of tactile or thermal sensation [22].

The lesion of tuberculoid leprosy (TT) is characterized by anaesthetic hypopigmented plaques with raised border that slopes inward (Fig. 16.1). The surface of the plaque looks dry with loss of hair and absence of sweating, and the feeder nerve may be thickened. Borderline tuberculoid leprosy (BT) is characterized by hypopigmented anaesthetic patch with regular to irregular margin. Pseudopodial extensions from margin and satellite lesions are characteristically present in BT patches (Fig. 16.2). The superficial peripheral nerves are likely to be enlarged in an asymmetrical pattern [23].

Mid-borderline leprosy (BB) is an unstable form and it exhibits characteristics of TT and LL pole. The skin lesions are asymmetrically distributed and there is moderate nerve impairment. Annular lesions with a well-defined, punched-out inner edge and an ill-defined outer-sloping edge that give the appearance of Swiss cheese/foveal spot form the classical morphology of BB. Borderline Lepromatous form (BL) is characterized by slightly infiltrated, round to oval macules of 2–3 cm in diameter that are distributed in asymmetrical patterns with areas of normal skin in between. However, papules, nodules, and plaques may develop with slope-like margins merging into the surrounding skin as the disease progresses. Peripheral nerve involvement is asymmetrical [23, 24].

There occurs continuous bacillary multiplication and systemic spread in LL due to absence of cellular immunity. In lepromatous leprosy (LL), the skin lesions tend to be multiple, symmetric and located in colder areas of body. The types of skin lesion include hypopigmented macules, erythematous to brownish nodules and papules, and diffuse and infiltrated skin (Fig. 16.3). Compared to BL the macules in LL

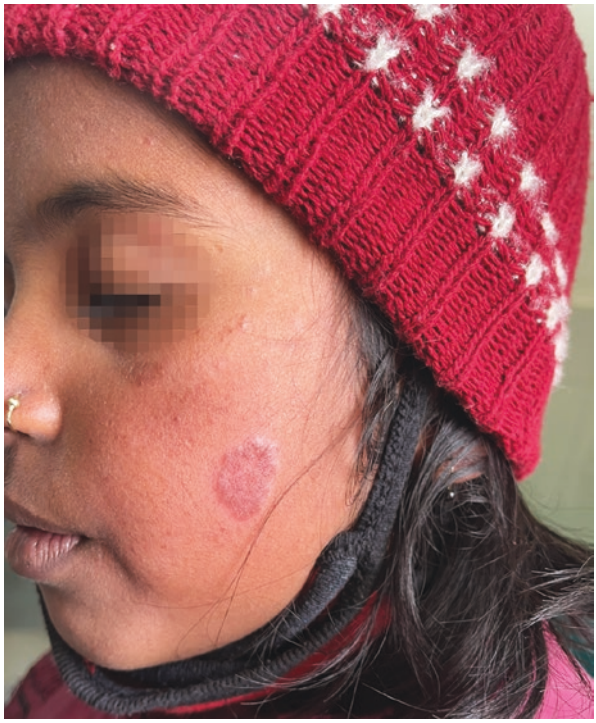

Fig. 16.1 Well-defined erythematous plaque over face with hypoesthesia suggestive of tuberculoid leprosy

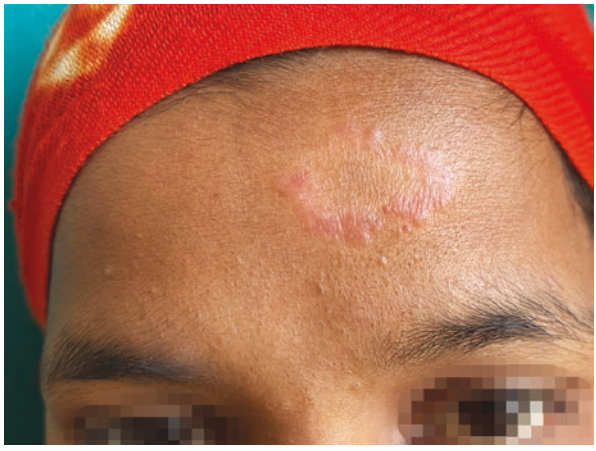

Fig. 16.2 Hypopigmented hypoanaesthetic patch with regular to irregular border with infiltrations at periphery in a female suggestive of borderline tuberculoid leprosy

are smaller, have indistinct edge, shiny surface, and are symmetrical in distribution. The patients of diffuse LL have shiny and thickened skin. The nodular is the advanced stage of LL characterized by presence of nodules over the ear lobes, face, trunk, joints, and extremities. Oedema of legs and feet is commonly found in LL patients. In the advanced stages of LL, the patient has a peculiar appearance

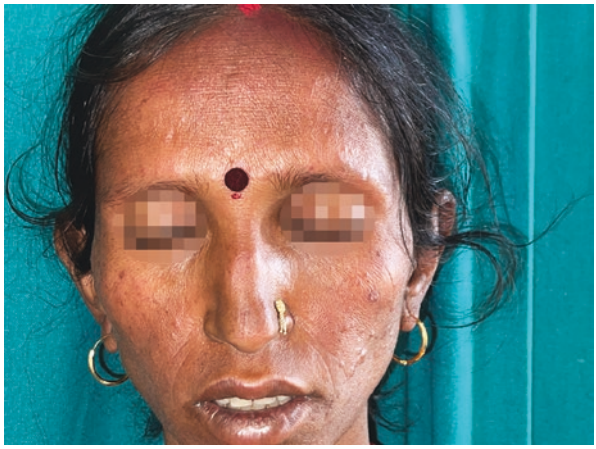

Fig. 16.3 Multiple papules and nodules over face with bilateral madarosis in a lepromatous leprosy female patient

(leonine facies) and madarosis (loss of lateral one-third of eyebrow hairs and eyelashes). Mucous membranes, eyes, bones, joints, lymph nodes, blood vessels, upper airways, teeth, and internal organs may be affected. The nerve trunks are rarely involved. Dermal nerve twigs are infiltrated by bacilli which give rise to symmetrical loss of sensation leading to glove and stocking type anaesthesia [21–24].

16.2.3 Pure Neuritic Leprosy

Pure neuritic leprosy presents with hypoesthesia/anaesthesia in absence of any skin lesions of leprosy but with involvement of nerves supplying the affected areas [25, 26]. It can be mononeuritic and polyneuritic basing upon the number of nerves involved [26].

16.2.4 Histoid Leprosy

Histoid leprosy is a rare variant of lepromatous leprosy characterized by painless discrete, smooth, dome-shaped skin coloured to yellow brown papules or subcutaneous nodules with apparently normal skin surrounding it. Lesions are usually found on the posterior and lateral aspects of the arms, buttocks, thighs, dorsum of the hands, lower part of the back, and over the bony prominences, especially over elbows and knees [27]. The acid-fast bacilli in histoid lesions are found in clusters, singles or tightly packed in macrophages in slit skin smear and appear longer with tapering ends compared to the ordinary lepra bacilli [27].

16.2.5 Lucio Leprosy

Lucio leprosy (LuLp) otherwise called lepra bonita or beautiful leprosy is a pure, primitive, and diffuse form of LL, commonly seen in Mexico and Costa Rica. The skin appears infiltrated waxy and shiny, so that natural wrinkles are obliterated and the person's face appears moist and myxoedematous complexion imparting healthy and beautiful appearance [28].

16.2.6 Lepra Reaction

Leprosy reactions occur due to alteration in the immune balance between the host and *M. leprae*. Such reactions are acute episodes that primarily affect the skin, nerves, mucous membranes, and other sites and change the uneventful course of the chronic disease. They can occur before institution of treatment, during treatment or after treatment. They are classified into two types: type 1 reaction and type 2 reaction [29, 30].

16.2.6.1 Type 1 Lepra Reaction

Type 1 Lepra reaction is a delayed hypersensitivity reaction. It mostly occurs in borderline leprosy. Female gender carries a higher risk than men [31]. This could be due to hormonal fluctuations [32]. Pregnancy and delivery carry an increased risk which is found to be the highest in the first 6 months after delivery (post-partum). These reactions are related to the cellular immune response against mycobacterial antigens and can result in improvement (reversal reaction, pseudo-exacerbation reaction, or upgrading reaction) or worsening (downgrading reaction) of the disease. In majority of situations, the downgrading of untreated patients from tuberculoid forms to lepromatous form occurs during type 1 reaction. In Type 1 reaction, there may be appearance of new lesion and the pre-existing lesions may become erythematous, oedematous, and hyperaesthetic (Fig. 16.4). In severe cases, the skin lesions may get ulcerated. Acral oedema is usually found in type 1 reaction. Neuritis is a prominent feature of type 1 reaction which is the major cause of disability and deformity in a leprosy patient [29, 30].

16.2.6.2 Type 2 Lepra Reaction

Type 2 reaction or erythema nodosum leprosum (ENL) is a type 3 hypersensitivity reaction occurring mostly in LL and sometimes in BL leprosy patients having high bacillary load. It occurs due to body's reaction to release of substances by

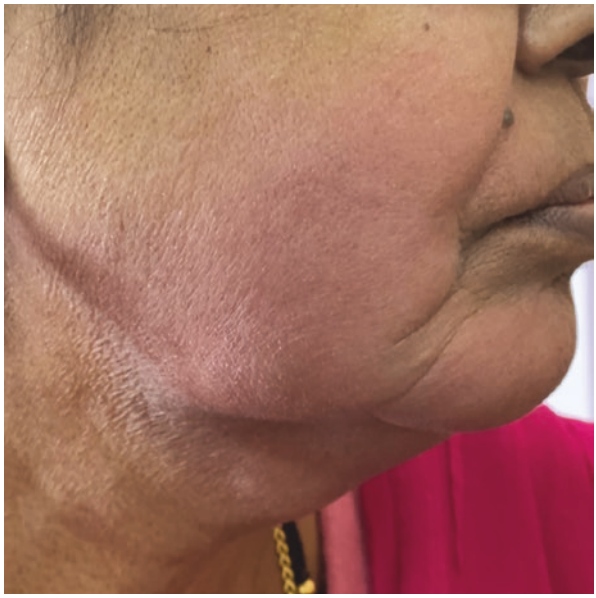

Fig. 16.4 Borderline tuberculoid leprosy with erythema and oedema on the plaque because of type 1 lepra reaction

destruction of bacilli and deposition of immune complex in different parts of body. Commonly ENL presents as sudden onset of erythematous, evanescent, tender nodules in crops over body associated with constitutional symptoms like fever, malaise, myalgia, oedema, and arthralgia. Other morphological presentations include papules, plaques, bullae, erythema multiforme like target lesions, PLEVA like lesions, ulcerated form or ENL necroticans (Fig. 16.5). As immune complex deposition occurs almost in all organs, ENL can present with varied systemic manifestations like lymphadenitis, iridocyclitis, uveitis, hepatosplenomegaly, rhinitis, laryngitis, epididymo-orchitis, myositis, arthritis, painful dactylitis, synovitis, nephritis, proteinuria, and renal failure. Neuritis is less common T2R as compared to T1R and in some patients of severe T2R neuritis may be found [29, 30].

16.2.7 Lazarine Leprosy

Lazarine leprosy is otherwise called ulcerating type 1 reaction which occurs in BT leprosy patients due to exaggerated delayed type hypersensitivity reaction. There occurs spontaneous ulceration of skin lesions [33]. Systemic corticosteroids are necessary for the treatment in addition to anti-leprosy drugs.

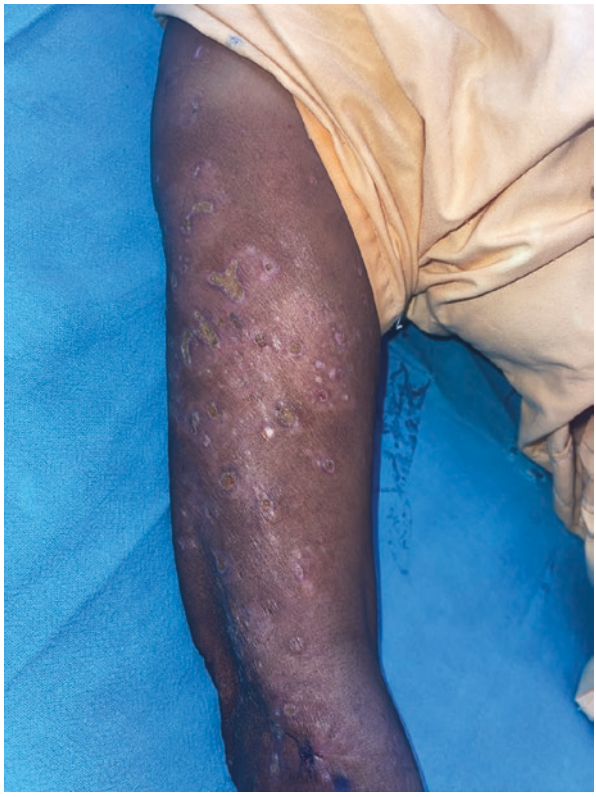

Fig. 16.5 Lepromatous leprosy female patient with necrotic erythema nodosum leprosum and healed scars

16.2.8 Lucio Phenomenon

Lucio phenomenon is a vasculo-necrotic reaction found in untreated or inadequately treated, well-established, diffuse, nonnodular form of leprosy known as Lucio leprosy [34, 35]. It also has been reported in the classic nodular form of lepromatous and borderline leprosy [36]. It usually starts as painful purpuric lesions which progress into well-defined, multi-angulated, jagged ulcers with a geometric shape in descending order of frequency, i.e. the feet, legs, hands, forearms, thighs, arms, and rarely, the trunk and face. Healing of ulcers occurs in about 2–8 weeks, leaving curvilinear jagged atrophic hypochromic scars with a surrounding halo of hyperpigmentation. There is no fever, constitutional symptoms, and systemic involvement and neuritis [37]. It is believed that LP occurs due to uninhibited multiplication of lepra bacilli resulting in diffuse infiltration of the integument in an anergic background and enhanced exposure of mycobacterial antigen to circulating antibodies, resulting in vasculitis. Lucio phenomenon may mimic vasculo-necrotic erythema nodosum leprosum. In ENL, presence of constitutional symptoms with neuritis differentiates it from Lucio phenomenon. Lucio phenomenon requires no specific treatment other than multibacillary multidrug therapy for leprosy. Whereas, necrotic ENL responds to systemic corticosteroid and thalidomide [37].

16.2.9 Leprosy and Pregnancy

Leprosy and pregnancy shape the course of one another. The change in body hormones during pregnancy led to change in immune status of the patient that may cause first appearance of leprosy, reactivation of the disease and relapse in cured patients which is more marked in the third trimester of pregnancy [38, 39]. Leprosy reactions occur during pregnancy because of the alteration in cell-mediated and humoral immunity [39]. A type 1 reaction (reversal reaction) occurs during postpartum phase, whereas a type 2 reaction (erythema nodosum leprosum) peaks during late pregnancy. Both forms of reaction can continue into lactation phase for a long time. Therefore, both leprosy and lepra reaction during pregnancy and postpartum time along with their sequelae make the infected women more vulnerable to several complications [23].

16.2.10 Effect of Leprosy on Fertility Status and Menstrual Cycle

There have been conflicting findings regarding gonadal involvement in female leprosy patients from several parts of the world. The Indian study found that primary infertility rate is higher in females affected with leprosy compared to the India's general population [40, 41]. Fifty four percent of female patients with leprosy were sterile in the study of Fleger et al., and the females reported gross menstrual abnormalities in the study of King and Marks [42, 43]. Bogush concluded in his study that in patients with leprosy, menstrual dysfunction could be avoided by the early start of therapy [44]. The Indian study by Khanna et al. found a significantly larger number of female patients with MB leprosy had irregular periods postdating the onset of leprosy than patients with PB leprosy [45]. The same study also found that gonadotropic hormone levels were elevated in slightly more MB leprosy patients relative to PB leprosy patients, and the mean levels of these hormones demonstrated a rising pattern from controls to PB patients to MB leprosy patients.

16.2.11 Diagnosis of Leprosy

The diagnosis of leprosy is mostly clinical and based upon the WHO criteria.

a. Hypopigmented hypoanaesthetic/anaesthetic skin lesions.
b. Peripheral nerves enlarged/or tender.
c. Slit skin smear for AFB should be positive.

Only one criterion is required for diagnosis of leprosy.

16.2.12 Investigations

16.2.12.1 Slit Skin Smear and Ziehl–Neelsen Staining

Slit skin smear is a simple technique which is very useful in diagnosis and prognosis of disease. Initially smears were obtained from multiple sites which included both ear lobes, both cheeks, forehead, chin, both buttocks, and additional six suspicious sites. Presently four sites are chosen for the test: (1) right earlobe, (2) forehead, (3) chin, and (4) left buttock in men and left upper thigh in women [46]. However, the smear can be taken from other active or doubtful lesions in PB leprosy. The BI is calculated by adding the values from all the skin sites examined (usually four) and then dividing the total by the number of sites examined (Table 16.1). The BI in TT is usually 0, BT 1+ to 2+, 2+ to 4+ in BB, more than 4+ to 5+ in BL, and 6+ in LL.

16.2.12.2 Morphological Index (MI)

Morphological index represents percentage of live bacilli. It is calculated as percentage of solid stained bacilli after examining 200 bacilli lying singly. The live bacilli/solid staining bacilli are uniformly stained, rounded at both the ends and have length of five times the width and parallel sides.

16.2.12.3 Histopathology of Skin and Nerve

In case of indeterminate leprosy, middle of the lesion should be considered for biopsy [47]. When multiple lesions are present, the most active lesion should be identified for biopsy. Always choose the active infiltrated edge for biopsy for better results. In the scenario of multiple skin lesions with different morphology, more than one biopsy is required for proper evaluation. Histopathology of nerve is more useful in diagnosis of pure neuritic Hansen. Histopathology of various types of leprosy and reactional states has been elaborated in Table 16.2.

Table 16.1 Calculation of bacillary index in slit skin smear

Examination by oil immersion field	Number of AFB	Bacillary Index (BI)
One field	>1000 bacilli in every field	6+
One field	100–1000 bacilli in every field	5+
One field	10–100 bacilli in every field	4+
One field	1–10 bacilli in every field	3+
10 fields	1–10 bacilli/10 fields	2+
100 fields	1–10 bacilli/100 fields	1+
100 fields	No bacilli/100 fields	0

Table 16.2 Histopathological findings of skin lesions of leprosy

Leprosy spectrum	Histopathology of skin lesions
Indeterminate leprosy	Early stage: occasional AFB in the non-inflamed nerve, erector pilorum, or subepidermal zone Late stage: lymphocyte and nonspecific histiocytic infiltration in the perineurium or nerve parenchyma suggestive of neural inflammation along with schwann cell proliferation
Tuberculoid leprosy	The tuberculoid granuloma is compact and well organized comprised of epithelioid cells surrounded by a mantle of lymphocytes. Langhans giant cells are found. The granuloma usually effaces the epidermis obliterating the subepidermal clear zone. The nerves damaged and replaced by the infiltrating epithelioid cells. AFB are usually not detected
Borderline tuberculoid leprosy	The epithelioid cell granuloma shows some admixture of macrophages and lymphocytes, relatively loose and follows the neurovascular bundles in branching pattern. Lymphocytes are relatively less in number compared to TT and the giant cells are often foreign body type. Neural infiltration with few AFB is seen (BI 1+ to 2+). Clear SEZ is always found
Mid-borderline leprosy	Granuloma of mid-borderline is not compact and shows almost equal numbers of epithelioid cells and macrophages. Lymphocytes are scattered and lesser in number. Clear SEZ is seen. Nerves are not completely destroyed and show cut-onion appearance on transverse section [48]. AFB may be frequent (BI 2+ to 4+)
Borderline lepromatous leprosy	Macrophage granuloma is found with isolated clumps of epithelioid cells. Lymphocytes are sparse and scattered. Nerves are not destroyed completely unlike TT and BT. Concentric perineural cell proliferation gives a cut-onion appearance. SEZ is free. Bacilli are always plenty
Lepromatous leprosy	Macrophage granuloma is a distinct feature of lepromatous leprosy (LL). Epidermis is thinned out and flattened due to expansion of granuloma. There is a clear subepidermal zone demarcating the granuloma and epidermis. Lymphocytes are rarely present. Histiocytes are abundant and have foamy appearance. The foamy macrophages contain plenty of AFB (BI 4–6)
Histoid leprosy	Epidermal atrophy is found because of dermal expansion of the underlying leproma and a grenz zone located immediately below the epidermis. Granuloma consists of fusiform histiocytes arranged in a whorled, criss-cross, or storiform pattern. The histiocytes resemble fibroblasts. Within the histiocytes, an abundance of acid-fast bacilli can be seen
Type 1 lepra reaction	There is increased infiltration of lymphocytes, macrophages, and neutrophils. Granulomas are disorganized due to increase oedema in dermis. The foreign body giant cells number is more and the Langhans giant cells also become larger and increased in number [49]. There is erosion of the epidermis with necrosis in case of severe type 1 reaction [50]
Type 2 lepra reaction	There is dense neutrophilic infiltration of dermis and granulomas. Vasculitis may cause full necrosis of the epidermis and erosion. Vasculitis is though not universally seen [51]
Lucio phenomenon	There is proliferation of endothelial cells in medium-sized vessels of mid-dermis along with colonization of the endothelial cells by acid-fast bacilli. In addition, neutrophilic infiltration, ischemic epidermal necrosis, and necrotizing vasculitis of the small vessels of the superficial dermis are seen [52]

16.2.12.4 FNAC of Skin Lesions and Nerve

FNAC nerve is more useful in diagnosis of pure neuritic leprosy and the cytological features can help in identifying the leprosy spectrum like histopathology. However, it is an invasive procedure and requires skill and expertise of an individual.

16.2.13 Advanced Diagnostic Methods

16.2.13.1 Serological Assay

Antibody-Based Immunological Tests

a. Phenolic glycolipid-1 (PGL-1) antibody assay ELISA (kit format): PGL-1 is a major glycolipid cell wall antigen of the bacterium. Hence PGL-1 assay can be used as a confirmatory marker for disease, as a predictor of disease outcome, an indicator of nerve damage and exacerbation and as a tool for preclinical intervention. PGL-1 antibody levels have been found to correlate with the bacterial load and the levels decline after adequate chemotherapy and hence can be useful to monitor leprosy patients under treatment [53].
b. MLflow test: ML flow test is an immunochromatographic assay which detects *M. leprae* specific anti PGL-1 IgM antibodies. It is easy to perform and can be used at primary health care centres [54].
c. 35-kD-based serology: 35 kDa protein is found in the membrane of M. leprae. 35 kDa assay using monoclonal antibody (MLO4) has been utilized for serological studies. The number of anaesthetic patches in patients found to positively correlate with the level of antibody. Also, the antibody levels correlate positively with the number of nerves involved in primary neuritic leprosy. After chemotherapy, the levels decline suggesting the role in monitoring the leprosy patients [55, 56].
d. LID-1 Assay (designated leprosy IDRI diagnostic): Two fusion proteins ML0405 and ML2331 (LID-1 designated leprosy IDRI diagnostic) have been tested for their antibody reactivity. The test was found to be more sensitive than PGL-1. Antibody level to LID-1 showed more rapid decline after MDT regimen compared to that of PGL-1 antibody level [57–59].

Cytokine Profile

Studies on cytokines have revealed involvement of Th1 cytokines like interleukin-2 and IFN-γ in TT leprosy and Th2 type cytokine like IL-4, IL-5, and IL-10 in LL patients. Th-1 and Th-2 cytokines are involved in type 1 and type 2 lepra reaction, respectively [60].

16.2.14 Polymerase Chain Reaction (PCR)

PCR is able to detect *M. leprae* DNA from even 10–30 fg of *M. leprae* component which is equivalent to 2.8–8.3 bacilli [59]. The samples for PCR could be taken from skin biopsy, skin smears, nerves, oral or nasal swabs, blood, ocular lesions,

and urine. PCR is helpful in early identification of difficult to diagnose cases. By this method, pure neural leprosy, indeterminate leprosy, and household contacts are detected early by PCR. PCR is confirmatory in cases of clinical and histopathological dispute [61].

16.2.14.1 Nerve Conduction Study

Electrophysiological study or NCS can detect changes in both sensory and motor components. For the motor nerves, parameters like distal motor latency, compound muscle action potential, and conduction velocity are recorded while for sensory nerves sensory nerve action potential (SNAP), onset latency, and conduction velocity are recorded. In the preclinical stage of the leprosy, where there are no signs and symptoms suggestive of nerve damage NCS can detect changes in sensory and motor fibres [62, 63].

16.2.15 High Resolution Ultrasonography (HRUS)

High-resolution ultrasonography is a non-invasive modality which can study the structural changes in nerve sites from which histopathology is difficult to obtain. Peripheral nerves can be visualized with reasonable precision by USG with broadband frequency of 10–14 MHz, CD frequency of 6–13 MHz and linear array transducer. One can idea regarding location and degree of nerve enlargement, nerve morphological alterations, echo texture, and fascicular pattern by HRUS [64]. Colour Doppler USG is being done to look for absence or presence of blood flow signals in the perineural plexus and interfascicular vessels of nerve trunks. Normal healthy nerve is hypo-vascular with neither the fascicles nor the epineurium showing CD signals. Detection of blood flow signal in colour doppler USG suggests hypervascularity and ongoing neural inflammation and nerve damage [64].

16.2.16 Management of Leprosy

Multidrug therapy (MDT) instituted by the Word Health Organization in 1981 has been considered the gold standard treatment for leprosy. The regimen has undergone different modifications regarding duration of therapy and doses. However, the currently recommended duration is 6 months for PB and 12 months for MB (Tables 16.3 and 16.4).

Table 16.3 Multidrug therapy (MDT) regime in leprosy

Feature	MB[a]	PB
Skin lesions	>5	1–5
Smear for AFB	Positive	Negative
MDT (adults)	Rifampicin: 600 mg MS Clofazimine: 300 mg MS; 50 mg daily Dapsone: 100 mg daily	Same as MB
MDT (children)	10–14 years Rifampicin 450 mg MS Clofazimine 150 mg MS, 50 mg daily Dapsone 50 mg daily <10 years or <40 kg Rifampicin 10 mg/kg MS Clofazimine 6 mg/kg MS and 1 mg/kg daily Dapsone 2 mg/kg daily	Same as MB
Duration	12 months course completed in 18 months period	6 months course completed in 9 months period

MB multibacillary, *PB* paucibacillary, *MDT* multidrug therapy, *MS* monthly supervised, *AFB* acid-fast bacilli
[a]As per NLEP 2009: patient with more than one thickened nerve is also classified as MB

Table 16.4 Treatment of Leprosy in special situation

Sl. No.	Clinical scenarios	Treatment modification/adjustment
1.	Co-existent tuberculosis and leprosy	Start treatment of tuberculosis first -Make the necessary additions or adjustments in the anti-leprosy treatment such that during the treatment course, patient is on at least three anti-leprosy drugs in case of MB leprosy and at least two anti-leprosy drugs in case of PB leprosy
2.	Non-acceptance of clofazimine	Ofloxacin 400 mg daily, or minocycline 100 mg daily as substitutes for clofazimine or Monthly ROM for 24 months
3.	Pregnancy	First time diagnosed: Start MDT irrespective of the trimester Already on MDT: continue MDT
4.	Severe dapsone toxicity	Stop dapsone immediately For MB leprosy, no further modification is required For PB leprosy, clofazimine may be substituted for dapsone for a period of 6 months

16.2.17 Treatment of Type 1 Lepra Reaction

Mild reaction should be treated with analgesics, such as acetylsalicylic acid or paracetamol. If there is nerve involvement, type 1 reactions should be treated with analgesics and corticosteroids, such as oral prednisolone.

16.2.17.1 Dose of Steroid in T1R Recommended as per WHO for the Field Purpose

Dose of prednisolone	Weeks of treatment
40 mg daily	1st and 2nd week
30 mg daily	3rd and 4th week
20 mg daily	5th and 6th week
15 mg daily	7th and 8th week
10 mg daily	9th and 10th week
5 mg daily	11th and 12th week

16.2.17.2 Dose of Steroid in T1R at Referral Centres

Start dose: 40–60 mg daily (up to a maximum of 1 mg/kg).

Tapering: reduced by 5 mg weekly or fortnightly after improvement of skin lesions and nerve tenderness subsides.

Maintenance dose: 15–20 mg for several months, then reduced by 5 mg for every 2–4 months.

Duration: BT—4–9 months, BB—6–12 months, BL—6–24 months.

16.2.18 Treatment of Type 2 Lepra Reaction

16.2.18.1 Severity Grading of T2R (Table 16.5)

Mild T2R
Only few ENL lesions with no other organ involvement
Severe T2R

1. High fever, body pain, myalgia
2. Extensive ENL with or without pustular/necrotic lesion

Table 16.5 Treatment of T2R

Type 2 reaction	Mild reaction	Severe reaction
First episode	1. Aspirin 2. Cholchicine 3. Paracetamol	Option 1: prednisolone (1 mg/kg BW till clinical improvement, then taper by 5–10 mg over 6–8 weeks. Maintenance dose of 20–40 mg needed for several weeks to prevent recurrence Or prednisolone with clofazimine-not responding corticosteroid or whom corticosteroids are contraindicated Option 2: Thalidomide 200 mg BD for 3–7 days or till reaction is under control, followed by tapering within 3–4 weeks or slow tapering
Recurrent ENL Or Chronic ENL		Combination treatment is preferred Option 1: clofazimine + prednisolone Option 2: Thalidomide + prednisolone

3. Pain/tenderness of one or more nerve or loss of function
4. Recent NFI (nerve function impairment)
5. Painful swelling of testes (orchitis)
6. Marked arthritis or lymphadenitis

16.2.18.2 Deformities in Leprosy in Females

Deformities in leprosy occur due to neuritis and inadequate care of anaesthetic parts. Females outnumbered males in having particular deformities in a study from Southeast Nigeria and the difference time of diagnosis from onset of problem was double in females as compared to males [65]. In developing countries, a significant proportion of females are homemaker and engaged in cooking and other domestic services and hence are vulnerable to repeated trauma, ulceration, and other grave deformities.

16.2.18.3 WHO Grading of Deformities in Leprosy [66]

Hands and feet

Grade 0 No anaesthesia, no visible deformity or damage

Grade 1 Anaesthesia present, but no visible deformity or damage

Grade 2 Visible deformity or damage present

Eyes

Grade 0 No eye problem due to leprosy; no evidence of visual loss

Grade 1 Eye problems due to leprosy present, but vision not severely affected as a result (vision: 6/60 or better; can count fingers at 6 metres).

Grade 2 Severe visual impairment (vision worse than 6/60; inability to count fingers at 6 metres); also includes lagophthalmos, iridocyclitis, and corneal opacities.

16.2.18.4 Leprosy and Stigma in Female

Stigma may be defined as "a social process, which is experienced or anticipated, characterized by exclusion, rejection, blame or devaluation that results from experience, perception or reasonable anticipation of an adverse social judgment about a person or group" [67]. From 1988 to 1997, a study of leprosy patients in South East Nigeria showed that the condition affected women more than men. Not only in the medical context, but even in socio cultural and economic ways, infections can have a different effect on women. Gender disparities will play a much larger part in labelling women as offenders because of their effects on body appearance and the social shame associated with them [68]. A survey in India showed that 18% of women surveyed mask their symptoms, and another Indian research found that women appear more than men to mask the signs and complications [69]. In sub-Saharan Africa, women afflicted by leprosy mask their health-seeking behaviour and are

unable to speak about their disease and are expecting its fearful implications for marriage and sexual life. Owing to the lack of schooling, knowledge, and value in the home, women with disease are forced to conceal their symptoms as long as possible in developing countries such as India. The responsibility of household care and home isolation also contributes to late detection and treatment of leprosy in women. For women failing to carry out domestic tasks, childcare, active sexual life because of leprosy, have been abandoned by husbands and companions. In addition, leprosy deformities and disability make the condition noticeable, adding much to women's social isolation. This leads to social breakdown, psychiatric disorder, and a feeling of being deprived of their basic characteristics as a capable female afflicted by leprosy.

16.3 Cutaneous Tuberculosis

Tuberculosis (TB) is a major public health issue all over the world with Southeast Asia being burdened with 10.4 million (45%) infective Tuberculosis cases [70]. In India, tuberculosis accounts for 0.1–0.9% of the total dermatology out-patients in India [71]. The estimated extrapulmonary tuberculosis is about 2% and it is about 14% of all tuberculosis cases in different study [72] (Table 16.6).

16.3.1 Tuberculosis Verrucosa Cutis (TVC)

TVC also known as warty TB, is the most common form of exogenous TB in adult. It results from direct inoculation of *M. tuberculosis* in individuals with moderate to high immunity. The lesion appears as painless, erythematous, isolated papule or

Table 16.6 Classification of cutaneous tuberculosis [73, 74]

Based on route of infection	
1. Exogenous route	Tuberculous chancre, LV, TVC
2. Endogenous route	
Contiguous spread	Scrofuloderma, Orificial TB
Hematogenous spread	Acute miliary TB, metastatic tuberculous Abscess (gummatous TB), tuberculids and LV
Lymphatic spread	LV
3. Tuberculids	
Micropapular	Lichen scrofulosorum
Papular	Papulonecrotic tuberculid
Nodular	Erythema induratum
Based on bacillary load	
1. Multibacillary	Tuberculous chancre, Scrofuloderma, Orificial TB, acute miliary TB, gummatous TB
2. Paucibacillary	TVC, LV, and tuberculids

LV Lupus vulgaris, *TVC* tuberculosis verrucose cutis, *TB* tuberculosis

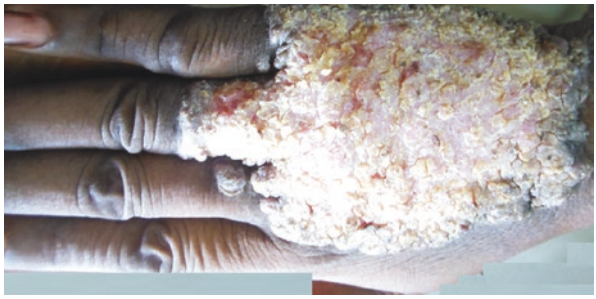

Fig. 16.6 Tuberculosis verrucosa cutis presenting as verrucous plaque on dorsum of hand

plaque with verrucous surface (Fig. 16.6). Rarely multiple lesions can be seen. There is always a predilection for trauma prone sites like extremity. The plaque is surrounded by a purplish inflammatory halo that evolves to asymptomatic verrucous plaques, with 1–5 cm in diameter [75]. The verrucous plaque may enlarge through peripheral extensions, accompanied by central atrophy [76]. Rarely ulceration may occur with extrusion of pus from the fissures or clefts [77]. Lymphadenopathy is rarely found. Sometimes secondary bacterial infection and elephantiasis can occur in case of extensive lesions affecting extremities [76].

16.3.2 Lupus Vulgaris (LV)

Lupus vulgaris is the most common form of cutaneous tuberculosis (CTB) all over the world. Women are commonly affected than men [78]. It occurs in patients with high degree of immunity against *Mycobacterium tuberculosis*. Inoculation of bacillus occurs endogenously by lymphohematogenous spread or by continuity, and rarely via exogenous routes like draining sinus of scrofuloderma, scar of TVC, scrofuloderma, or BCG vaccination [79]. Morphologically LV presents a well-demarcated skin coloured to erythematous, nodule or plaque which rarely ulcerate. The nodular lesion evolves slowly with occurrence of new lesions in the adjoining areas which may coalesce to form a plaque. The plaque grows peripherally, with serpiginous or verrucous borders, may reach a size over 10 cm in diameter with central atrophy and skip areas (Fig. 16.7). The ulcerative and atrophic forms rarely occur. Types include flat, hypertrophic, ulcerated, vegetative, and mutilating type. On diascopy of the lesion may give "*apple jelly nodules*" look in fair individual; however, it is rarely seen in dark complexed. Regional lymphadenopathy is found commonly in lupus vulgaris [79].

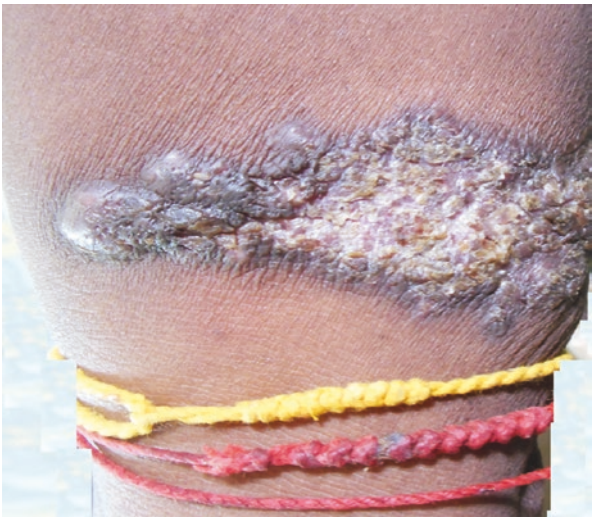

Fig. 16.7 Lupus vulgaris presenting as reddish-brown well-defined plaque with central atrophy and scarring

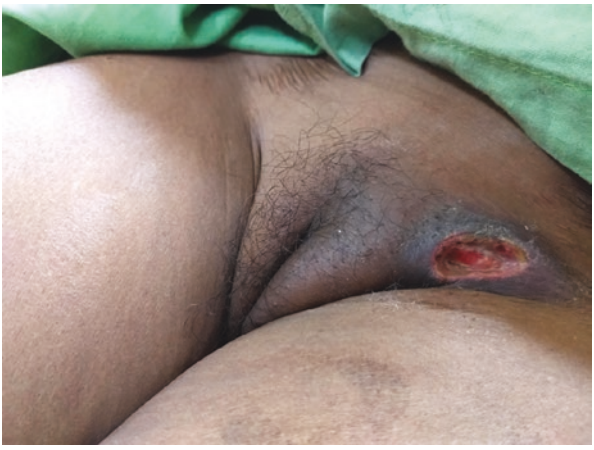

Fig. 16.8 Scrofuloderma presenting a subcutaneous swelling with sinus formation in inguinal area

16.3.3 Scrofuloderma

Scrofuloderma, also known as *tuberculosis colli quativa cutis* is a common form of cutaneous tuberculosis in developing countries like Brazil and India. The inoculation of bacillus occurs from direct extension of endogenous tubercular infection to lymph node, bone, joints, or testicles neck, axillae, groin, and cervical lymph nodes. Lesions may be single or multiple. Lesions start as painless subcutaneous skin coloured nodules which gradually progress to form cold abscesses and later rupture to sinuses with seropurulent discharges (Fig. 16.8). The skin overlying the abscess looks pigmented suggesting chronic inflammation [76]. Spontaneous involution may occur leaving puckered scar with retractions [78].

16.3.4 Tuberculous Chancre

Tubercular chancre also known as primary tubercular chancre is a rare form of cutaneous TB. The mycobacterial inoculation occurs directly into the skin following local trauma. It affects previously un-sensitized individuals, especially children, who have not been vaccinated or had no contact with environmental *M. tuberculosis*. Exposed areas like face and extremities are often affected. It starts as a firm, painless nodule that enlarges and ruptures to form shallow ulceration with undermined edge and covered with thick crust. The borders of the ulcer are undermined. A painful regional lymphadenopathy occurs after 2 weeks. Spontaneous regression with scarring and calcification of regional lymph node may occur [73].

16.3.5 Tuberculous Gumma

Tuberculous gumma, also called metastatic tuberculous abscess occurs following a hematogenous spread of bacilli in an individual with immunosuppression especially those with HIV/AIDS and malnourished children. Commonly widespread distribution of lesions is found because of hematogenous dissemination of bacilli all over the body. The commonest sites involved include trunk and extremities. The lesions start as subcutaneous nodule which in due course of time becomes fluctuant like abscess and subsequently rupture to form ulcer or sinus with serous or seropurulent discharge resembling scrofuloderma [77]. The edge of the ulcer is undermined with bluish discolouration at the border. Regional adenopathy is usually absent. The prognosis is relatively poor in these patients. If not treated the lesions may persist for years or spontaneous resolution can occur sometimes [77].

16.3.6 Orificial Tuberculosis

Orificial tuberculosis, or *tuberculosis cutis orificialis* occurs commonly at mucocutaneous junctions, around the orifices (mouth, anus, urethra, and palate). The infection occurs by self-inoculation of mycobacteria by the individual herself with an active focus of infection like in lung, intestine, and urogenital system under the state of immunosuppression. Skin lesions are friable, painful, erythematous papules or nodules with severe underlying visceral disease [77].

16.3.7 Acute Miliary Tuberculosis

It is a rare and severe form of tuberculosis which occurs in individuals with impaired cellular immunity, anergic child with negative PPD, and HIV patients with CD4 count below 100 cells/μL. Skin involvement occurs because of acute bacteraemia

with primary focus of infection in the lungs. The lesions are widespread and occur in the form of erythematous macules, papules, papulo-vesicles and central umbilication, ulceration or crusting [77]. Rarely exanthematous rash is seen. The lesions tend to regress in 1–4 weeks, leaving depressed and hypopigmented scars. There is associated systemic symptoms like fever, anorexia, asthenia, and weight loss.

16.3.7.1 Histopathological Findings of Different Types of Cutaneous Tuberculosis

Basing upon location and type of granuloma along with presence or absence of necrosis, various types of cutaneous TB are differentiated in histopathology (Table 16.7) [80].

a. Well-formed granulomas with absence of caseous necrosis—LV, Lichen scrofulosorum
b. Intermediate forms-granuloma with caseous necrosis—TVC, primary cutaneous TB, acute miliary TB, Tuberculosis orificialis
c. Poorly formed granuloma with intense caseous necrosis—Scrofuloderma, metastatic abscess, and gumma

Table 16.7 Histopathology of cutaneous TB [80]

Clinical types	Epidermis	Dermis	Types of cell	AFB status
Lupus vulgaris	Atrophic or hypertrophic Acanthosis, papillomatosis	Well-formed epithelioid granuloma Small foci of caseous necrosis rarely Lymphocytic infiltrate is dense	1. Langerhans type 2. Foreign body like 3. Sarcoidosis-like	Infrequent
Lichen scrofulosorum	Discrete rectification of epidermis	Well-formed epithelioid granuloma surrounded by lymphocytes in more superficial dermis No caseous necrosis	Giant cells absent	Absent
TVC	Hyperkeratosis, acanthosis, papillomatosis	Caseous necrosis of moderate intensity	Tuberculous granuloma	Can be found
Primary cutaneous TB	Normal	Recent lesion—necrotizing neutrophilic infiltrate	Late lesion—organization of granuloma	Numerous in recent lesions, gradually decreases

(continued)

Table 16.7 (continued)

Clinical types	Epidermis	Dermis	Types of cell	AFB status
Acute miliary tuberculosis	Normal	Nonspecific inflammatory infiltrate and focal caseous necrosis with microabscess	Infiltrate contains lymphocytes + plasma cells	Bacilli vary directly with the severity
Tuberculosis orificialis	Normal or atrophic	Granuloma around a median central superficial ulcer with caseous necrosis in deep dermis	Tuberculoid type	Infrequent
Papulonecrotic tuberculid		Area of necrosis into dermis	Granulomatous infiltrate with leukocytoclastic vasculitis, perivascular oedema, or follicular necrosis with suppuration	Negative
Scrofuloderma	Atrophic or hypertrophic or ulceration	Massive central necrosis with abscess and suppuration	Periphery showing traces of granuloma	Can be found
Metastatic abscess or gumma	Normal	Central ulceration with abundant caseous necrosis	Rim of giant cell and macrophages surrounding necrosis	Frequent

16.3.8 Tuberculids

Tuberculids are believed to be a cutaneous immunological reaction to the presence of occult TB in a patient with moderate to high immunity. They indicate active tuberculosis and/or episodic bacteraemia with a hyperergic expressions of active TB [81]. Types include papulonecrotic form, erythema induratum of Bazin, and lichen scrofulosorum.

16.3.8.1 Papulonecrotic Tuberculid

It is characterized by painless erythematous to violaceous papulonodular lesions around the face, ears, extensors of trunk, extremities, and buttocks. The lesions resolve spontaneously leaving varioliform scars [73]. AFB is usually negative [82]. In histology dermis shows granulomatous infiltrate with leukocytoclastic vasculitis, perivascular oedema, or follicular necrosis with suppuration [82].

16.3.8.2 Lichen Scrofulosorum

Lichen scrofulosorum is also known as "tuberculosis cutis lichenoides". It is a rare tuberculid characterized by numerous minute lichenoid papules in children and adolescents with tuberculosis. The lesions are usually asymptomatic, closely grouped, yellow-red to brown-red follicular or perifollicular papules of size 1–5 mm present preferably over trunk, abdomen, and proximal parts of the limbs. Strongly positive tuberculin reaction is found in the affected patients [83]. Usually the lesion has a smooth surface; however, spiny projections with fine scales may be found occasionally. Histopathology shows non-caseating, epithelioid cell granulomas in upper dermis and around dermal appendages. AFB is not found. The lesions respond rapidly within 4–6 weeks of starting anti-tubercular treatment with complete clearance in 12 weeks, irrespective of the systemic tubercular focus [77, 84].

16.3.8.3 Erythema Induratum of Bazin

Erythema Induratum of Bazin (EIB) is a granulomatous lobular panniculitis associated with tuberculosis. Young and middle aged are affected with lower limb being the site of predilection [85, 86]. Cold temperature, associated circulatory disorders of lower limbs, and obesity are associated risk factors. It starts as purplish to red subcutaneous nodules on posterior legs and thighs and subsequently ulcerates to discharge caseous materials. The ulcers are usually shallow with violaceous border with necrotic slough at the base. The ulcers heal with depressed scars with or without treatment. Histology shows predominantly lobular panniculitis with fat necrosis, mixed inflammatory infiltrate of lymphocytes, plasma cells, and histiocytes forming granulomas. In two-third cases, non-caseating granulomatous inflammation is found.

16.3.9 Treatment of Cutaneous Tuberculosis

The cutaneous TB usually responds to anti-tubercular drugs. The ATT have been classified into first line and second line (Tables 16.8, 16.9, and 16.10)

First-line anti-tubercular drugs	Second-line anti-tubercular drugs
Isoniazid	Streptomycin
Rifampicin	Amikacin
Rifapentine	Capreomycin
Ethambutol	Ethionamide
Pyrazinamide	Cycloserine
	p-amino salicylic acid
	Levofloxacin
	Moxifloxacin

Table 16.8 Dosing schedule of first-line anti-tubercular drug [80]

Medication	Adult dose	Children dose
Isoniazid (H)	5 mg/kg daily, max 300 mg 15 mg/kg TIW, max 900 mg	10–15 mg/kg daily 20–30 mg/kg intermittently
Rifampicin (R)	10 mg/kg daily, max 300 mg mg/kg TIW, max 300 mg	10–20 mg/kg daily or BIW
Pyrazinamide (Z)	20–25 mg/kg daily, max 2 g 30–40 mg/kg daily, max 3 g	15–30 mg/kg daily 40–50 mg/kg BIW
Ethambutol (E)	15–20 mg/kg daily, max 1600 mg 25–35 mg/kg TIW, max 2400 mg	15–20 mg/kg daily 50 mg/kg BIW

Table 16.9 Regimen of anti-tubercular drug

Regimen	Drugs	Duration (months)
Intensive phase	RHZE	2
Maintenance phase	RH	6

Table 16.10 Regimen of anti-tubercular dosing in special situations [80]

Special situation	Dosing
Elder patient	Same dose adjusted with weight
Renal insufficiency	Dose decreased if creatinine clearance >30 ml/mine
Hepatic insufficiency	Should avoid hepatotoxic drugs like isoniazid, rifampicin, and pyrazinamide
Pregnancy	Ethambutol and streptomycin are contraindicated due to teratogenic effect

16.4 Atypical Mycobacteria

16.4.1 Classification of Atypical Mycobacterium Species [87]

Rapid growing	Slow growing
Mycobacterium abscessus	*Mycobacterium avium intracellular complex*
Mycobacterium chelonae	*Mycobacterium haemophilum*
Mycobacterium fortuitum	*Mycobacterium kansasii*
	Mycobacterium marinum
	Mycobacterium scrofulaceum
	Mycobacterium ulcerans
	Mycobacterium xenopi
	Mycobacterium malmoense

16.4.2 *Cutaneous Manifestation of Atypical Mycobacterial Infection* (Table 16.11)

M. marinum: It causes swimming pool granuloma or fish tank granuloma at the site of inoculation mostly the trauma prone areas like extremities with finger being the commonest area [88, 89]. Cutaneous lesions include erythematous papules or pustules, nodules, verrucous plaques, or multiple granuloma with or without ulceration. In immunocompromised patients, there is disseminated lesions involving tendons,

Table 16.11 Treatment of atypical mycobacterial infection [95]

Species	Treatment
M. marinum	*Antibiotic therapy* 1. Tetracyclines monotherapy—Minocycline or doxycycline 100 mg BD till complete resolution 2. Clarithromycin 500 mg twice a day, rifampicin 600 mg daily, and ethambutol 25 mg/kg daily till complete resolution 3. Co-trimoxazole monotherapy 4. Streptomycin 5. Ethionamide *Other modalities* 1. Surgery, cryotherapy, electrode therapy, and irradiation 2. Co-trimoxazole effective
M. kansasii	1. Daily isoniazid (300–600 mg/day), rifampicin (600 mg/day), and ethambutol (15 mg/kg/day) for 18–24 months 2. Surgical debridement of the lesions combined with oral ethambutol, cycloserine, and rifampicin
M. abscessus	Clarithromycin 1000 mg/day for 12 months along with surgical debridement of localized disease
M. ulcerans	1. Rifampicin combined with amikacin (15 mg/kg IM twice daily) or streptomycin (15 mg/kg IM daily) with or without surgical therapy for 4 to 8 weeks 2. Clofazimine and cotrimoxazole
M. chelonae	1. Minocycline monotherapy 2. Surgical debridement combined with IV cefoxitin for 1 month and oral ciprofloxacin for 6 weeks
Mycobacterium Avium-Intracellulare	1. Three-times-weekly regimen [clarithromycin (1000 mg) or azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg)] 2. Daily regimen of clarithromycin (500–1000 mg) or azithromycin (250 mg), rifampicin (600 mg) or rifabutin (150–300 mg), and ethambutol (15 mg/kg) with consideration of three-times-weekly amikacin or streptomycin 3. Monotherapy with minocycline 100 mg twice a day Treatment should be given for 1 year
Mycobacterium Scrofulaceum	1. Quinolones, tetracyclines, and anti-tubercular drugs, such as isoniazid, rifampicin, and ethambutol 2. Clarithromycin monotherapy

bones, joints, and bursae. Histopathology shows nonspecific inflammation in most of the cases with granulomatous infiltrate in some. Healing occurs with scarring.

M. kansasii: Cutaneous lesions include papules and pustules which subsequently turn into verrucous or granulomatous plaques or nodules which can ulcerate. A sporotrichoid distribution and cellulitis like presentation may be seen [90]. Histopathology shows granulomatous inflammation with mixed inflammatory infiltrate, and acid-fast bacilli in histiocytes.

M. abscessus: Cutaneous lesions include erythematous papules, pustules, and ulcerated nodules mostly involving lower extremities, upper extremities, and trunk [91]. Histopathology shows nodular or granulomatous pattern [92].

M. ulcerans: More common in young patients with female preponderance. The lesion starts as a painless subcutaneous swelling commonly on legs and forearms that rapidly enlarges to form firm nodules which subsequently ulcerate [93, 94]. The ulcer is painless, shallow, necrotic and named as buruli ulcer. Granulomatous inflammation with predominant subcutaneous fat necrosis is usually found in histology.

M. chelonae: Multiple erythematous papules and nodules with draining fistulas appear in a non-contiguous and nonlinear pattern involving distal extremity. Histopathology shows suppurative granuloma without caseation [95].

M. fortuitum: The lesions appear at the surgical site or at the site of trauma in immunocompromised patients. Lesions can vary from painful nodules, abscesses, ulcers, draining sinus tracts, or cellulitis. Suspicion should arise when patients present with nonhealing furuncles on the lower extremity with history of recent procedure [96]. Histopathology of acute lesions shows suppurative granulomas without caseation and mixed infiltrate [95].

Mycobacterium Avium-Intracellulare: Cutaneous lesions appear as painful or painless subcutaneous nodules in the cervical, submandibular, submaxillary, or preauricular region [95]. The nodules are usually unilateral and may ulcerate discharging serosanguineous material. Granulomatous inflammation with presence of macrophages containing large numbers of acid-fast bacilli is found in histopathology [95].

Mycobacterium Scrofulaceum: Cutaneous lesions present as lymphadenitis with fistulas in submandibular or submaxillary region. Other variants include erythematous papules and ulcerated nodules [95]. Skin lesions also present as erythematous papules that slowly progress to ulcerated nodules. Histopathology shows central necrosis and abscess formation surrounded by tuberculoid granuloma with neutrophils, epithelioid histiocytes, and lymphocytes [95].

16.5 Mycetoma

Mycetoma is a chronic, granulomatous infection of the subcutaneous tissue, which gradually affects the deep structures and bone. Mycetoma can be due to bacteria (actinomycetoma) or fungi (eumycetoma) [97]. Male to female ratios are in the

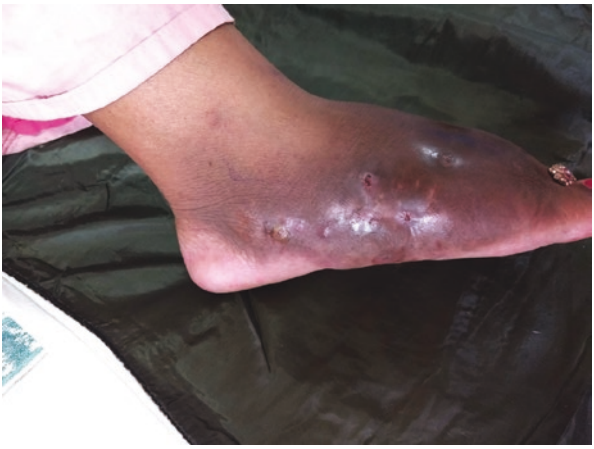

Fig. 16.9 Mycetoma in a female presenting with firm to hard pigmented swelling with multiple sinus

range of 1·6–6·6:1 both in children and adults [97]. The triad includes painless subcutaneous nodules, multiple sinus formation, and discharge of grains. The disease starts as a small subcutaneous nodule (at site of entry of the organism) which gradually spreads to other areas of the skin and deep structures along with sinus formation (Fig. 16.9). There is woody induration of skin and subsequently the solid mass causes deeper structure involvement resulting in deformity and loss of function [97].

Diagnosis of mycetoma is mostly clinical in endemic areas. However, ultrasound and fine needle aspiration can confirm the diagnosis easily. Grains are seen as sharp hyper-reflective echoes in USG. Cavities are seen in eumycetoma with or without acoustic enhancement, whereas in actinomycetoma, the grains are not distinct because of small size and absence of cement and found at the bottom of the cavities [98]. Examination of the grains under microscope can help in differentiating actinomycetoma and eumycetoma. Fine filaments which can take Gram stain are seen in actinomycetoma, whereas filaments of eumycetoma take periodic acid–Schiff stain. Grains can be inoculated in culture media to identify the specific organisms [97]. Histopathologic examination of mycetoma shows a marked inflammatory response, scarring, suppuration, ulceration, and epithelial hyperplasia. The inflammatory response surrounds the ball of organisms "grains". The morphology of grains often helps in differentiating eumycetoma and actinomycetoma.

Treatment of mycetoma depends upon causative organism. Small size mycetoma can be easily treated and has good prognosis. Actinomycetoma usually responds to prolonged medical treatment and eumycetoma requires prolonged antifungals along with surgical management. Currently, the first-line treatment for actinomycetoma includes 48 mg/kg/day of co-trimoxazole (trimethoprim and sulfamethoxazole in a ratio of 1:5) in cycles for 5 weeks and amikacin 15 mg/kg/day in a divided dose every 12 h for 3 weeks. The 2-week interval of amikacin in the 5-week cycle is used for renal and audiometric monitoring. Amongst the antifungals itraconazole gives relatively good results with lesion size reduction making the surgery less mutilating [99]. Terbinafine has limited efficacy in eumycetoma [100]. Other antifungals tried in eumycetoma with promising results include voriconazole, posaconazole, isavuconazole, and fosravuconazole [101, 102].

16.6 Leishmaniasis

Leishmaniasis is caused by *Leishmania donovani*. The animals (canines and rodents-zoonotic cycle) and humans act as reservoir of the organism. The disease is usually transmitted by sand fly (Lutzomyia and phlebotomus). A total of 12 million people are estimated to be infected worldwide and 2 million new cases are reported annually [103]. Leishmaniasis can be of cutaneous type and visceral type [104, 105] (Tables 16.12, 16.13, and 16.14).

Table 16.12 Clinical manifestations of Leishmaniasis [104, 105]

Disease type	Species	Clinical features
Visceral leishmaniasis	*Leishmania donovani*	Fever, weight loss, hepatosplenomegaly, lymphadenopathy, pancytopenia, bleeding hypergammaglobulinemia, skin pigmentation Death due to severe secondary infection
Post-kalazar dermal leishmaniasis	*Leishmania donovani*	Skin lesions around mouth and other parts of body Hypopigmented macules, nodular lesions
Cutaneous leishmaniasis	Most common type *Leishmania donovani*	Most common type Ulcerated or crusted papule
Leishmaniasis recidivans	*Leishmania tropica*	Tuberculoid lesions develop around scars of healed cutaneous ulcers
Diffuse cutaneous leishmaniasis	*L. mexicana* complex	Dissemination of skin lesions occurs over face and extremities, high parasite numbers due to poor cell-mediated immune response
Mucocutaneous leishmaniasis	*L. mexicana* complex	Mainly in south America. (espundia) Involve nose, oral cavity, and pharynx resulting in difficulty with eating, secondary infection

Table 16.13 Treatment modalities [106–110]

Local treatment	Systemic treatment
1. Local heat (37–43 degree) for 12 h in a day 2. Curettage 3. Cryosurgery—freezing with CO_2 snow 4. Intralesional—5% mepacrine and 5-aminolevulinic acid with photodynamic therapy, pentavalent antimony 1–2 ml 5. Topical imiquimod, 15% paromomycin in 12% methyl benzethonium chloride ointment	1. Sodium stibogluconate/meglumine antimonate (20 mg/kg body weight, max 850 mg) intravenously or intramuscularly till the lesion regresses clinically, usually takes 15–30 days 2. Pentamidine isethionate (4 mg/kg) once weekly until clinical regression (preferred for *L. aethiopica*) 3. Miltefosine—2.5 mg/kg/day bin two or three divided doses for 1–2 months 4. Lipoid amphotericin B—Preferred in resistant and destructive MCL (mucocutaneous leishmaniasis) 0.15–0.2 mg/kg/BW by drip infusion, if tolerated 50 mg over 6–8 h in 2–4 doses in a week for 6–17 weeks 5. Maesabalide III (isolated from Maesa balansae) 6. ketoconazole—400–800 mg/day for 4–8 weeks 7. Others—rifampicin, metronidazole, levamisole, dapsone, and chloroquine

Table 16.14 Cutaneous manifestations [111, 112]

Clinical feature	Causative agent	Initial lesion	Evolution
Schistosomal dermatitis	*S. haematobium*	Papular itchy eruption	Papules with central haemorrhage or vesiculation followed by crusting Heals by 1–3 weeks
Urticarial reaction (Katayama disease/ urticarial fever)	*S. japonicum* *S. mansoni*	Redish wheals Associated with fever, arthralgia, abdominal pain, hepatosplenomegaly	Cutaneous lesions include urticaria, purpura and transient oedema of face, limbs, genitalia
Paragenital fistulous tract	*S. haematobium* *S. japonicum* *S. mansoni*	Papular lesion	Progress to nodular, warty, vegetating or polypoidal mass Granulomatous mass with sinuses and fistulous tract Secondary lymphoedema, elephantiasis
Ectopic cutaneous schistosomiasis		Pruritic papules in paraumbilical area	Coalesce to oval plaques with scaly surface Older lesions ulcerate May have dermatomal distribution

16.7 Schistosomiasis

Schistosomiasis is caused by *S. haematobium* and *S. mansoni*. In childhood and adolescence, it presents with fever, haematuria, weakness, anaemia, weight loss, lower genital tract disease, poor growth, obstructive uropathy, liver cirrhosis, and delayed puberty. In adult females, *S. haematobium* causes liver cirrhosis, obstructive uropathy and *S. mansoni* leads to portal hypertension and gastro-intestinal obstruction.

Treatment of schistosomiasis

1. Praziquantel (drug of choice for all species)—40 mg/kg single dose in two divided doses 4–6 h apart
2. Oxamniquine (*S. mansoni*)—15 mg/kg single dose
3. Metrifonate (only against *S. haematobium*)—10 mg/kg three doses at 2 weekly intervals

16.8 Dracunculiasis/Guinea Worm

Dracunculiasis is caused by the agent "*Dracunculus medinensis" and transmitted by* crustaceans called copepods or water fleas which harbour inactive larvae. Ingested copepods are killed by digestive juice in stomach, the larvae are released and move to small intestine. They penetrate the intestinal wall and migrate to connective tissues of the thorax, where male and female larvae are released and mate

60–90 days after infection. Females mature and migrate to surface of body, where they form burrows in subcutaneous tissues. With maturity a blister is formed which eventually ruptures exposing worm. Systemic features include severe pruritus, pain, nausea, vomiting, diarrhoea, and dizziness. Worms emerge in the lower extremities, but also can appear in upper extremities, trunk, buttocks, and genitalia. No treatment or vaccine is available. The worm may be gently removed by rolling it over a stick with care of ulcer [113].

16.9 Onchocerciasis

Onchocerciasis is caused by *Onchocerca volvulus.* Skin lesions include hypo- or hyperpigmentation, skin atrophy, excoriation alone or in combination. Pruritus is caused by dead filaria left under skin after invasion of live parasite which produces scratching and acute popular skin eruption. Systemic symptoms include generalized body ache, joint pain, and poor vision. During pregnancy, there is rapid exacerbation of skin lesions and deterioration of papular and pustular lesions. Ivermectin once yearly for 10–15 years is given as treatment [114].

16.10 Lymphatic Filariasis

Lymphatic filariasis is caused by microfilaria of *Wuchereria bancrofti*, *Brugia malayi and Brugia timori* (Asia) [lymphatic dweller], *Onchocerca volvulus* [subcutaneous dweller]. Transmission occurs by *Culexquinque fasciatus*. Majority of patients have asymptomatic microfilaremia. Symptoms include fever, lymphadenitis in the form of inguinal swelling, and lymphoedema of legs. However, it can involve arms, breasts, and genitalia [115, 116]. Allergic response to organism can lead to vesiculobullous and urticarial lesions amongst the patients. Long-standing filariasis can be complicated with secondary infection, filarial abscess, chronic obstructive filariasis, and elephantiasis nostrosa. Treatment of filariasis includes diethylcarbamazine (DEC) for 12 days. Other drugs like ivermectin 12 mg, metrifonate 10–15 mg/kg every 14 days for 5–16 courses, levamisole (2.5 mg/kg/week), mebendazole (500 mg tid for 3 weeks), and doxycycline 200 mg/day for 4–6 weeks have been found to be useful. For lymphoedema limb elevation, exercises, skin and wound care, compression therapy, and surgery are being done [117–119].

References

1. Pandey KR. From health for all to universal health coverage: Alma Ata is still relevant. Glob Health. 2018;14(1):62. https://doi.org/10.1186/s12992-018-0381-6.
2. Amazigo U. Onchocerciasis and women's reproductive health: indigenous and biomedical concepts. Trop Dr. 1993;23(4):149–51.

3. http://www.who.int/neglected_diseases/en/. Accessed 18 January 2021.
4. Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: Review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis. 2009;3:e412.
5. Molyneux DH. The 'neglected tropical diseases': now a brand identity, responsibilities, context and promise. Parasit Vectors. 2012;5:23.
6. https://www.cdc.gov/globalhealth/ntd/diseases/index.html. Accessed 15 January 2021.
7. Yotsu RR. Integrated management of skin NTDs-lessons learned from existing practice and field research. Trop Med Infect Dis. 2018;3(4):120.
8. Engelman D, Fuller L, Solomon A, McCarthy J, Hay R, Lammie P, Steer A. Opportunities for integrated control of neglected tropical diseases that affect the skin. Trends Parasitol. 2016;32:843–54.
9. Mitja O, Marks M, Bertran L, Kollie K, Argaw D, Fahal AH, Fitzpatrick C, Fuller LC, Garcia IB, Hay R, et al. Integrated control and management of neglected tropical skin diseases. PLoS Negl Trop Dis. 2017;11:e0005136.
10. https://www.who.int/data/gho/data/indicators/indicator-details/GHO/number-of-new-leprosy-cases. Accessed 24 January 2021.
11. Galhotra A, Panigrahi SK, Pal A. Leprosy–a raging persistent enigma. J Family Med Prim Care. 2019;8:1863–6.
12. https://www.jfmpc.com/text.asp?2019/8/6/1863/261391. Accessed 15 January 2021.
13. Rao PN, Suneetha S. Current situation of leprosy in India and its future implications. Indian Dermatol Online J. 2018;9(2):83–9.
14. Shepard CC. The nasal excretion of Mycobacterium leprae in leprosy. Int J Lepr. 1962;30:10–8.
15. Martins AC, Miranda A, Oliveira ML, Bührer-Sékula S, Martinez A. Estudo da mucosa nasal de contatos de hanseníase, com positividade para o antígenoglicolipídiofenólico 1. Braz J Otorhinolaryngol. 2010;76:579–87.
16. Job CK. Nasal mucosa and abraded skin are the two routes of entry of Mycobacterium leprae. Star. 1990;49:1.
17. Ghorpade A. Inoculation (tattoo) leprosy: a report of 31 cases. J Eur Acad Dermatol Venereol. 2002;16:494–9.
18. Santos AR, Balassiano V, Oliveira ML, Pereira MA, Santos PB, Degrave WM, et al. Detection of Mycobacterium leprae DNA by polymerase chain reaction in the blood of individuals, eight years after completion of anti-leprosy therapy. Mem Inst Oswaldo Cruz. 2001;96:1129–33.
19. Melsom R, Harboe M, Duncan ME, Bergsvik H. IgA and IgM antibodies against Mycobacterium leprae in cord sera and in patients with leprosy: an indicator of intrauterine infection in leprosy. Scand J Immunol. 1981;14:343–52.
20. Pedley JC. The presence of M. leprae in human milk. Lepr Rev. 1967;38:239–42.
21. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A fivegroup system. Int J Lepr Other Mycobact Dis. 1966;34:255–73.
22. Cardama JE. Early lesions (indeterminate forms). In: Latapi F, Saul A, Rodriguez O, Malacara M, Browne SG, editors. Leprosy. Amsterdam: Excerpta Medica; 1980. p. 68–74.
23. Sarkar R, Pradhan S. Leprosy and women. Int J Women Dermatol. 2016;2(4):117–21.
24. Lastória JC, Abreu MA. Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects - part 1. An Bras Dermatol. 2014;89(2):205–18.
25. Dongre VV, Ganapati R, Chulawala RG. A study of mono-neuritic lesions in a leprosy clinic. Lepr India. 1976;48(2):132–7.
26. Pradhan S, Padhi T, Sirka CS, Nayak BP, Dash M. Clinico-epidemiological profile of pure neuritic Hansen's disease in western Odisha: a hospital based retrospective cross sectional study. Indian J Lepr. 2018;90:253–9.
27. Annigeri SR, Metgud SC, Patel JR. Lepromatous leprosy of histoid type: a case report. Indian J Med Microbiol. 2007;25:70–1.
28. Latapi F, Zamora AC. The spotted leprosy of Lucio: an introduction to its clinical and histopathological study. Int J Lepr Other Mycobact Dis. 1948;16:421–9.

29. Nery JAC, Sales AM, Illarramendi X, Duppre NC, Jardim MR, Machado AM. Contribuiçãoaodiagnóstico e manejo dos estadosreacionais: Uma abordagemprática. An Bras Dermatol. 2006;81(4):367–75.
30. Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. An Bras Dermatol. 2008;83:75–82.
31. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from North India. Int J Lepr Other Mycobact Dis. 2004;72:125–33.
32. Lockwood DN, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. Int J Lepr Other Mycobact Dis. 1999;67:6–12.
33. Nanda S, Bansal S, Grover C, Garg V, Reddy BS. Lazarine leprosy-revisited? Indian J Lepr. 2004;76:351–4.
34. Costa IMC, Kawano LB, Pereira CP, Nogueira LSC. Lucio's phenomenon: a case report and review of the literature. Int J Dermatol. 2005;44(7):566–71.
35. Prem Anand P, Oommen N, Sunil S, Deepa MS, Potturu M. Pretty leprosy: another face of Hansen's disease! A review. Egypt J Chest Dis Tuberc. 2014;63(4):1087–90.
36. Chandrashekar L, Kumari R, Thappa D, et al. Is it Lucio phenomenon or necrotic erythema nodosum leprosum? Indian J Dermatol. 2013;58(2):160.
37. Sehgal VN. Lucio's phenomenon/erythema necroticans. Int J Dermatol. 2005;44(7):602–5.
38. Duncan ME, Melsom R, Pearson JM, Ridley DS. The association of pregnancy and leprosy. I. New cases, relapse of cured patients and deterioration in patients on treatment during pregnancy and lactation- results of a prospective study of 154 pregnancies in 147 Ethiopian women. Lepr Rev. 1981;52(3):245–62.
39. Duncan ME, Pearson JM, Ridley DS, Melson R, Bjune G. Pregnancy and leprosy: the consequences of alteration of cell mediated and humoral immunity during pregnancy and lactation. Int J Lepr Other Mycobact Dis. 1982;50(4):425–35.
40. Jejeebhoy SJ, Sebastian MP. Actions that protect: promoting sexual and reproductive health and choice among young people in India. New Delhi: Population Council; 2003.
41. Sharma SC, Kumar B, Dhall K, Kaur S, Malhotra S, Aikat M. Leprosy and female reproductive organs. Int J Lepr Other Mycobact Dis. 1981;49(2):177–9.
42. Fleger J, Biric B, Prica S. Importance of leprosy in gynaecology and midwifery. Trop Dis Bull. 1963;60:446–7.
43. King JA, Marks A. Pregnancy and leprosy; a review of 52 pregnancies in 26 patients with leprosy. Am J Obstet Gynecol. 1958;76(2):438–42.
44. Bogush TG. The question of the menstrual function in women with lepromatous leprosy before pubescence. Sci Works Lepr Res Inst. 1976;9:116–8.
45. Khanna N, Singh M, Rasool S, Ammini A, Bhatla N, Garg V. Menstrual irregularities, fertility status, and ovarian function in female patients with leprosy in India. Int J Dermatol. 2014;53(9):1114–8.
46. Chacko CJ. Microbiology. In: Thangaraj RH, editor. A manual of leprosy. 4th ed. New Delhi: The Leprosy Mission; 1985. p. 43–60.
47. Ridley DS. Skin biopsy in leprosy. 2nd ed. Basle: Documenta-Giegy; 1985.
48. Murthy SV, Rao SM, Thejaswini A, Mannan K. De novo histoid leprosy. J Lab Phys. 2011;3(2):110–2.
49. Lockwood DN, Lucas SB, Desikan KV, Ebenezer G, Suneetha S, Nicholls P. The histological diagnosis of leprosy type 1 reactions: identification of key variables and an analysis of the process of histological diagnosis. J Clin Pathol. 2008;61:595–600.
50. Tripathy T, Panda M, Kar BR, et al. Facial lazarine leprosy in post-elimination era: a case report. Indian J Lepr. 2018;90:313–8.
51. Adhe V, Dongre A, Khopkar U. A retrospective analysis of histopathology of 64 cases of lepra reactions. Indian J Dermatol. 2012;57:114–7.
52. Vargas-Ocampo F. Diffuse leprosy of Lucio and Latapí: a histologic study. Lepr Rev. 2007;78(3):248–60.

53. Izumi S, Fujiwara T, Ikeda M, Nishimura Y, Sugiyama K, Kawatsu K. Novel gelatin particle agglutination test for serodiagnosis of leprosy in the field. J Clin Microbiol. 1990;28:525–9.
54. Buhrer-Sekula S, Smits HL, Gussenhoven GC, et al. Simple and fast lateral flow test for classification of leprosy patients and identification of contacts with high risk of developing leprosy. J Clin Microbiol. 2003;41:1991–5.
55. Sinha S, McEntergart A, Girdhar BK, Bhatia AS, Sengupta U. Appraisal of two Mycobacterium leprae-specific serological assays for monitoring chemotherapy in lepromatous (LL/BL) patients. Int J Lepr Other Mycobact Dis. 1989;57:24–32.
56. Chaturvedi V, Sinha S, Girdhar BK, Sengupta U. On the value of sequential serology with a Mycobacterium leprae-specific antibody competition ELISA in monitoring leprosy chemotherapy. Int J Lepr Other Mycobact Dis. 1991;59:32–40.
57. Duthie MS, Ireton GC, Kanaujia GV, Goto W, Liang H, Bhatia A, et al. Selection of antigens and development of prototype tests for point-of-care leprosy diagnosis. Clin Vaccine Immunol. 2008;15:1590–7.
58. Spencer JS, Duthie MS, Geluk A, Balagon M, Kim HJ, Wheat WH, et al. Identification of serological biomarkers of infection, disease progression and treatment efficacy for leprosy. Mem Inst Oswaldo Cruz. 2012;107:79–89.
59. Sengupta U. Recent laboratory advances in diagnostics and monitoring response to treatment in leprosy. Indian Dermatol Online J. 2019;10:106–14.
60. Venturini J, Soares CT, Belone Ade F, Barreto JA, Ura S, Lauris JR, et al. In vitro and skin lesion cytokine profile in Brazilian patients with borderline tuberculoid and borderline lepromatous leprosy. Lepr Rev. 2011;82:25–35.
61. Bang PD, Suzuki K, Phuong LT, Chu TM, Ishii N, Khang TH. Evaluation of polymerase chain-reaction based detection of Mycobacterium leprae for the diagnosis of leprosy. J Dermatol. 2009;36:269–76.
62. Marquees W, Barreira AA. Normal median nerve near potential. Braz J Med Biol Res. 1997;30:1431–5.
63. Samant G, Shetty VP, Upelkar MW, Antia NH. Clinical and electrophysiological evaluation of nerve function impairment, following cessation of multidrug therapy in leprosy. Lepr Rev. 1999;70:10–20.
64. Jain S, Visser LH, Praveen TL, Rao PN, Surekha T, Ramesh E, et al. High-resolution sonography: a new technique to detect nerve damage in leprosy. PLoS Negl Trop Dis. 2009;3:498.
65. Peters ES, Eshiet AL. Male–female (sex) differences in leprosy patients in south eastern Nigeria: females present late for diagnosis and treatment and have higher rates of deformity. Lepr Rev. 2002;73(3):262–7.
66. https://www.who.int/bulletin/volumes/89/7/10-085662/en/. Accessed 31 January 2021.
67. Salih MH, Landers T. The concept analysis of stigma towards chronic illness patient. Hos Pal Med Int J. 2019;3(4):132–6.
68. Ahmedani BK. Mental health stigma: society, individuals, and the profession. J Soc Work Values Ethics. 2011;8(2):41–416.
69. Le Grand A. Women and Leprosy: A Review. Lepr Rev. 1997;68:203–11.
70. World Health Organization. Lobal tuberculosis report 2017: Leave no one behind - Unite to end TB. 2017.
71. Pandhi D, Reddy BS, Chowdhary S, Khurana N. Cutaneous tuberculosis in Indian children: the importance of screening for involvement of internal organs. J Eur Acad Dermatol Venereol. 2004;18:546–51.
72. van Zyl L, du Plessis J, Viljoen J. Cutaneous tuberculosis overview and current treatment regimens. Tuberculosis. 2018;95:629–38.
73. Azulay RD, Azulay DR, Azulay DR. Dermatologia. 5th ed. Rio de Janeiro: Guanabara Koogan; 2011.
74. Bravo FG, Gotuzzo E. Cutaneous tuberculosis. Clin Dermatol. 2007;25:173–80.
75. Lai-Cheong JE, Perez A, Tang V, Martinez A, Hill V, Menagé HP. Cutaneous manifestations of tuberculosis. Clin Exp Dermatol. 2007;32:461–6.

76. Abebe F, Bjune G. The protective role of antibody responses during Mycobacterium tuberculosis infection. Clin Exp Immunol. 2009;157:235–43.
77. MacGregor RR. Cutaneous tuberculosis. Clin Dermatol. 1995;13:245–55.
78. Hu Y, Coates A. Non-multiplying bacteria are profoundly tolerant to antibiotics. Handb Exp Pharmacol. 2012;211:99–119.
79. Ramos-E-Silva M, Castro MCR. Cutaneous tuberculosis. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. 2th ed. New York: Mosby Elsevier; 2008. p. 1114–9.
80. Santos JB, Figueiredo AR, Ferraz CE, Oliveira MH, Silva PG, Medeiros VL. Cutaneous tuberculosis: diagnosis, histopathology and treatment - part II. An Bras Dermatol. 2014;89(4):545–55.
81. Concha M, Fch F, Rabagliati R, et al. Cutaneous tuberculosis: two case reports and review. Rev Infectol. 2011;28(3):262–8.
82. Vashisht P, Sahoo B, Khurana N, Reddy BS. Cutaneous tuberculosis in children and adolescents: a clinicohistological study. J Eur Acad Dermatol Venereol. 2007;21:40–7.
83. Singhal P, Patel PH, Marfatia YS. Lichen scrofulosorum: a diagnosis overlooked. Indian Dermatol Online J. 2012;3(3):190–2.
84. Frankel A, Penrose C, Emer J. Cutaneous tuberculosis: a practical case report and review for the dermatologist. J Clin Aesthet Dermatol. 2009;2:19–27.
85. Tyring A, Stephen K, Lupi A, Omar A, Hengge A, Ulrich R. Tropical dermatology. 2nd ed. Edinburgh: Elsevier; 2017.
86. Sharon V, Goodarzi H, Chambers CJ, Fung MA, Armstrong AW. Erythema induratum of Bazin. Dermatol Online J. 2010;16:1.
87. Rahama O, Thaker H. Atypical mycobacteria: an important differential for the general physician. Clin Med. 2013;13(5):504–6.
88. Kullavanijaya P. Atypical mycobacterial cutaneous infection. Clin Dermatol. 1999;17:153–8.
89. Van Seymortier P, Verellen K, De Jonge I. Mycobacterium marinum causing tenosynovitis. "Fish tank finger". Acta Orthop Belg. 2004;70(3):279–82.
90. Hsu PY, Yang YH, Hsiao CH, et al. Mycobacterium kansasii infection presenting as cellulitis in a patient with systemic lupus erythematosus. J Formos Med Assoc. 2002;101(8):581–4.
91. Tang P, Walsh S, Murray C, et al. Outbreak of acupuncture-associated cutaneous Mycobacterium abscessus infections. J Cutan Med Surg. 2006;10(4):166–9.
92. Prinz BM, Michaelis S, Kettelhack N, et al. Subcutaneous infection with Mycobacterium abscessus in a renal transplant recipient. Dermatology. 2004;208(3):259–61.
93. Gart GS, Forstall GJ, Tomecki KJ. Mycobacterial skin disease: approaches to therapy. Semin Dermatol. 1993;12:352–6.
94. Wagner D, Young LS. Nontuberculous mycobacterial infections: a clinical review. Infection. 2004;32:257–70.
95. Bhambri S, Bhambri A, Del Rosso JQ. Atypical mycobacterial cutaneous infections. Dermatol Clin. 2009;27(1):63–73.
96. Redbord KP, Shearer DA, Gloster H, et al. Atypical Mycobacterium furunculosis occurring after pedicures. J Am Acad Dermatol. 2006;54:520–4.
97. Zijlstra EE, van de Sande WWJ, Welsh O, Mahgoub ES, Goodfellow M, Fahal AH. Mycetoma: a unique neglected tropical disease. Lancet Infect Dis. 2016;16(1):100–12.
98. Fahal AH, Sheik HE, Homeida MM, Arabi YE, Mahgoub ES. Ultrasonographic imaging of mycetoma. Br J Surg. 1997;84:1120–2.
99. Fahal AH, Rahman IA, El-Hassan AM, Rahman ME, Zijlstra EE. The safety and efficacy of itraconazole for the treatment of patients with eumycetoma due to Madurellamycetomatis. Trans R Soc Trop Med Hyg. 2011;105:127–32.
100. N'diaye B, Dieng MT, Perez A, Stockmeyer M, Bakshi R. Clinical efficacy and safety of oral terbinafi ne in fungal mycetoma. Int J Dermatol. 2006;45:154–7.
101. Kloezen W, Meis JF, Curfs-Breuker I, Fahal AH, van de Sande WW. In vitro antifungal activity of isavuconazole against Madurellamycetomatis. Antimicrob Agents Chemother. 2012;56:6054–6.

102. Ahmed SA, Kloezen W, Duncanson F, et al. Madurellamycetomatis is highly susceptible to ravuconazole. PLoS Negl Trop Dis. 2014;8:e2942.
103. Okwor I, Mou Z, Liu D, Uzonna J. Protective immunity and vaccination against cutaneous leishmaniasis. Front Immunol. 2012;3:128.
104. Mohamed K, Narayani K, Arvidan K. Indigenous cutaneous leishmaniasis. Indian J Dermatol Venereol Leprol. 1990;56:228–9.
105. Kalla G, Singhi MK. Cutaneous leishmaniasis in Jodhpur District. Indian J Dermatol Venereol Leprol. 1996;62:149–51.
106. Currie MA. Treatment of cutaneous leishmaniasis by curettage. Br Med J. 1983;287:1053–6.
107. Leibovici V, Arman H. Cryotherapy in acute cutaneous leishmaniasis. Int J Dermatol. 1986;25:473–5.
108. Ramesh V, Katara GK, Verma S, Salotra P. Miltefosine as an effective choice in the treatment of post-kala-azar dermal leishmaniasis. Br J Dermatol. 2011;165:411–4.
109. Dogra J, Lal BB, Mishra SN. Dapsone in the treatment of cutaneous leishmaniasis. Int J Dermatol. 1986;25:398–400.
110. Kjetland EF, Leutscher PD, Ndhlovu PD. Trends Parasitol. 2012;28:58–65.
111. Milligan A, Burns DA. Ectopic cutaneous schistosomiasis and schistosomal ocular inflammatory disease. Br J Dermatol. 1988;114:793–8.
112. Mahmoud AAF. Praziquantel for the treatment of helminthic infections. In: Stollerman GH, editor. Advances in internal medicine. Chicago: Year Book Medical Publishers; 1987. p. 419–34.
113. https://www.cdc.gov/parasites/guineaworm/disease.html. Accessed 13 February 2021.
114. https://www.cdc.gov/parasites/onchocerciasis/index.html. Accessed 13 February 2021.
115. Dondero TJ, Bhattacharya NC, Black HR. Clinical manifestations of Bancroftian filariasis in suburbs of Calcutta (India). Am J Trop Med Hyg. 1976;25:64–73.
116. Saran R, Sanyal RK. Diurnal variation in eosinophil count and vacuolation of eosinophils in tropical eosinophilia. Indian J Chest Dis. 1971;15:209–13.
117. Moulia JP. Combination ivermectin plus diethylcarbamazine a new effective tool for control of lymphatic filariasis. Trop Med Parasitol. 1995;46:9–12.
118. Goodwin LG. Recent advances in research on filariasis: chemotherapy. Trans R Soc Trop Med Hyg. 1984;78:1–8.
119. https://www.cdc.gov/parasites/lymphaticfilariasis/treatment.html. Accessed 13 February 2021.

Chapter 17
Vulvar Disorders

Athota Kavitha

Normal vulva in various age groups:

In infants labia minora are poorly developed and vestibule is more exposed.

At puberty labia majora and mons pubis become more prominent due to deposition of fat. Pubic hair grows. Lactobacilli increase giving a normal vaginal acidic pH of 4.5.

Pregnancy: Increased pigmentation of the vulvar structures is noted. Venous distension leading to vulvar varicosities is common in pregnancy due to increased progesterone levels.

Menopause: External genitalia atrophy due to loss of subcutaneous fat. Hair growth is reduced. Due to lowered estrogen levels there is dryness.

17.1 Clinical Examination

Common vulvar symptoms are pruritus, pain, burning, soreness, dysuria, and dyspareunia. Good history taking is important for diagnosis and management of vulvar disorders. Menstrual history, vaginal discharge, hygiene or clothing habits, are relevant to vulvar area. Single or married, sexually active or not, any associated diseases like diabetes, thyroid disorders, previous surgical history, etc. are taken into consideration.

Signs of vulvar diseases are often subtle and atypical compared to the classic cutaneous presentations. Entire anogenital area should be examined, vulva is inspected for any erythema, papules, plaques, swelling, hypo- or hyperpigmentation, lichenification, atrophy, erosions, ulcers, architectural changes, scarring, etc.

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17.2 Investigations

After thorough clinical history and physical examination few investigations are needed to evaluate vulvar pruritus. A pH strip test, bacterial swabs, Tzanck smear, fungal scrapings, cultures, KOH mount are helpful in diagnosing infections.

Dermoscopy: Dermoscopy is a noninvasive tool that aids to support the diagnosis and helps to avoid biopsy. With the help of dermoscopic photographs course of the disease can be monitored and response to treatment can be assessed. In genital areas to avoid contamination the glass plate of the dermoscope is cleaned with isopropyl alcohol and protected by a thin plastic cling film.

Biopsy: Punch or excision biopsy is usually preferred. 3 or 4 mm punch is adequate. Biopsy is done after injecting local anesthetic like 1–2% lidocaine or under topical EMLA. Site selection is key in doing a vulvar biopsy. Edge of the lesion is biopsied in ulcerative lesion, darkest area in a pigmented lesion and in case of erosion intact skin at the edge of the erosion is biopsied. Multiple morphologies may need multiple biopsies. Biopsy is done in cases when diagnosis is uncertain, or when there is no response to treatment with presumptive diagnosis or in cases suspecting malignancy.

17.3 Normal Variants

There are few normal variants of the vulva which do not require treatment and the clinicians should be aware of these conditions to give reassurance to the patients.

Fordyce spots: Fox-Fordyce disease is a rare disorder which occurs due to obstruction of the apocrine sweat duct. Small painless white or yellowish spots of 1–3 mm size are seen along the inner aspects of labia minora and edge of the clitoris. Treatment is not required.

Vestibular papillomatosis: These are papillary growths of vestibular mucosa located within Hart's line. They are often diagnosed as condylomata. They are finger-like projections in the central margin of vulvar vestibule.

Epidermoid cysts: They are multiple cysts resulting from implantation of superficial epidermal tissue into dermis or subcutis following trauma of childbirth or episiotomy.

Vulvar varicosities: They are common in pregnant women (Fig. 17.1) and also seen in women with varicose veins of pelvis and lower extremity. They usually present with vulvar edema or fullness or pain in the genital area. Occasionally seen in older women due to prolonged standing. Applying ice or heat to the area, wearing supportive underwear, and sleeping on the left side to avoid pressure on the vena cava are few measures during pregnancy. They subside on their own after delivery.

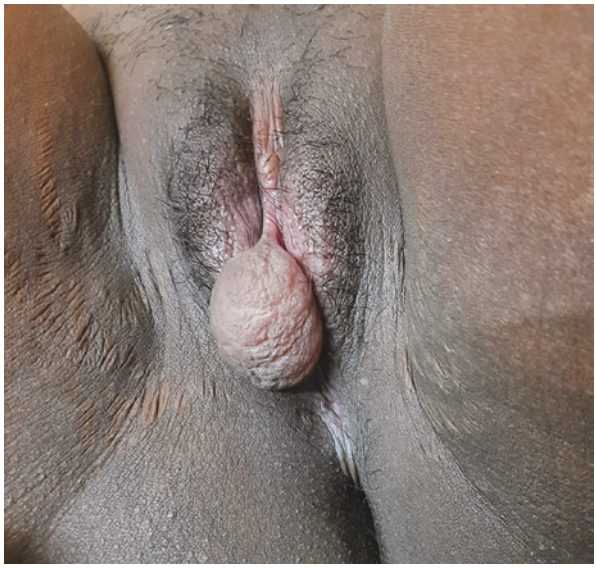

Fig. 17.1 Vulval varicosities at 20th week gestation

17.4 Vulvar Dermatoses

Infections:

Bacterial: Staphylococci causing folliculitis, Bartholin's abscess, toxic shock syndrome

Streptococci causing necrotizing fasciitis

Tuberculosis of the vulva

Fungal: Candidal vulvovaginitis, Tinea cruris

Viral: Herpes simplex, Molluscum contagiosum, Genital warts

Inflammatory dermatoses:

Lichen sclerosus, Lichen planus, Lichen simplex chronicus, Psoriasis, Plasma cell vulvitis

Eczematous disorders:

Atopic eczema, Seborrheic dermatitis, Contact dermatitis, Urticaria

Pigmentary disorders:

Vitiligo, Dowling Degos disease, Lentigines, Acanthosis nigricans

Bullous disorders:

Pemphigus, Hailey-Hailey, Bullous pemphigoid, Fixed drug eruption, Stevens–Johnson syndrome, Toxic epidermal necrolysis

Ulcers:

Aphthous ulcers, Lipshultz ulcers, Behcet's disease

Benign lesions:

Acrochordon, Angiokeratomas, Syringomas, Lymphangioma circumscriptum

Premalignant disorders:

Bowenoid papulosis, Vulvar intraepithelial neoplasia, Paget's disease

Malignancies:
Squamous cell carcinoma, Basal cell carcinoma, Malignant melanoma
Miscellaneous:
Hidradenitis suppurativa, Crohn's disease, Vulvodynia

The common vulvar diseases (non-venereal) which we see often are discussed here.

17.5 Infections

The two most common vulvar infections are bacterial vaginosis and candidiasis.

Bacterial Vaginosis: Bacterial vaginosis is a common condition caused by overgrowth of organisms present as normal vaginal flora. Unpleasant fishy odor after contact with semen during intercourse is the characteristic feature. Amsel's diagnostic criteria [1] are white discharge, vaginal pH 4.5, clue cells on direct microscopy, and fishy odor with addition of 10% KOH. This condition is to be differentiated from bacterial vaginitis caused by group B Streptococci presenting with inflammatory features of irritation, rawness, soreness, and dyspareunia.

Treatment: Oral metronidazole 500 mg twice a day for 1 week or 2 g single dose are the standard therapies. Topical metronidazole twice daily insertion or clindamycin 2% vaginal cream are effective therapies.

17.6 Vulvovaginal Candidiasis

The most common cause of vulvovaginal pruritus is candidiasis. Candida albicans is responsible for 90% of the cases. The lesions usually involve the genitocrural folds (Fig. 17.2). Erythema, excoriations, edema, white cottage cheese-like discharge, and satellite pustules are the common presenting features. The pustules break easily leaving small erosions with peripheral collarette of scales. Linear fissures can occur in the creases when intertriginous folds are involved. Diabetes, immunosuppressive states, and prolonged use of topical steroids are the aggravating factors for candidiasis. The differentials to be considered are pruritic conditions like licen simplex chronicus (LSC), contact dermatitis, lichen sclerosus (LS), and psoriasis. Coexistence of candidiasis with these dermatoses is common. Non-albicans Candida causes burning hence it has to be differentiated from erosive lichen planus (LP)

Diagnosis: KOH mount to detect the fungal spores and mycelia from the vulvar skin scrapings or from discharge supports the diagnosis. Candida culture is done in chronic, recurrent cases and in unresponsive cases.

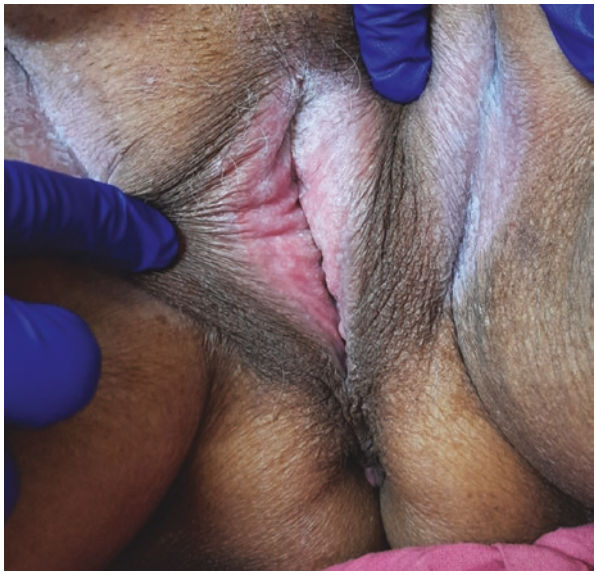

Fig. 17.2 Candidiasis with redness, discharge, and involvement of genitocrural folds

Treatment: Topical and oral azoles are the frequently used drugs. Uncomplicated vulvovaginal candidiasis (VVC) is treated with Clotrimazole 1%, Miconazole 1% creams for 7–14 days, Fenticonazole 2% cream for 7 days, Butoconazole and Terconazole are used as intravaginal creams. Clotrimazole, Miconazole, Econazole, and Nystatin are available as vaginal pessaries [2]. Systemic therapy with Fluconazole 150 mg single dose, Ketoconazole 200 mg bd or 400 mg for 5 days or Itraconazole 400 mg single dose are recommended. In recurrent VVC, Fluconazole 150 mg weekly, Ketoconazole 100 mg daily, Itraconazole 100 mg daily, and Boric acid vaginal pessaries are continued for 6 months. Resistance to treatment is common with nonalbicans species.

17.7 Bacterial Infections

Staphylococcus aureus causes folliculitis, furunculosis, and abscesses in the vulvar region. It also causes acute infection of the Bartholin's duct causing Bartholin's abscess.

17.7.1 Contact Dermatitis

Contact dermatitis is a common cause of vulvar pruritus. It can be due to exogenous irritants or allergens.

Irritant contact dermatitis: Common irritants are body fluids like urine, sweat, semen, faeces, and vaginal secretions Feminine hygiene products like depilatories, douches, lubricants, deodorants, bubble baths, soaps can also cause irritant contact dermatitis.

Excessive washing, tight clothing, sanitary pads, spermicides, condoms, over the counter anti-itch creams and topical medications are also few causes. Podophyllin, cantharidin, and fluorouracil are strong irritants.

Allergic contact dermatitis: Common vulvar allergens are local anesthetics—lidocaine, benzocaine, topical antibiotics—neomycin, polymyxin, antiseptics—chlorhexidine, gentian violet, preservatives in creams and hygiene products, antifungal creams like imidazoles, nystatin and fragrances. Patch testing is of use in diagnosing allergic contact dermatitis [3].

Pruritus, pain, soreness, and burning are the presenting symptoms. Acute stage manifests as erythema, edema, and vesicles leading to erosions and ulceration. Subacute and chronic stages manifest as erythematous patches and plaques with scaling and excoriations (Fig. 17.3).

Acute contact dermatitis should be differentiated from candidiasis, herpes simplex, erosive LP, pemphigus, and fixed drug eruption. Chronic forms are differentiated from psoriasis, LSC, and candidiasis. Biopsy shows spongiotic epidermis in both forms.

Treatment: All the allergens and irritants are to be discontinued. Educating the patient is important. They are advised to wear loose clothing and avoid soap, cleansers, douches, etc. Plain petrolatum can be applied as emollient. Topical steroids in

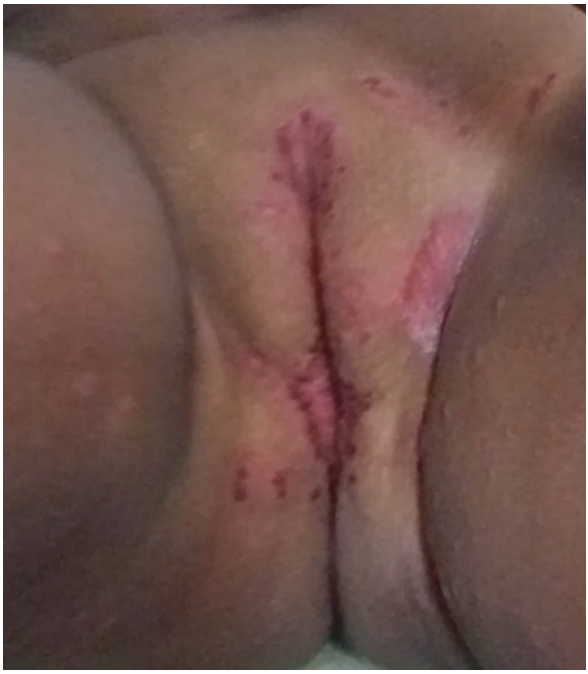

Fig. 17.3 Irritant contact dermatitis in a 6-year-old girl

ointment form are used to control the inflammation. In severe cases, systemic steroids like prednisolone 0.5–1 mg/kg/day with gradual tapering are advised. Antihistamines are used to treat the pruritus. Antibiotics are used to treat the secondary infection.

17.7.2 Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) results from chronic scratching of the vulva and is seen commonly in young and middle aged women. It is considered as localized chronic variant of atopic dermatitis—Primary LSC [4]. Secondary LSC develops on itchy vulvar dermatoses like eczema, psoriasis, lichen sclerosus, or fungal infections.

Clinical features: LSC presents with intense itching which is more severe at night and has been present for months or years. Premenstrual exacerbation of itching is common. Continued irritation caused by rubbing leads to the itch-scratch-itch cycle. Thickened plaques with accentuated skin markings and hair loss are seen unilaterally or bilaterally. Excoriations, ulcerations, and darkening of the skin are seen in chronic cases. Heat, sweating, friction, tight clothing, sanitary pads, and topical medications are the aggravating factors.

Diagnosis: Underlying conditions like candidiasis, contact dermatitis, psoriasis, and lichen sclerosus are to be ruled out. Bacterial and fungal cultures are done to diagnose secondary infections. Biopsy shows hyperkeratosis, hypergranulosis, acanthosis, spongiosis, and a chronic inflammatory infiltrate.

Treatment: Topical potent steroids help to break the itch-scratch cycle. Topical Xylocaine 2% jelly and topical Doxepin are also useful. Sedative antihistamines and tricyclic antidepressants like amitriptyline and doxepin 2 h before bedtime are effective.

17.7.3 Lichen Planus

Lichen planus (LP) affects the vulva along with other mucous membranes, skin, and nails. It is a T-lymphocyte-mediated inflammatory disorder. Association with other autoimmune disorders is also seen.

Pain, pruritus, soreness, and dysuria are the common symptoms of vulvar LP.

Three forms of vulvar LP are classic, hypertrophic, and erosive form.

In the classic papulosquamous form papules and Wickham's striae are seen in the inner aspects of labia and clitorial hood (Fig. 17.4).

Hypertrophic form affects the labia majora, perineum, and perianal area. It has greatest risk of malignancy.

Erosive form is the most severe form of vulvar LP and leads to scarring and adhesions of the labia minora and vulvar trigone causing dyspareunia. Erosive form involves the vagina leading to purulent discharge. Synechiae formation and scarring

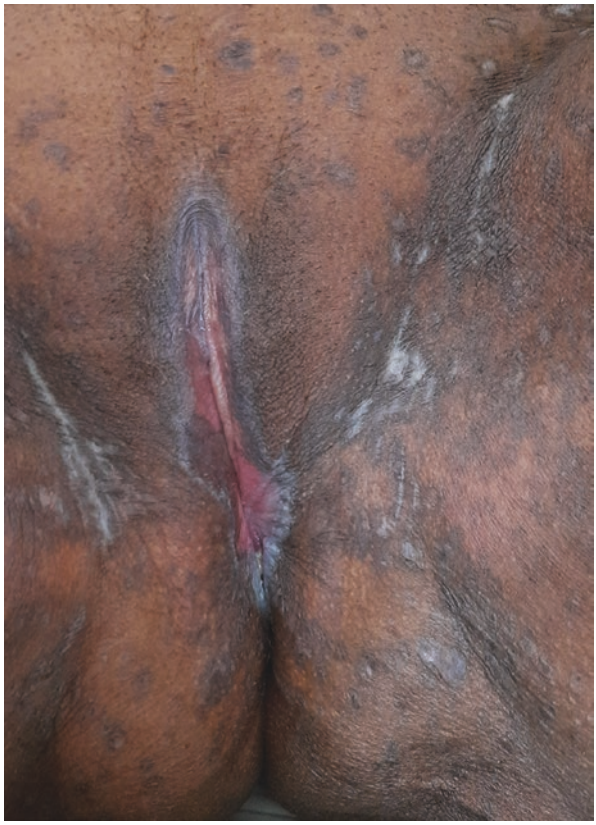

Fig. 17.4 Lichen planus: Lacy pattern and violaceous pigmentation

due to delay in the diagnosis can be extensive leading to significant impact on the sexual function and the quality of life.

Involvement of vulva, vagina, and the oral mucosa leads to vulvovaginal gingival syndrome or Hewitt–Pelisse syndrome which is considered as a variant of erosive LP [5].

Erosive LP should be differentiated from LS, cicatricial pemphigoid, pemphigus, vulvar intraepithelial neoplasia, plasma cell vulvitis, and genitourinary syndrome of menopause (atrophic vaginitis).

Dermoscopy: Wickham's striae with various patterns like reticular, dotted, starry skin, rounded or globular are the hallmark of vulvar LP. Thick linear irregular vessels are also seen in vulvar LP [6].

Biopsy: Histopathology of erosive LP shows thinned out epidermis with parakeratosis, presence of basal layer hydropic degeneration with civatte body formation and predominance of plasma cells in the band-like infiltrate in the upper dermis.

Treatment: The first line of treatment is ultrapotent steroid clobetasol propionate. It resolves the symptoms in more than 90% of patients. Hydrocortisone foam is a better method of delivering steroid in case of vaginal LP. Hydrocortisone

suppositories 25 mg inserted into the vagina twice daily for 2 months are used in vaginal LP. Topical calcineurin inhibitors are also effective. Erosive and hypertrophic forms require long-term treatment. Systemic steroids, methotrexate, mycophenolate mofetil, cyclosporine, and azathioprine are all tried as in cutaneous LP with variable results. Adhesions and synechiae formation needs surgical treatment in experienced hands. Dilator therapy is effective for distending mild to moderate vaginal synechiae. Early diagnosis and treatment are very important to prevent these complications. Risk of squamous cell carcinoma in patients with vulvar LP is postulated in few studies but not confirmed [7].

17.7.4 Lichen Sclerosus

Lichen sclerosus (LS) is one of the commonest chronic inflammatory disorders of vulva. It has a bimodal peak of incidence one in the prepubertal and second in the postmenopausal age group.

The cause of LS is unknown but multiple etiologies are proposed.

Genetic-HLA class II antigen associated particularly HLADQ7 [8].

Infections-Borrelia burdorferi

Autoimmune-Autoimmune dysfunction of extracellular matrix protein1 (ECM1) found at the dermoepidermal junction is implicated in the pathogenesis of LS. Along with ECM1 various other genetic and immune targets like upregulation of miR-155, TNF, IL-6, galectin-7, collagen (type I, II, and V), and p53 showed enhanced expression [9] in LS patients. LS is associated with autoimmune thyroiditis, pernicious anemia, vitiligo and alopecia areata.

Clinical features: Pruritus is the main presenting complaint, but depigmentation, dysuria, dyspareunia, and constipation are also seen. Ivory white atrophic plaque with wrinkled cigarette paper like appearance is pathognomonic of Lichen sclerosus. The lesions are usually symmetrical seen on the inner aspects of labia majora, minora, clitoris, and perineum. Perianal area can be involved giving a "figure of eight" appearance (Fig. 17.5). Ecchymosis, purpuric spots, erosions, and ulcers can be seen (Fig. 17.6). As the disease progresses, there is loss of normal morphology. Scarring with labial resorption, burying of clitoris, and narrowing of introitus are noted (Fig 17.7). In children, ecchymosis is striking and mistaken for sexual abuse. Other clinical features are similar to that in adult. Dermoscopy is useful in pediatric LS where biopsy cannot be done.

Dermoscopy: Dermoscopic features correspond to sclerosis and hyalinization which are the main pathologic changes in LS. Dotted vessels are observed in the early stage. Patchy structureless areas, white-yellowish in color over a white background were a constant dermoscopic feature [6].

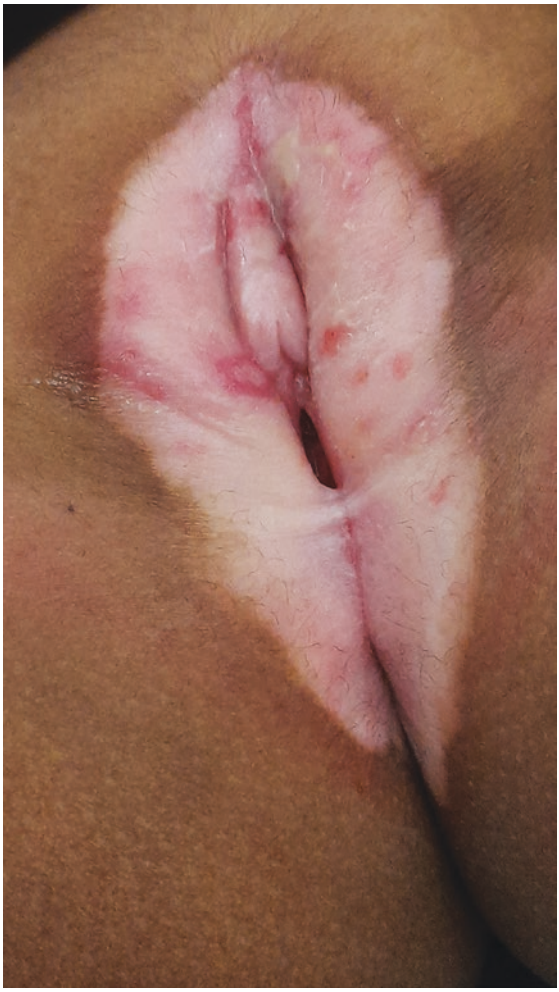

Fig. 17.5 Lichen sclerosus with ecchymosis and hyperkeratosis

Histopathology: Thinned epidermis with hyperkeratosis, a wide band of homogenized collagen beneath the dermoepidermal junction, and a lymphocytic infiltrate beneath the homogenized area are the classical features of uncomplicated LS [10].

Vitiligoid LS: The cases with clinical appearance of vitiligo and histological features of LS were considered as vitiligoid LS.

Lichen sclerosus should be differentiated from LP, LSC, psoriasis, vitiligo, morphea, and VIN. Persistent indurated plaque, hyperkeratotic area, or an ulcer should be biopsied. Risk of developing malignancy in LS is 3.5–5% [11]. However, in well-controlled cases malignancy risk is much less.

Fig. 17.6 Lichen sclerosus with figure of eight pattern involving the perianal area

Treatment: Clobetasol propionate ointment once daily for a month, alternate day for 1 month is the first-line treatment for LS. Mometasone furoate is also equally effective. Topical tacrolimus and pimecrolimus are also used mainly for maintenance. Intralesional steroids, phototherapy (UVA1), systemic drugs like methotrexate, cyclosporine, and hydroxyurea are also tried with few reports [12].

Follow-up: It should be according to the patient need. Initial follow-up at 3 months,6 months, and then annually till the disease is under control. In cases of persistent rawness or thickening of the skin, a repeat biopsy is advised. In childhood LS long-term follow-up is required.

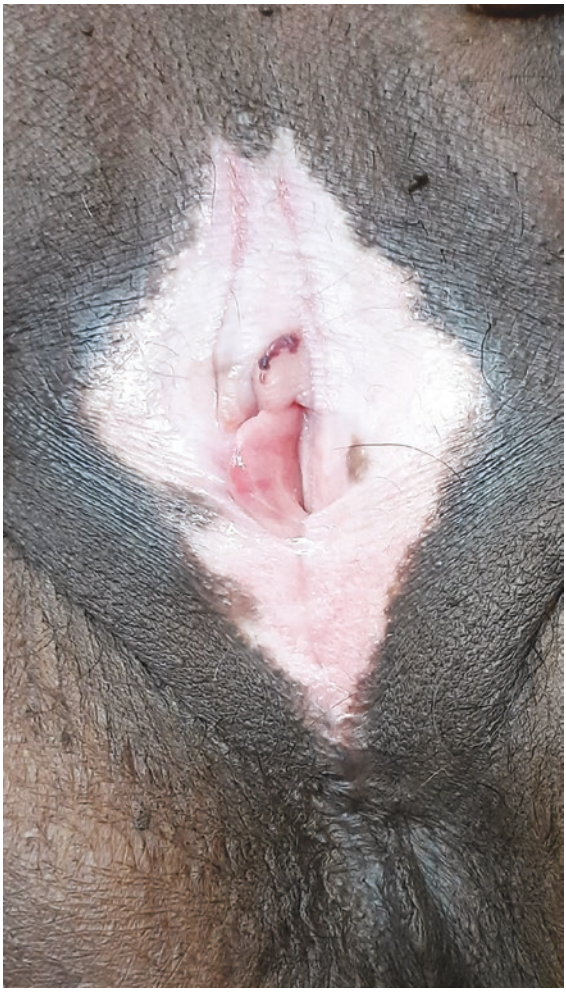

Fig. 17.7 End stage LS with resorption of labia and narrowing of introitus

17.7.5 Psoriasis

Psoriasis is a chronic relapsing inflammatory dermatosis. Genital psoriasis presents as part of plaque psoriasis or flexural psoriasis or rarely limited to that area. The appearance is different from the classical psoriasis due to the warmth, moisture, and friction in that area leading to maceration, fissuring, and absence of scaling. Impetigo herpetiformis is psoriasis of pregnancy which can affect the vulva.

Clinical features: Pruritus, burning sensation, and soreness are the presenting symptoms. Symmetrical, well-demarcated, erythematous lesions affecting the hair bearing areas like mons pubis, labia majora are seen (Fig. 17.8). Biopsy is confirmatory.

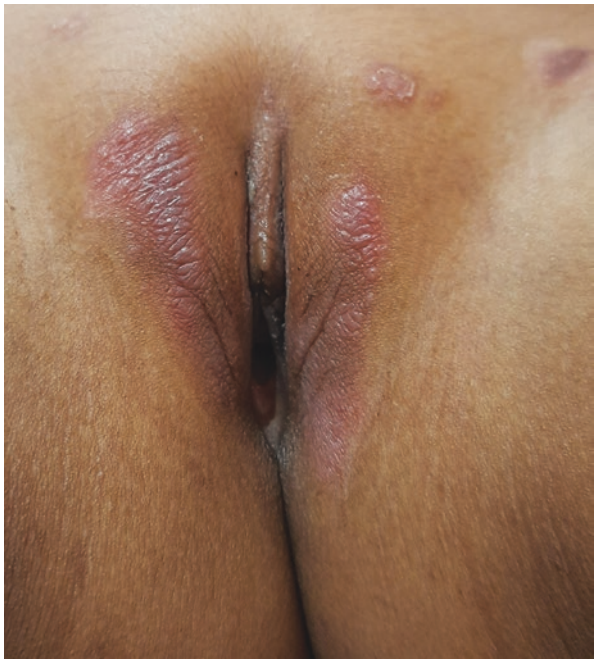

Fig. 17.8 Psoriasis of the vulva with scaly plaques

Dermoscopy: Genital lesions lack scaling and show a light red background. Psoriasis lesions have dilated and tortuous capillaries with typical "bushy" homogenous or dotted vessels with a uniform and regular arrangement [6].

Treatment: Low to medium strength topical steroids are the first-line treatment. Vitamin D analogues either as monotherapy or mixed with steroids are the second line. Topical tacrolimus or pimecrolimus are also used [13]. Severe extensive disease needs systemic therapies like methotrexate, cyclosporine, and mycophenolate mofetil.

17.7.6 Plasma Cell Vulvitis

This is a rare inflammatory disorder of the vulva also known as zoon's vulvitis. It is commonly seen in the postmenopausal women. Etiology is unknown but various causes like trauma, viral, autoimmune and hormonal factors are proposed [14].

Clinical features: Common symptoms are pruritus, burning pain, and dyspareunia or it can be asymptomatic. Erythematous plaques either single or multiple, bilateral and symmetrical are seen on the inner aspects of labia minora and periurethral mucosa. Purpuric cayenne-pepper spots are characteristic of zoon's vulvitis. It should be differentiated from LP, VIN, LS, FDE, Candidiasis, and Paget's disease of the vulva.

Histopathology: Epidermis is atrophic. Dermis shows predominantly plasmocytic infiltrate along with vascular proliferation, erythrocyte extravasation, and hemosiderin deposition.

Treatment: Topical steroids, topical calcineurin inhibitors, imiquimod cream, topical misoprostol, CO2 laser ablation, and surgical resection are various modes of treatment.

17.8 Pigmentary Disorders

17.8.1 Vitiligo

Vitiligo is an acquired pigmentary disorder due to loss of melanocytes. Well-defined, symmetrical lesions without textural changes are characteristic of vitiligo. Labia majora and inguinal folds are commonly involved. It can be genital vitiligo or as a part of vitiligo vulgaris involving the vulval area. As autoimmune etiology is proposed, it can be associated with other autoimmune disorders. Differentiation from Lichen sclerosus is often difficult mainly in pediatric patients. Dermoscopy is helpful in such cases.

Dermoscopy: Well-demarcated, dense glowing, white areas are the main feature for diagnosing vitiligo. Perifollicular pigmentation and leukotrichia are specific for vitiligo and is the differentiating feature from other depigmenting disorders [15].

Biopsy: Absent or decrease in melanin pigment and interface dermatitis are seen in vitiligo.

Treatment: Topical steroids, topical calcineurin inhibitors, topical calcipotriol are used. Excimer laser is also tried with variable results.

17.8.2 Acanthosis Nigricans

Acanthosis nigricans (AN) presents as thickened, hyperpigmented velvety skin of the flexures. It can involve any area but predominant in the genitocrural area and the labia majora. Plaques with warty texture and skin tags are seen. AN is associated with insulin resistance, in adults it can be a cutaneous sign of underlying malignancy [16]. Rapid progression is the feature in malignant cases. The most common malignancy is adenocarcinoma of the gastrointestinal tract especially stomach in 55% of cases [17].

AN should be differentiated from pseudoacanthosis nigricans seen in obese individuals and is related to friction and moisture. Biopsy is diagnostic and shows hyperkeratosis and papillomatosis. There is no increase in melanocytes. Endocrine evaluation to see for insulin resistance is required.

Treatment: Weight reduction and treatment of hyperinsulinemia helps. Topical keratolytics, retinoids, and laser treatment are tried but irritation caused by them should be taken care.

17.8.3 Benign Lesions

Fox–Fordyce disease: Uncommon pruritic disorder affecting the apocrine sweat glands. Pale, white or yellow spots of 1–3 mm diameter are seen on the labia. Reassuring the patient about the benign nature is enough but electrodessication and CO_2 laser are tried if necessary.

Syringomas: Syringomas are small benign lesions of the eccrine sweat glands. They can be asymptomatic or pruritic. They present as skin colored or yellowish papules on the labia. Electrodessication or CO_2 laser can be done in symptomatic cases.

Angiokeratomas: Angiokeratomas are benign vascular proliferations with hyperkeratosis on the surface. Erythematous or skin colored papules affect women between 20 to 40 years. Dermoscopy shows multiple lacunae of different colours that vary from red to bluish red, bluish-white and a peripheral white area. It is useful to differentiate from other benign conditions of the vulva. Often they are asymptomatic or may present with dyspareunia and bleeding. Treatment with radiofrequency cautery, chemical cautery, cryotherapy, or surgical excision can be done [18].

Lymphangioma circumscriptum: Lymphangioma circumscriptum is a benign lymphatic malformation caused by dilatation of lymphatic vessels in the skin and subcutaneous tissue. Small clusters of clear white fluid filled vesicles are seen on the labia (Fig. 17.9). Often asymptomatic but may cause edema, psychosexual dysfunction and cosmetic concern. Their clustered appearance on a smooth skin is compared to frog spawn. They are confused with genital warts, molluscum contagiosum,

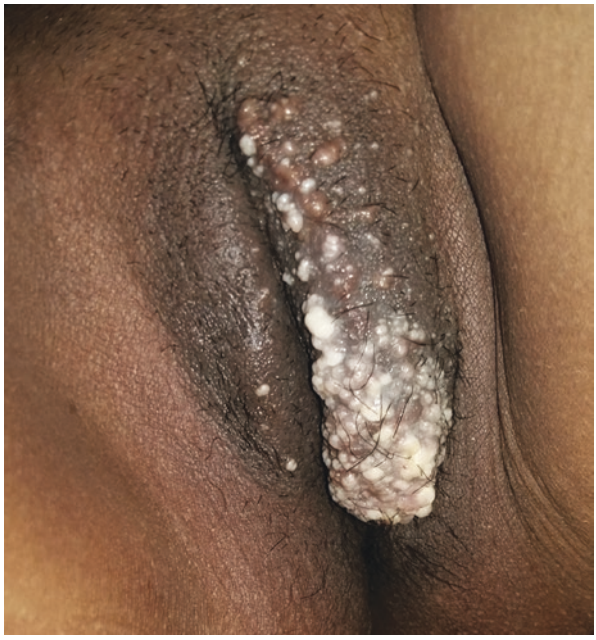

Fig. 17.9 Lymphangioma circumscriptum

and angiokeratoma. Biopsy aids in confirming the diagnosis by showing numerous dilated lymphatic channels in the epidermis and papillary dermis. Treatment is surgical removal, electrodessication, vaporization with CO_2 laser, sclerotherapy, and topical imiquimod 5% cream. Even with the best option recurrences are common.

17.9 Premalignant Conditions of the Vulva

17.9.1 Vulvar Intraepithelial Neoplasia

Vulvar intraepithelial neoplasia (VIN) is a non-invasive precursor of squamous cell carcinoma. International Society for Study of Vulvar Diseases (ISSVD) classified VIN as usual type and VIN differentiated type [19].

VIN usual type (uVIN) or High grade squamous intraepithelial lesion (HSIL)

It is further divided as—VIN warty type, basaloid type, and mixed type (warty/basaloid).

uVIN is Human Papilloma Virus (HPV) driven, affects younger women (third to fifth decade) and is a multicentric disease. HPV 16 is the common type followed by HPV 33. Smoking, multiple sexual partners, and immunosuppression are the risk factors for uVIN.

VIN differentiated type (dVIN) It occurs mostly in postmenopausal women in the sixth to eighth decade and is often associated with Lichen sclerosus or Lichen planus. It is mostly unifocal (Table 17.1).

Clinical Features: VIN may be asymptomatic or present with pruritus, pain, or dysuria. uVIN presents as raised well-demarcated asymmetrical whitish or erythematous plaques. dVIN may appear as gray-white discoloration with roughened surface or as an ill-defined plaque or ulcer (Fig. 17.10).

Table 17.1 Differences between usual and differentiated types of vulvar intraepithelial neoplasia

uVIN	dVIN
Young women	Older women
Multifocal	Unifocal
Related to HPV [16, 18, 20]	Not related to HPV Associated with Lichen sclerosus and Lichen planus
More common in hair bearing labia majora	More common in non-hair bearing area
20% changes to invasive cancer	80% changes to invasive cancer
Histopathology Atypia involving two-thirds to full thickness of the epidermis (VIN 2 or VIN3)	Atypia confined to basal layer of epidermis (VIN 3 differentiated)
Immunohistochemistry P53 negative P16 positive	P53 positive P16 negative

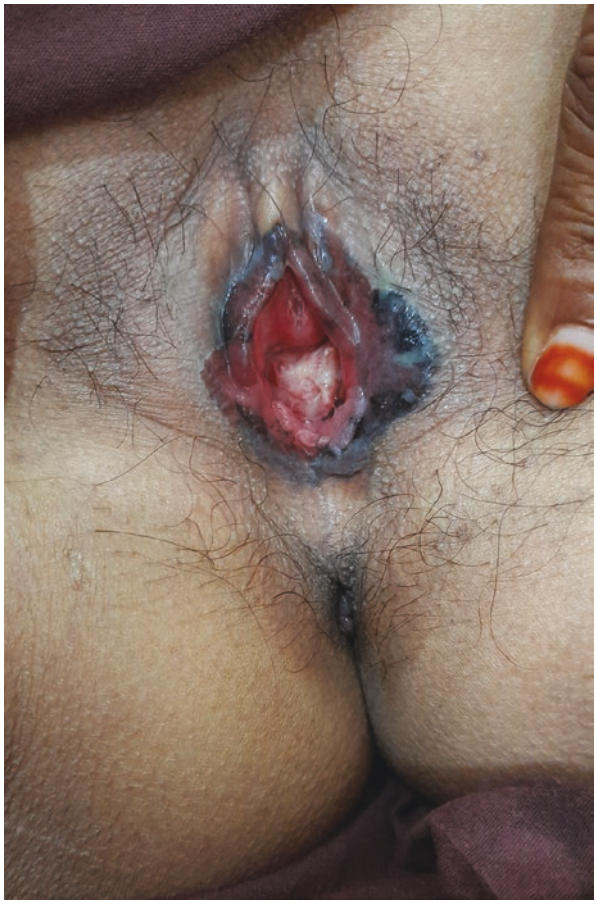

Fig. 17.10 Vulvar intraepithelial neoplasia (Bowen's disease)

Differential diagnosis: Condyloma acuminate and condyloma lata are to be differentiated from uVIN. Lichen sclerosus, lichen planus, candidiasis, Paget's disease are the differentials to be considered for dVIN.

Dermoscopy of uVIN: Numerous white dots surrounded by glomerular vessels with irregular patchy distribution, focal structureless bluish-brown areas, and peripheral gray-brownish dots arranged in a linear fashion are the classic features [21]. dVIN: Pink to red structureless background with red areas due to superficial erosions and vascular structures consisting of curvy, short serpentine and dotted vessels are noted on dermoscopy [22]. Diagnosis has to be confirmed by a biopsy.

Histopathology shows loss of epithelial cell maturation, loss of polarity with high nuclear to cytoplasmic ratio, nuclear hyperchromatism and pleomorphism; cellular crowding and abnormal mitosis are the key features on biopsy.

Treatment: Surgical excision is the first line of treatment. Wide local excision, simple vulvectomy, skinning vulvectomy are usually done depending on the extent of involvement. In the early stages, topical Imiquimod cream 3 times weekly for

12–20 weeks gives good results. 5-fluorouracil twice daily for several weeks, cidofovir 1% [23] ointment, and photodynamic therapy are other alternative treatments. Ablative treatment with CO_2 laser is also tried but with higher recurrence rates.

HPV Vaccination: Prophylactic HPV vaccines are used to reduce premalignancies and malignancies. Bivalent vaccine targets high risk HPV types 16 and 18. Quadrivalent vaccine targets 16, 18, 6, and 11. Newer recombinant nanovalent vaccine [24] is against 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Recommended schedule: Females <15 years—2 dose schedule (0.6 months)

Above 15 years—3 dose schedule (0, 2, 6) is recommended

Risk factors for recurrence are immunosuppression, multifocal or multicentric disease, large lesions, positive margins on excision specimen and age more than 50 years. Prognosis for biopsy confirmed cases that receive prompt treatment is good.

17.9.2 Vulvar Paget's Disease

Vulva is the commonest site for extramammary Paget's disease (EMPD). It is a nonsquamous intraepithelial lesion of the vulva. Ninety percent of all Paget's disease are mammary Paget's disease and 10% are EMPD [25]. Mean age group is sixth to eighth decade of life. Vulvar Paget's disease can be primary arising from the epithelium of the vulva or secondary arising from urothelial or anorectal carcinoma.

Clinical features: Pruritus, burning, pain, and bleeding are the common presenting symptoms. The lesions can involve labia majora, minora, introitus or can extend to the perianal area and inner thigh. Lesions present as erythematous, scaly or moist plaques or erosive, ulcerated lesions that are well demarcated. Scattered areas of erosion and white scale give rise to a "strawberry and cream" appearance [26]. Underpants-pattern erythema is a distinct clinical aspect of genital extramammary Paget's disease starting in the groins and spreading to the areas covered by underwear. It has an ominous prognosis with rapidly fatal distant metastases.

Histopathology: Vacuolated Paget's cells in the epidermis are the main feature. They may occur singly or in clusters. They have abundant pale staining basophilic cytoplasm and large centrally placed nuclei with prominent nucleolus. Immunohistochemistry helps in differentiating from melanoma and VIN which are the main histological differentials. Primary EMPD is CK7+, CK20-ve [27]. Secondary EMPD is both CK7 and CK20 positive.

Other investigations like cervicovaginal smear, rectocoloscopy, cystoscopy, abdominal ultrasound, CT scan, mammography, and tumor markers like CEA, CA19-9, and CA15-3 are done to rule out other malignancies.

Treatment: Topical 5-Flurouracil, Imiquimod cream, and Bleomycin are useful in early stages. Surgical treatments like wide local excision, vulvectomy, and Mohs micrographic surgery are the mainstay. CO_2 ablation, photodynamic therapy with topical aminolevulinic acid, radiotherapy, chemotherapy with intralesional alfa-2b are other modalities that are tried.

Prognosis: It is favorable except with underlying visceral or adnexal carcinoma wherein mortality is >50%. Decreased survival is associated with increased CEA levels, tumor invasion level, presence of nodules in the primary lesion, and lymph node metastasis [28].

17.9.3 Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the common vulvar malignancy. SCC is of 3 types [29]—classic bowenoid type and verrucous type are HPV associated. Third type is the non-HPV associated keratinizing or differentiated type. Risk factors for HPV positive SCC are smoking, alcohol use, immunosuppression and VIN. HPV negative SCC is due to long-term lichen sclerosus and lichen planus.

Clinical features: Pruritus, pain, dysuria, and bleeding are the common presenting symptoms or may be asymptomatic. Inguinal lymphadenopathy is seen in advanced cases. Single vulval plaque, growth, or ulcer are seen on the background of uVIN or lichen sclerosus. As multifocality is a feature of SCC all suspicious areas are to be biopsied. Spread of SCC can be directly to adjacent structures like vagina, urethra, or lymphatic spread to regional lymph nodes or hematogenous spread.

Treatment: Surgery is the standard treatment depending on the staging of vulval carcinoma (FIGO Staging of vulval cancer). Chemotherapy and radiotherapy depending on the extent and spread of the disease.

17.10 Miscellaneous Conditions

17.10.1 Vulvar Edema

Vulvar edema is often a diagnostic challenge as it is caused by both medical conditions and also vulvar conditions. Isolated vulvar edema is seen in contact dermatitis, Hidradenitis suppurativa, Crohn's disease, physiological causes like pregnancy and prolonged delivery, pelvic obstruction due to tumor, radiation, surgery, and trauma. Vulvar edema can occur secondary to medical conditions like renal and cardiac failure and severe malnutrition. Benign and malignant vulvar masses can cause edema which mimics vulvar edema. These are lipomas, Bartholin gland cysts, lymphangioma circumscriptum, angiomyxomas, and lymphomas.

Treatment: First-line management of vulvar edema depends on the cause. The underlying medical condition should be identified for successful management. In cases resistant to treatment, other tumors and neoplasms are to be considered.

17.10.2 Vulvodynia

Vulvodynia is defined by International Society for the Study of vulvovaginal Diseases (ISSVD) as "Vulvar pain of at least 3 months duration without clear identifiable cause, which may have potential associated factors" [30]. The potential factors associated with vulvodynia are hormonal factors, other pain syndromes like painful bladder syndrome, fibromyalgia, etc. It is a diagnosis of exclusion, in which all causes like trauma, infections, inflammatory and neoplastic conditions are ruled out.

Vulvodynia can be generalized involving the whole vulva or localized involving the vestibule (vestibulodynia) or clitoris (clitorodynia). It can be provoked by physical contact, intercourse or clothing pressure or unprovoked where pain is spontaneous without any trigger [30].

Pathogenesis: It is a complex and multifactorial disease. Neuropathic factors are strongly hypothesized and supported by persistent burning quality of the pain, hyperpathia, and absence of physical findings on examination. Psychosexual dysfunction is also proposed as the primary cause of vulvodynia [31].

Differential diagnosis: Candidiasis is the common condition to be differentiated. Wet mount is helpful. Culture is useful to differentiate from bacterial vulvovaginitis. Erosive lichen planus and lichen sclerosus may present with pain or soreness but they are mostly associated with pruritus.

Treatment: Educating the patient about their condition and psychological support forms an important part of the management. Pelvic floor exercises play a major role in the treatment. Local anesthetic ointment like 5% lidocaine can be applied before intercourse.

Topical Amitriptyline, Nitroglycerin, 5% Doxepin, and topical estrogen are helpful.

Systemic: Tricyclic antidepressant Amitriptyline forms the first-line treatment. It is started at a dose of 10–25 mg daily and gradually increased by 10–25 mg weekly. Venlafaxine and Duloxetin (60 mg twice a day) are also used. In patients who do not respond with antidepressants, anticonvulsants like Gabapentin and Pregabalin are useful in treating vulvodynia. Triamcinolone injection into the affected area decreases the pain in 1 or 2 weeks [32]. Intralesional injections of Botulinum toxin A is tried in few studies [33]. Treatment should be individualized to the patient needs.

17.10.3 Red Vulva Syndrome

Red vulva syndrome is the persistent redness of the vulva in adult women due to prolonged use of topical steroids. These women do not have any other infective, inflammatory, neurogenic, or neoplastic diseases. Pruritus and burning are the common presenting symptoms. Sharp borders, absence of scaling and excoriations differentiate it from psoriasis and atopic dermatitis. Discontinuation of topical steroids

is the mainstay of treatment. Withdrawal symptoms are seen on stopping the steroids, so counselling the patient is helpful.

Treatment: Carvedilol is an important option in managing red vulva syndrome [20]. Carvedilol 6.25 mg alternate day is used to minimize the side effects of beta blockers. Beta blockers cause vasoconstriction of cutaneous arteries and carvedilol also has anti-inflammatory and antioxidant effects.

17.11 Summary

Dermatologists are the experts of skin care and vital for vulvar care. Starting vulvar clinics help to improve the management of women with vulvar diseases. Long-term supervision is required in many of these diseases. Most of them are chronic diseases so compliance and adherence to treatment are to be addressed.

References

1. Udayalakshmi A, Gopalakrishna B, Subbannayya K, Shalini S. Comparison of the methods of diagnosis of bacterial vaginosis. J Clin Diagn Res. 2011;5(3):498–501.
2. Edwards L. The diagnosis and treatment of infectious vaginitis. Dermatol Ther. 2004;17(1):102–10. https://doi.org/10.1111/j.1396-0296.2004.04010.x.
3. Zug KA, McGinley-Smith D, Warshaw EM, Taylor JS, Rietschel RL, Maibach HI, et al. Contact allergy in children referred for patch testing: North American contact dermatitis group data, 2001-2004. Arch Dermatol. 2008;144(10):1329–36.
4. Lynch PJ. Vulvar pruritus and lichen simplex chronicus. In: Black M, editor. Obst and gynaec dermatology. St. Louis: Mosby; 2002. p. 157–66.
5. Eisen D. The vulvo-vaginal gingival syndrome of lichen planus: the clinical characteristics of 22 patients. Arch Dermatol. 1994;130:1379.
6. Borghi A, Virgili A, Corazza M. Dermoscopy of inflammatory genital diseases: practical insights. Dermatol Clin. 2018;36:451–61.
7. Lewis FM, Harrington CI. Squamous cell carcinoma arising in vulval lichen planus. Br J Dermatol. 1994;131(5):703.
8. Marren P, Yell J, Charnock FM, et al. The association between lichen sclerosus and antigens of the HLA system. Br J Dermatol. 1995;132:197–203.
9. Tran DA, Tan X, Macri CJ, Golstein AT, Fu SW. Lichen Sclerosus. An autoimmunopathogenic and genomic enigma with emerging genetic and immune targets. Int J Biol Sci. 2019;15(7):1429–39. https://doi.org/10.7150/ijbs.34613.
10. Hewitt J. Histologic criteria for lichen sclerosus of the vulva. J Reprod Med. 1986;31:781–7.
11. Micheletti L, Preti M, Radici G, et al. Vulvar LS and neoplastic transformation: a retrospective study of 976 cases. J Low Genit Tract Dis. 2016;20:180–3.
12. Kirtschig G, Becker K, Unthert AG, Jasaitiene D, et al. Evidence based (S3) guideline on (anogenital) lichen sclerosus. J Eur Acad Dermatol Venerol. 2015;29(10):1–43.
13. Kragballe K, Austad J, Barnes L, et al. A 52 week randomized safety study of a calcipotriol/betamethasone in the treatment of psoriasis vulgaris. Br J Dermtol. 2006;154:1155–60.
14. Virgilli A, Levratti A, Marzola A, et al. Retrospective histopathologic reevaluation of 18 cases of plasma cell vulvitis. J Reprod Med. 2005;50(1):3–7.

15. Errichetti E, Lallas A, Dimitros I. Hypopigmented dermatoses. In: Lallas A, Errichetti E, Dimitros I, editors. Dermoscopy in general dermatology, vol. 1. Boca Raton: CRC Press; 2019. p. 121.
16. Lewis F, Boglioatto F, Beurden M. Practical guide to vulval disease: diagnosis and management. Disorders of pigmentation on the vulva. Hoboken: Wiley; 2017. p. 111–9.
17. Lewis F. Dermatoses of the female genitalia. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rooks textbook of dermatology. Hoboken: Wiley; 2016. p. 112–21.
18. Dhawan AK, Pandhi D, Gopal S, Bisherwal K. Angiokeratoma of vulva. J Obstet Gynaecol. 2014;64:148–9.
19. Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med. 2005;50:807.
20. Hajj C, Ayoub N. Carvediol for treatment of red vulva syndrome. JAMA Dermatol. 2018;154(6):731–3. https://doi.org/10.1001/jamadermatol.2018.0246.
21. Vincezo M, Enzo E, Laure D, et al. Usual type vulvar intraepithelial neoplasia: a report of a case and its dermoscopic features. Int J Dermatol. 2016;55:12.
22. Vaccari S, Barisani A, et al. VIN and vulvar scc differential dermoscopic features in a case series. Clin Exp Dermatol. 2018;43:458–73.
23. Helm CW. Is Cidofovir better treatment than Imiquimod for high grade VIN. BJOG. 2018;125(9):1178.
24. WHO: summary of the WHO Position paper on vaccines against HPV. 2017. http://www.who.int/immunization/policy/position_papers/pp_hpv_may2017_summary.pdf. Accessed 15 February 2021.
25. Van der Linden M, Meeuwis KA, Bulten J, Bosse T, Poelgeest MI, de Hullu JA. Paget disease of the vulva. Crit Rev Oncol Hematol. 2016;101:60–74.
26. Murata Y, Kumano K, Tani M. Underpants pattern erythema: a previously unrecognized cutaneous manifestation of extramammary Paget's disease of the genitalia with advanced metastatic spread. J Am Acad Dermatol. 1990;40:949–56.
27. Lam C, Funaro D. Extramammary Paget's disease: summary of current knowledge. Dermatol Clin. 2010;28(4):807–26. https://doi.org/10.1016/j.det.2010.08.002.
28. McDaniel B, Brown F, Crane JS, et al. Extramammary Paget's disease. Treasure Island: StatPearls; 2021.
29. Venkatesan A. Pigmented lesions of the vulva. Dermatol Clin. 2010;28(4):795–805. https://doi.org/10.1016/j.det.2010.08.007.
30. Bornstein J, Goldstein AT, Stockdale CK, Bergeron S, Pukall C, Zolnoun D, et al. Consensus Vulvar Pain Terminology Committee of the International Society for the study of vulvovaginal disease, The International Society for the study of Women's Sexual health, and the International Pelvic Pain Society. Obstet Gynecol. 2016;127:745–51.
31. Lewis FM, Bogliatto F, Beurden M. Practical guide to vulval disease: diagnosis and management. Hoboken: Wiley; 2017. p. 201–7.
32. Edwards L. New concepts in vulvodynia. Am J Obstet Gynecol. 2003;189(3):24–30.
33. Dykstra DD, Presthus J. Botulinum toxin type A for the treatment of provoked vestibulodynia:an open label pilot study. J Reprod Med. 2006;51:467–70.

Chapter 18
Sexually Transmitted Diseases in Females

Taru Garg and Apoorva Maheshwari

18.1 Introduction

Transmission of an infective agent, between sexual partners, through various routes of sexual contact like vaginal, anal or oral, leads to sexually transmitted diseases (STDs), also known as sexually transmitted infections (STIs) [1]. The global incidence of STDs is increasing, leading to increased healthcare costs incurred. According to WHO data, more than one million STDs are contracted every day with more than 376 million cases of 1 of 4 STDs: chlamydia, gonorrhoea, syphilis and trichomoniasis [2]. Women are more vulnerable to acquire these infections because of fragility of the receptive mucosa and lesser awareness regarding the mode of transmission. STDs in females have wider implications, as complications may arise not only in the patient, but infection can also be transmitted to newborns born to afflicted mothers. Since STDs are widely preventable diseases, by means of appropriate treatment of the diseased and counselling regarding the mode of spread of the infection, it is vital that as venereologists, we should be equipped to diagnose these clinically or with the help of point of care (POC) tests and laboratory methods available at our disposal. In this chapter we will discuss clinical presentations, methods of diagnosis and treatment options of commonly encountered STDs in women.

18.2 Bacterial STDs

Common bacterial STIs can present as genital ulcers, cervicitis, vaginitis and urethritis or can lead to pelvic inflammatory disease as a complication.

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18.2.1 Syphilis

Syphilis is caused by a treponeme *Treponema pallidum subsp. pallidum.* It is a delicate, thin, motile and closely coiled organism with tapering ends. Since conventional microscope is unable to visualize its structure due to its thinness, dark ground illumination (DGI) is required for the same. Bending, flexing, translational and corkscrew motility may be seen, with angular movements being characteristic [3].

18.2.1.1 Epidemiology

Between 2014 and 2018, the rates of primary and secondary syphilis in females in the USA escalated from 1.1 to 3 cases per 1,00,000 females. About 1306 cases of congenital syphilis were reported in 2018, which represented 39.7% rise in statistics compared to 2017 data for the same [4].

18.2.1.2 Clinical Features

Syphilis can present as primary, secondary, latent or tertiary syphilis. Latent syphilis, a phase with no clinical features but positive serology, has been divided into early and late latent syphilis, cut off for which is 2 years according to World Health Organization (WHO) and National AIDS Control Organization (NACO) and 1 year according to Centre for Disease Control (CDC). The importance of this distinction lies in the fact the patients in early latent syphilis are considered infectious as they can relapse into secondary syphilis and because organisms in late latent syphilis are considered to divide more slowly, requiring longer duration of treatment for adequate disease eradication [5].

After an incubation period (IP) of 10–90 days, patient develops a papule, which breaks into a superficial ulcer with sharply demarcated, elevated edges and smooth, indurated, non-purulent and avascular base. It is usually painless. Commonest sites include labia and posterior fourchette as these sites suffer microtrauma during intercourse. However, they may be present on cervix and the patient may thus remain asymptomatic. This may be accompanied by firm, bilateral, rubbery and non-tender lymphadenopathy. Chancre usually resolves in 12–21 days [6].

All untreated patients progress to secondary syphilis, which can manifest itself in myriad clinical presentations, but commonest are skin rash (67–92%) and lymphadenopathy (63–100%). Commonest variant is macular or maculopapular eruption. Others include macular (roseola syphilitica), papular, papulosquamous, psoriasiform, lichenoid, pustular, follicular, annular eruptions and specific arrangements of the above in the form of corona veneris (along hairline on the forehead) and necklace of venus (depigmented macules left after resolved lesions over back and sides of the neck) [5].

According to Oslo study of untreated syphilis, 2/3rd of patients in late latency undergo remission due to unintended antibiotic use and 1/3rd progress to tertiary syphilis, which may manifest as benign syphilitic gummas, cardiovascular syphilis or neurosyphilis [7]. Neurosyphilis may however accompany any stage of syphilis and is not an exclusive presentation of tertiary syphilis.

18.2.1.3 Diagnosis

Syphilis can be diagnosed either by direct detection of the organism (by darkfield microscopic examination and histopathological evaluation) or by direct detection of presence of antigen {using direct fluorescent antibody for *T. pallidum* (DFA-TP), enzyme immunoassay (EIA) and polymerase chain reaction (PCR)} or by serological investigations. Serological investigations may be non-treponemal like venereal disease research laboratory (VDRL), rapid plasma regain test (RPR) and toluidine red unheated serum test (TRUST). Treponemal tests include fluorescent treponemal antibody absorption test (FTA-ABS), *T. pallidum* hemagglutination assay (TPHA), *T. pallidum* particle agglutination (TPPA) and *T. pallidum* enzyme immunoassay (TP-EIA) [8].

Darkfield microscopy is the POC test, which if performed correctly, allows direct detection of *T. pallidum* from primary and secondary syphilis lesions, demonstrating its characteristic angular and bending motility [5, 9]. DFA-TP is more sensitive and specific than darkfield microscopy and also can differentiate pathogenic from non-pathogenic treponemes [5]. Histology, if performed, shows endothelial swelling, obliterative endarteritis, infiltration with lymphocytes and plasma cells and silver staining reveals organisms in lower epidermis and around involved blood vessels [10].

Non-treponemal tests provide quantitative titres which fall on appropriate treatment and are thus performed to monitor treatment adequacy. Seroconversion occurs in about 3–6 weeks after infection [11]. Sensitivity and specificity of VDRL and RPR in chancre has been found to be about 62–78% [12]. Treponemal tests remain positive for life, irrespective of treatment. They are reported as reactive or non-reactive and thus cannot differentiate between recent and remote infection or treated or untreated infection [13]. Various rapid serologic tests are available as POC tests, that are mainly treponemal tests and can be used to guide treatment in patients who may not return for follow-up [14]. Some laboratories are now preferring the reverse screening algorithm, in which first a treponemal test is performed and non-treponemal test is used to screen positive samples. Discordance between the test results warrants testing with a second treponemal test to reach diagnostic conclusion and guide treatment. However, no consensus has been reached whether the reverse algorithm should be preferred over the traditional screening procedure or not [15].

18.2.1.4 Treatment

After a presumptive diagnosis (i.e. with a non-treponemal and a treponemal test), patient should be treated with penicillin G, administered parenterally, in preparation, dosage and duration depending on whether the chancre is accompanied by symptoms of neurosyphilis [16]. CDC recommended treatment for chancre is benzathine penicillin G 2.4 million units IM, half in each buttock after sensitivity testing. Recommended regimen for neurosyphilis is aqueous crystalline penicillin G 18–24 million units per day, administered as 3–four million units IV every 4 h or as a continuous infusion, for 10–14 days [17].

Follow-Up Clinical and serological follow-up should be done at 6 and 12 months. The titres should fall fourfold within 6–12 months in patients with adequate treatment [17].According to NACO guidelines, follow-up should be done at 3, 6, 12 and 24 months [16].

18.2.1.5 Partner Management

While partners who have had sexual contact with a patient with chancre in past 90 days should be treated presumptively even if the serological investigations are negative, all partners who had sexual contact >90 days before diagnosis must be examined and investigated and treatment should be based on investigations and clinical stage [17].

Pregnancy All pregnant patients should be treated with penicillin-based regimen. In case of penicillin allergy, desensitization should be done [17].

HIV Co-infection Patients co-infected with HIV should be treated with same regimen as HIV uninfected patients [17].

18.2.2 Chancroid

Chancroid is caused by a Gram negative bacterium *Haemophilus ducreyi*. It is non-motile, non-spore forming, facultative anaerobe with fastidious growth requirements.

18.2.2.1 Epidemiology

Incidence of chancroid is decreasing with less than 100 annual cases since 2000. Less than 20 annual cases have been reported since 2011 with only three cases in 2018 in the United States [18].

18.2.2.2 Clinical Features

After inoculation of the pathogenic organism, usually through intercourse-induced microtrauma, there is localized proliferation of the organism, which usually results in formation of an erythematous and tender papule, which leads to formation of a pustule followed by ulceration of the same within another 2–3 days [19]. According to an experimental human model, inoculation of about 30 colony forming units leads to 95% papule formation rate and 69% pustule formation rate [20].

Ulcer(s), single or multiple, are non-indurated, deep, with irregular and undermined edges, which bleed on touch. These are usually painful [19]. Various clinical patterns like dwarf chancroid, giant chancroid, phagedenic chancroid, pseudogranuloma inguinale like chancroid, serpiginous chancroid, chancroidal ulcers, transient chancroid, follicular chancroid and mixed chancroid may be seen [21].

Ulcer may be accompanied or followed by development of inguinal lymphadenopathy. It usually appears within 7–14 days of development of ulceration. It is unilateral in 3/4th cases. The bubo so formed after suppuration, is unilocular and ruptures with a single sinus opening. Usually accompanying constitutional signs are absent and Groove sign is negative. Apart from lymphadenopathy, psychological impact of pain in ulcer, autoinoculation to other cutaneous sites, balanitis, phimosis and paraphimosis are complications associated with chancroid [21].

18.2.2.3 Diagnosis

According to CDC, probable diagnosis of chancroid is made if all 4 of the below are positive: [22].

1. Presence of painful genital ulcers.
2. Ulcer presentation and lymphadenopathy, characteristic of chancroid.
3. No evidence of *T. pallidum* on darkfield examination or serology, performed at least 7 days after ulcer onset.
4. Negative HSV culture or HSV PCR.

Microscopy, antigen detection, culture, nucleic acid amplification test (NAAT) and serology have been used for confirmation of the diagnosis.

Gram's stain performed on ulcer exudate shows characteristic Gram negative coccobacilli in rail road or school of fish arrangement. It is POC but its diagnostic value is limited due to low sensitivity and specificity. Although not routinely done, direct immunofluorescence antigen detection performed on ulcer exudates has been found to be useful, with relatively higher sensitivity (89–100%) and specificity (63–81%) [23].

Culture is still considered gold standard despite only 80% PCR comparative sensitivity [23]. Gonococcal agar and Mueller–Hinton agar supplemented with 2% bovine haemoglobin and 1% IsovitaleX have been found to be optimal [24].

Clinical laboratory improvement amendments (CLIA) approved combination PCR (multiplex PCR) techniques for *T. pallidum*, *H. ducreyi* and HSV are being

used. However, none of these are FDA approved [25]. Antibody detection has been tried, with sensitivity and specificity of about 55–100% and 23–96% respectively [23, 26].

18.2.2.4 Management

CDC recommends azithromycin 1 g orally in a single dose or ceftriaxone 250 mg IM in a single dose or ciprofloxacin 500 mg orally twice a day for 3 days or erythromycin base 500 mg orally three times a day for 7 days [22].

Follow-Up Patients should be re-examined 3–7 days after treatment. If objective improvement cannot be documented at day 7, then it is advisable to consider the following:

- Incorrect diagnosis
- Non-compliance with treatment
- Co-infection with other STI or HIV
- Resistance to prescribed antimicrobial [22]

Partner Management All sexual partners who had contact with the patient within 10 days of onset of their symptoms should be presumptively treated irrespective of symptoms [22].

HIV Co-infection Patients co-infected with HIV might require longer therapy or repeat courses and thus must be monitored strictly [22].

18.2.3 Lymphogranuloma Venereum (LGV)

LGV is caused by *Chlamydia trachomatis (C. trachomatis)* serovar L1, L2 or L3, intracellular obligate organism. It is more common in men who have sex with men (MSM), with commonest serovar being L1. However, recently, there has been a slow epidemiologic rise in L2b serovar, called Amsterdam strain, especially in MSM [27].

18.2.3.1 Epidemiology

There is paucity of studies to elucidate the burden of disease in women. It is believed that while both men and women are equally affected, acute manifestations are more common in males, while females usually present with late complications as the initial stages of the disease go unnoticed in them [28].

18.2.3.2 Clinical Features

Patients may suffer three stages of the disease. Primary stage reflects the stage of genital ulceration, secondary stage occurs due to involvement of draining lymph nodes (inguinal syndrome), and tertiary stage is stage of complication, seen mainly in MSM and women who were asymptomatic in previous two stages [29].

LGV is characterized by transient, asymptomatic papule or pustule that ulcerates, into usually a single, superficial or deep ulcer with, elevated margins and non-vascular, occasionally indurated base and is variably painful [30]. This however goes unnoticed and this thus may complicate into secondary stage of infection i.e. that of lymphadenopathy, site of which depends on the site of original ulcer and its lymphatic drainage. Most common is inguinal group of nodes which suppurate to form bubo, which can be clinically indistinguishable from bubo of chancroid to inexperienced eye [31]. However, there are clinical pointers that can differentiate the two. Bubo in LGV appears 10–30 days after ulceration and thus ulcer is usually absent when lymphadenopathy develops. It is multilocular and thus it ruptures to form multiple sinuses. Constitutional signs may be present and Groove's sign is present in about 20% patients [21].

Untreated LGV can complicate to tertiary stage of genito-anorectal syndrome with disfiguring ulcerations and tissue hypertrophy called "esthiomene", chronic proctocolitis and rectal strictures [29]. Painful urination, bleeding per rectum, pain during passing stools, abdominal pain and tenesmus may accompany.

18.2.3.3 Diagnosis

Ulcer exudate and lymph node aspirate can be subjected to culture, NAAT and serology. Other tests like histological analysis of ulcer or bubo by Giemsa staining, antigen detection using EIA and rapid assays and immunotyping of isolates can be performed if facilities are available [29].

Cell lines like HeLa 229, baby hamster kidney cells (BHK-21) and McCoy cells are used for culture. However, organism recovery from primary stage is seen in only 30% of samples [32].

NAAT for LGV is a two-step process. The samples are subjected to NAAT for *C. trachomatis.* Positive samples are subjected to LGV-specific serotyping PCR [33, 34]. This technique can correctly identify LGV serovars in 96.6% patients [35]. Complement fixation tests are most commonly performed serological assays for LGV, with a titre of >1:64 being considered significant [32].

18.2.3.4 Management

Recommended regimen comprises of doxycycline 100 mg orally twice a day for 21 days. Erythromycin base 500 mg orally four times a day for 21 days can be given in patients with contraindication to tetracyclines [22].

Partner Management All sexual partners who had sexual contact within 60 days of symptom onset in patient should be evaluated for chlamydial infection and treated presumptively with doxycycline 100 mg twice daily orally for 7 days or azithromycin 1 g single dose orally [22].

Pregnancy Pregnant and lactating women should be treated with erythromycin [22].

HIV All patients with LGV and HIV co-infection should be treated with same regimen as in non-co-infected patients. However, longer treatment may be required and patients and clinicians may notice delay in resolution of symptoms [22].

18.2.4 Donovanosis

The causative organism of donovanosis is *Klebsiella granulomatis*, which is intracellular, Gram negative coccobacilli and is identified as Donovan body in histological specimens. This organism was earlier called *Calymmatobacterium granulomatis.* However, on DNA sequencing, it was found to have 99% genomic similarity with *Klebsiella pneumoniae* and *Klebsiella rhinoscleromatis* and was thus renamed [36].

18.2.4.1 Epidemiology

Donovanosis is endemic in few hotspots like Brazil, Papua New Guinea, Australia and few parts of India [37].

18.2.4.2 Clinical Features

After an IP of 1–4 weeks, it presents as a papule or subcutaneous nodule that ulcerates on progression. Four main variants are recognized:

1. Commonest variant is ulcerogranulomatous which is characterized by beefy red, fleshy, exuberant, non-tender ulcers that bleed on touch.
2. Ulcer with raised and irregular edge is called hypertrophic or verrucous variant. It may have a walnut-like appearance.
3. Necrotic variant is characterized by deep and foul smelling ulcer and is associated with significant tissue loss.
4. Sclerotic variant with formation of excessive fibrosis and scar tissue and thus it is also called cicatricial variant [36].

Autoinoculation may lead to kissing or mirror lesions. Outward progression of ulcers may lead to a “snake like” appearance. Donovanosis may rarely be complicated by pseudoelephantiasis, malignant transformation or secondary dissemination to organs like liver and bones [37].

18.2.4.3 Diagnosis

High degree of suspicion is necessary to evaluate donovanosis in non-endemic countries.

Donovan bodies can be identified, albeit with low sensitivity, on Giemsa staining of the ulcer exudate [38]. Histological examination can be done in cases of diagnostic dilemma, where cytology has failed to reveal Donovan bodies. Bacteria can be found in Giemsa stained smears, both within and outside histiocytes [36]. Ulcer exudate can be cultured on Hep-2 cells and human monocyte co-culture [39]. While PCR may be considered highly sensitive, no FDA approved PCR test is available. PCR-based colorimetric assay has been used for detection of the organism in a study [40]. Indirect immunofluorescence, antigen detection and complement fixation can be done where facilities are available [38].

18.2.4.4 Management

Recommended regimen consists of azithromycin 1 g orally once a week or 500 mg daily for at least 3 weeks and until all lesions have completely healed [22]. Alternative regimens are given for at least 3 weeks and until all lesions have completely healed. Dosages include doxycycline 100 mg orally twice a day or ciprofloxacin 750 mg orally twice a day or erythromycin base 500 mg orally four times a day or trimethoprim-sulfamethoxazole one double-strength (160/800 mg) tablet orally twice a day [22].

Partner Management All sexual contacts within 60 days of symptom onset in patient should be evaluated and offered therapy [22].

Pregnancy All pregnant patients should be treated with macrolide regimen (erythromycin or azithromycin) which can be supplemented with aminoglycoside (gentamycin 1 mg/kg every 8 h IV) if improvement is not noted within few days [22].

HIV While the treatment regimen to be followed is same as the one followed for non-co-infected patients, addition of gentamicin 1 mg/kg every 8 h can be considered in case improvement is not evident in first few days of treatment [22].

18.2.5 Gonorrhoea and Chlamydia

Gonorrhoea is caused by *Neisseria gonorrhoeae*, which is intracellular Gram negative diplococci (ICGND). Chlamydia is caused by *Chlamydia trachomatis*, which is intracellular obligate bacterium. Both these organisms present as cervicitis and/or urethritis, with extragenital complication in untreated cases.

18.2.5.1 Epidemiology

According to CDC 2018 statistics, about 100.4 to 145.8 cases per 100,000 females were reported to have gonorrhoea and 692.7 cases per 100,000 females had chlamydia infection [41, 42].

18.2.5.2 Clinical Features

Patient of cervicitis primarily presents with abnormal vaginal discharge. Profuse to moderate, mucopurulent or mucoid discharge is seen (Fig. 18.1). While profuse, mucopurulent discharge is suggestive of gonorrhoea, scanty to moderate, mucoid discharge is suggestive of chlamydial infection. Usually vaginitis is not present in either of the two. There may be history of associated post-coital or intermenstrual bleeding and dyspareunia. Pain in abdomen may be present. Per speculum examination shows mucoid or mucopurulent discharge at the os with cervical friability on taking a swab [43].

In gonococcal cervicitis, initial colonization starts in urethra, skene's glands and bartholin's glands, after which infection ascends to cervix, and untreated cases may suffer from involvement of uterus and fallopian tubes. Exudation of pus into inflamed fallopian tubes results in formation of pyosalpinx, which if becomes adherent to ovary, may rupture to form tubo-ovarian abscess. Haematological dissemination may lead to disseminated gonococcal infection (DGI) characterized by arthritis, dermatitis, endocarditis, myocarditis, pericarditis, meningitis, pneumonitis, hepatitis and pyelonephritis [43].

Extragenital involvement in gonococcal and chlamydial infections in the form of anorectal and pharyngeal infection may occur due to peno-anal contact, fellatio and cunnilinghus. In a review, the proportions were 0.6–35.8% for rectal gonorrhoea, 0–29.6% for pharyngeal gonorrhoea, 2.0–77.3% for rectal chlamydia and 0.2–3.2%

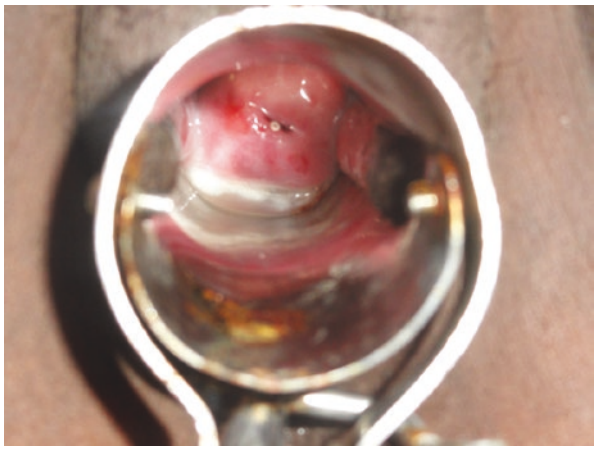

Fig. 18.1 Per speculum examination showing mucopurulent cervical discharge

for pharyngeal chlamydia [44]. Fitz-Hugh–Curtis syndrome is perihepatitis, i.e. inflammation of liver capsule, which can be seen in patients of pelvic inflammatory disease (PID). It is characterized by fever, nausea, vomiting and upper abdominal pain [45]. Conjunctivitis can occur due to autoinoculation in both etiologies [43, 46].

18.2.5.3 Diagnosis

18.2.5.3.1 Gonorrhoea

Gram's staining is the commonest investigation performed and is POC test, which demonstrates polymorphonuclear cells and ICGND. Sensitivity of about 30–50% is reported [43]. Culture helps in assessment of antibiotic resistance, which is its major advantage. Sensitivity is 72–95%. The most commonly used medium is Thayer–Martin agar. Rayon, dacron or calcium alginate swabs must be used for sample collection [47]. Major disadvantage is that culture reports are unavailable before minimum of 48 h. NAAT techniques like polymerase chain reaction (PCR), strand displacement amplification (SDA) and transcription-mediated amplification (TMA) can be used. It is gold standard for diagnosis. Major advantages are provision of highly sensitive (almost 100%) and specific results within hours and ability of the test to produce reproducible results even on non-invasive samples like urine and vaginal swabs, while disadvantage is that antimicrobial resistance cannot be assessed [48, 49]. Several cartridge-based rapid NAAT tests, with almost 100% sensitivity, performed on site at the laboratories, are now available and being used [50].

18.2.5.3.2 Chlamydia

NAAT is gold standard for diagnosis, as it is not only highly sensitive, but co-infection with *N. Gonorrhoeae* can also be detected [49]. Rapid POC assays like the XPert and CT/NG assay (binx io) are available, results of which can be obtained within 90 and 30 min, respectively [51, 52]. Other tests that can be performed if facilities are available include culture, serology, antigen detection and gene probe assays.

18.2.5.4 Management

Treatment is based on isolation of ICGND from cervical or vaginal smears. Specimen should be sent for NAAT in all patients to confirm the diagnosis and to diagnose co-infection [53].

Gonococcal cervicitis is treated with cephalosporins, preferably administered intramuscularly. After surge of fluoroquinolone resistance in gonococcal infections in 2007, CDC's guidelines recommended dual treatment of the patients with a

cephalosporin with either azithromycin or doxycycline, irrespective of whether *C. trachomatis* co-infection was suspected at the time of presentation [54].

Recommended regimen up until recently was ceftriaxone 250 mg IM in a single dose plus azithromycin 1 g orally in a single dose [53]. However, according to CDC update on treatment of gonorrhoea, the recommendation now is Inj. ceftriaxone 500 mg IM single dose, which should be combined with doxycycline 100 mg twice daily for 7 days if chlamydial co-infection is diagnosed or cannot be ruled out [55].

Partner Treatment All sexual partners should be evaluated, tested and presumptively treated with same regimen as the patient, if sexual contact was within 60 days of onset of patient's symptoms [43]. Expedited partner therapy (EPT) is a provision wherein if the partners are unable to visit for evaluation and testing, single oral doses of cefixime 400 mg and azithromycin 1 g can be given to the patient for partner treatment [56].

Pregnancy All patients of gonococcal cervicitis should be treated with ceftriaxone 250 mg IM in a single dose plus azithromycin 1 g orally in a single dose. Patients with chlamydial cervicitis/non-gonococcal cervicitis should be treated with azithromycin 1 g orally in a single dose as doxycycline is contraindicated in second and third trimester. Test-of-cure should be performed in all patients at 3–4 weeks post treatment in chlamydial infection as severe sequelae can occur in mother and neonate if infection persists [43, 57].

HIV Same treatment regimen is to be followed as non-co-infected patients [43, 57].

18.2.6 Bacterial Vaginosis (BV)

Bacterial vaginosis (BV) is not due to one organism. Instead, quantitative imbalance in numbers of lactobacilli and anaerobes like *Gardnerella vaginalis (G. vaginalis)*, *Atopobium vaginae*, *Leptotrichia amnionii*, *Sneathia* and *Megasphaera* species is the aetiology. BV may affect sexually inactive and virgin females as well and thus it is considered sexually enhanced but not necessarily sexually transmitted [58].

18.2.6.1 Epidemiology

According to CDC 2018 statistics, 21.2 million women in the USA had BV with it being commonest vaginal condition in women aged 15–44 years [59]. In an epidemiological study from India, out of 200 women with vaginal discharge, 51% were diagnosed with bacterial vaginosis, 25.5% with candidiasis and 0.03% with trichominasis [60].

18.2.6.2 Clinical Features

The primary complaint is vaginal discharge and malodour. Alkaline pH, after sexual intercourse or during menstruation leads to increased production of amines like putrescine, cadaverine and trimethylamine, by the anaerobic bacteria and thus enhances the malodour. Scanty to moderate, white or grey, homogenous, malodourous is discharge seen, uniformly coating the vaginal walls (Fig. 18.2). Vaginal and vulval erythema may be present. Per speculum examination shows vaginal discharge coating vaginal walls. Cervicitis is not seen [58].

Various complications associated with BV include adverse pregnancy outcomes like premature rupture of membranes, preterm labour, low birth weight baby and spontaneous second trimester miscarriages; odour leading to embarrassment; acquisition of other STI like gonorrhoeae, chlamydia and HIV; PID and post-hysterectomy cuff cellulitis [58].

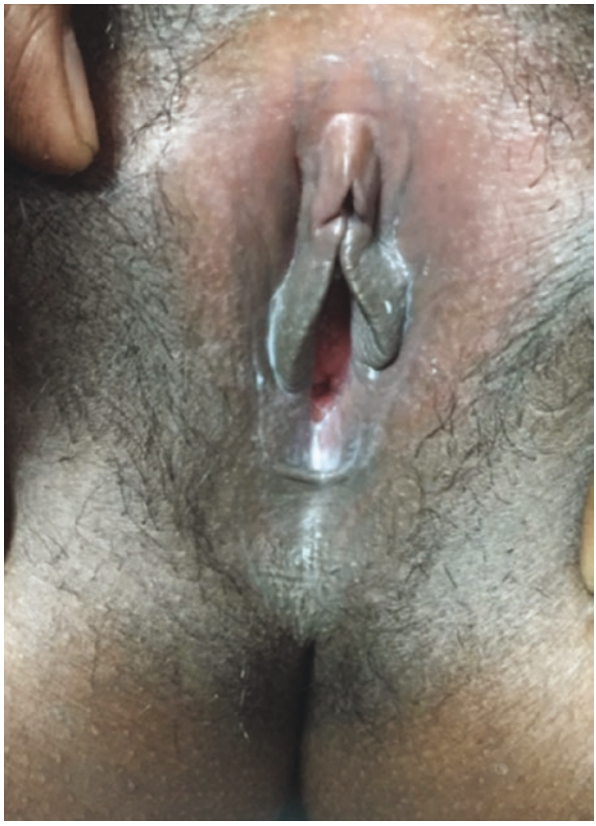

Fig. 18.2 Thin, homogenous, greyish discharge (image courtesy: Dr. Mahima Agarwal)

18.2.6.3 Diagnosis

The diagnosis of BV is based on Amsel's criteria [61], which includes:

- Homogenous, thin discharge, uniformly coating the vaginal walls
- Vaginal pH >4.5
- Positive whiff test
- And presence of clue cells, accounting for >20% of all epithelial cells in the smear.

At least 3 out of these 4 should be present for the diagnosis of BV. When compared with Nugent's criteria, sensitivity is about 90% [62].

When compared with Nugent's criteria (gold standard), Hay/Ison criteria has shown sensitivity of >97% [63, 64]. Culture is of limited value as it may be positive in about 55% of healthy women and it represents the presence of organisms like *G. vaginalis*, which are normally encountered in vaginal flora [65].

Various commercially available molecular diagnostic procedures are now FDA approved.

OSOM BVBlue gives results in less than 10 min, sensitivity and specificity in range of 84–88% and 91–98%, respectively. It detects elevated sialidase levels in the vaginal fluid samples [66]. Affirm VPIII is another FDA approved DNA probe test that detects the concentration of *G. vaginalis* and requires about 60 min to produce results with sensitivity and specificity of 95% and 97%, respectively [67]. Aptima BV is a NAAT that quantitatively detects lactobacilli, *G. vaginalis* and *A. vaginae*, with a sensitivity of about 95% [68]. Another quantitative PCR method is BD Max system that measures lactobacilli like *Lactobacillus jensenii* and *Lactobacillus crispatus* along with *G. vaginalis*, *A. vaginae* and *Megaspheara-1,* with a sensitivity of about 90% and specificity of about 85% [69].

18.2.6.4 Management

Recommended regime is metronidazole 500 mg orally twice a day for 7 days or metronidazole gel 0.75% 5 g intravaginally, once a day for 5 days or clindamycin cream 2%, 5 g intravaginally at bedtime for 7 days [70].

Alternatively, tinidazole 2 g orally once daily for 2 days or 1 g orally once daily for 5 days or clindamycin 300 mg orally twice daily for 7 days or 100 mg ovules intravaginally once at bedtime for 3 days, can be tried [70]. Patients with persistence or recurrence after first episode should be retreated with same recommended regime [71].

Follow-up visits are not required unless the patient has persistent or recurrent symptoms [70]. However, NACO recommends follow-up visit 7 days later to document symptomatic cure [16].

Multiple recurrences, which can be very distressing, can be treated with metronidazole 0.75% gel twice weekly for 4–6 months [72] or with metronidazole or tinidazole 500 mg twice daily for 7 days followed by intravaginal boric acid 600 mg gelatin capsules daily for 3 weeks followed by metronidazole 0.75% gel twice weekly for 4–6 weeks [73] or with metronidazole 2 g plus fluconazole 150 mg orally monthly [74].

Partner Treatment Treatment of asymptomatic sex partners is not recommended [70].

Pregnancy All symptomatic pregnant patients should be treated. In a study it was found that metronidazole 500 mg orally twice daily was as efficacious as topical metronidazole gel and thus pregnant patients can be treated with any oral or topical recommended regimen [70]. NACO, however, recommends treatment with metronidazole 400 mg twice a day for 7 days [16].

HIV HIV co-infected patients should be treated with same regime as non-co-infected patients [70].

Clinical features of the bacterial STIs are summarized in Table 18.1, while the diagnostic modalities and treatment summed in Table 18.2.

Table 18.1 Summary of clinical features of bacterial infections

Disease	Clinical features
Syphilis	Painless, well demarcated, superficial, indurated, ulcer (primary chancre) at the site of inoculation of organism. Secondary syphilis presents as skin rash, which may go unnoticed and untreated patients may progress to tertiary syphilis (gumma or cardiovascular syphilis). Neurosyphilis may accompany any stage
Chancroid	Single or multiple, painful, non-indurated, deep ulcer(s) that bleed on touch. Untreated cases may suffer from unilocular bubo that may rupture to form a sinus
LGV	Transient, superficial, avascular, painless, avascular ulcer followed by development of inguinal bubo (usually) which may rupture to form multiple sinuses. Untreated patients may develop the stage of complication, i.e. genito-anorectal stage
Donovanosis	Usually single, painless, beefy red, indurated ulcer that bleeds on touch
Gonorrhoea and Chlamydia	Moderate to profuse, mucoid/purulent/mucopurulent cervical discharge along with dyspareunia, intermenstrual or post-coital bleeding. Haematological dissemination may lead to DGI and there may be anorectal or pharyngeal involvement depending on mode of sexual activity
Bacterial vaginosis	Moderate, homogenous, grey-white, malodourous vaginal discharge that uniformly coats the vaginal walls

Table 18.2 Brief summary of diagnostic modalities and treatment of bacterial diseases

Disease	Diagnostic modalities	Management
Syphilis	Dark ground illumination; direct antigen detection by EIA, DFA-TP, PCR; treponemal and non-treponemal serological investigations	Inj. Benzathine penicillin 2.4 MU IM single dose for infectious syphilis and 3 doses a week apart for non-infectious syphilis
Chancroid	Gram's stain; antigen detection by direct immunofluorescence; culture; PCR and serology	Azithromycin 1 g orally
LGV	Culture; NAAT; serology; histology and antigen detection using EIA	Doxycycline 100 mg orally twice a day for 21 days
Donovanosis	Giemsa staining; histology; culture; PCR; antigen detection and complement fixation	Doxycycline 1 g once a week or 500 mg daily for at least 3 weeks
Gonorrhoea and Chlamydia	Gram's staining; culture; NAAT; antigen detection and serology (for chlamydia)	Inj. Ceftriaxone 500 mg IM with doxycycline 100 mg twice daily for 7 days
Bacterial vaginosis	Amsel's criteria; Gram's stain using Nugent or Hay/Ison criteria and molecular tests	Metronidazole 500 mg orally twice a day for 7 days

18.3 Viral STDs

18.3.1 Herpes Genitalis

Herpes genitalis is caused by *Herpes simplex virus* 1 and 2 (HSV 1 and 2), double stranded DNA viruses of Herpes viridae family. The virus persists for life in the body of the patient, as latency is a common property shared by all herpes viruses [75].

18.3.1.1 Epidemiology

HSV infection is considered the commonest cause of sexually transmitted genital ulcer disease (GUD) [76]. According to global estimates published in 2015, about 500 million people were infected with HSV [77]. According to CDC statistics, while seropositivity in women for HSV 1 increased from 16.5% to 31.6% when data of years 1999–2010 were compared with that of 2011–2016, seropositivity for HSV 2 decreased from 77.6% to 63.3% in the same period [78].

18.3.1.2 Clinical Features

Herpes genitalis can present as primary genital herpes, first episode non-primary genital herpes and recurrent genital herpes.

Primary genital herpes is associated with erythematous macular or papular lesions in groups, which subsequently vesiculate and lead to multiple, superficial, coalescing ulcers with erythematous, irregular margins and serous, non-indurated and non-vascular base (Fig. 18.3). These ulcers are usually painful. This can be accompanied by external dysuria and lymphadenopathy which is firm, tender and bilateral. Episode may last upto 3 weeks [79]. Concurrent viraemia may coincide with systemic symptoms like fever, headache and malaise in 24% of patients [80]. Various complications include disseminated herpes, encephalitis, aseptic meningitis, hepatitis, cervicitis, pneumonitis, PID and neonatal herpes [81].

First episode non-primary genital herpes occurs in patients who are already seropositive for either HSV1 or 2 and genital inoculation occurs with the other strain without antibodies. The antibodies already present, try to neutralize this virus and thus the episode is less severe than primary episode [82].

Recurrent herpes genitalis occurs five times less commonly if the infecting virus is HSV1. Recurrent episodes are most common in first year after primary episode and decrease in frequency thereafter. Individual episodes are less severe than primary episode in terms of number of lesions, duration required for resolution and constitutional symptoms [79].

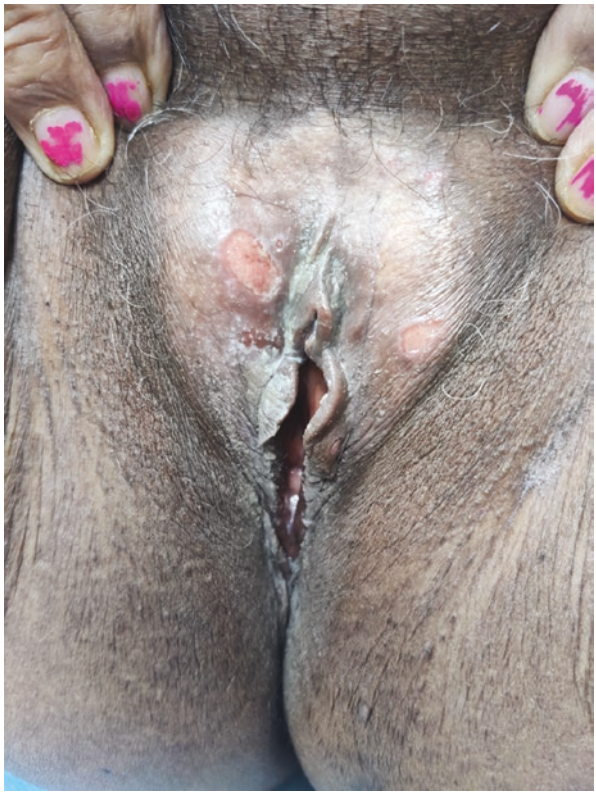

Fig. 18.3 Multiple, well-defined ulcers of Herpes genitalis

18.3.1.3 Diagnosis

Herpes genitalis can be diagnosed using cytological tests (POC), viral culture, viral antigen detection, serological evaluation and molecular tests [83]. Tzanck smear shows acantholytic cells (ballooning degeneration), multinucleate giant cells along with inflammatory cells with an approximate sensitivity of 46.7% (Fig. 18.4) [83]. Viral culture is considered "gold standard". Its specificity is almost 100%, with a variable sensitivity depending upon the type of lesion from which sample is derived (70–80% from a swab from ulcer base) [83]. Immunofluorescence detects infected cells from genital ulcers with specificity of >95% [84]. NAAT, like Aptima HSV 1 and 2, have the highest sensitivities [85].

Serology can be done in the following situations: [22].

- Clinical diagnosis without laboratory confirmation.
- Recurrent or atypical symptoms with negative PCR or culture results.
- Patient whose partner has herpes genitalis.

HerpeSelect ELISA is FDA approved serological test, with a sensitivity and specificity of 96–100% compared to western blot assay, which is gold standard for antibody detection [86].

18.3.1.4 Management

Primary episode can be treated with acyclovir 400 mg orally thrice a day for 7 days [16]. CDC recommends acyclovir 400 mg orally thrice a day for 7–10 days or acyclovir 200 mg orally five times a day for 7–10 days or valacyclovir 1 g orally twice a day for 7–10 days or famciclovir 250 mg orally thrice a day for 7–10 days [22].

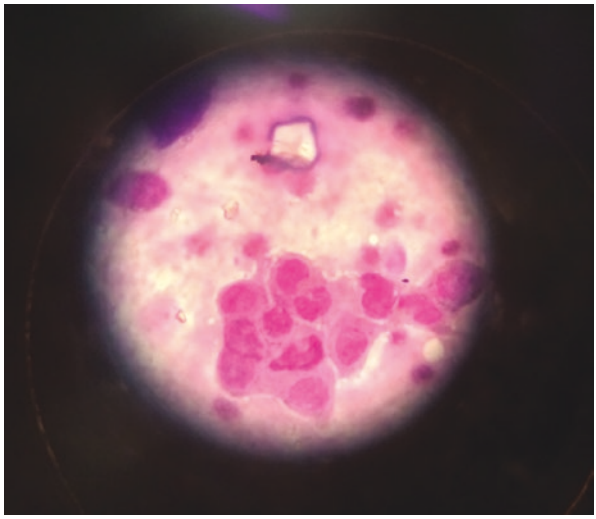

Fig. 18.4 Tzanck smear depicting multinucleate giant cells (100×, oil immersion)

Suppressive therapy can be offered in patients with >6 recurrences in a year. It reduces the frequency of recurrences by 70–80%. Recommended regimens include acyclovir 400 mg orally twice a day or valacyclovir 1 g orally once a day or famciclovir 250 mg twice a day [22]. Episodic therapy can be done with acyclovir 400 mg orally thrice a day for 5 days or valacyclovir 1 g orally once a day for 5 days or famciclovir 125 mg orally twice daily for 5 days [22].

Severe or complicated infection (pneumonia, hepatitis or dissemination) or CNS involvement should be treated with intravenous acyclovir in a dose of 5–10 mg/kg IV every 8 h for 2–7 days or until clinical improvement is observed, followed by oral therapy to complete 10 days of treatment. Encephalitis however has to be treated for 21 days [22].

Partner Management Asymptomatic partners can be offered type-specific serological evaluation. Only symptomatic partners are to be treated [22].

Pregnancy Type-specific serology can help in identifying women at risk of acquisition of infection. All women with no history of genital herpes should be asked to abstain from sexual intercourse in third trimester and also oro-genital contact if history of orolabial herpes is absent. There is approximately 30–50% chance of neonatal transmission near the time of delivery but very low chance (<1%) if infection is acquired before pregnancy or in first trimester. Acyclovir can be safely administered to all women orally or parenterally depending on severity of infection. Women with active lesions or symptoms of prodrome should be delivered by caesarean section to reduce neonatal transmission [22]. American College of Obstetricians and Gynaecologists recommends suppressive therapy from 36th week of gestation in women with history of recurrent genital herpes. Acyclovir 400 mg orally thrice a day or valacyclovir 500 mg orally twice a day is recommended [87]. NACO recommends the acyclovir regimen [16].

HIV In a patient with herpes genitalis, concomitant HIV infection increases viral shedding. Antiretroviral therapy may reduce frequency and severity of symptomatic genital herpes but asymptomatic, subclinical shedding may still occur. Suppressive therapy should thus be considered in these patients as it decreases the severity of clinical manifestations in co-infected patients. Episodic treatment can be considered in patients unwilling for suppressive therapy. Recommended regimen for acyclovir and valacyclovir are same in dosage as HIV uninfected patients but given for 5–10 days [22].

18.3.2 Genital Warts

Genital warts are caused by Human Papillomavirus (HPV), mainly type 6 and 11. HPV is a non-enveloped, double-stranded DNA virus, belonging to Papovaviridae family. Its genome has 6 early-open reading frames (E1,2,4,5,6,7) and 2 late-open

reading frames (L1,2). While the former is responsible for viral replication and encoding proteins, latter encodes viral capsid proteins [87].

18.3.2.1 Epidemiology

In a study conducted in 2013–2014, 42.5% of population in age group 18–59 years was found to be infected with HPV [88].

18.3.2.2 Clinical Features

Anogenital warts are of 3 main morphological variety: acuminate, flat/macular and papular variant. Acuminate warts are primarily seen on mucosal aspect of the genitalia and have an irregular surface and finger-like projections (Fig. 18.5). Flat warts, as the name suggests, are macular and are difficult to clinically distinguish from intraepithelial neoplasia. Third variant, the papular variety, is seen on the extramucosal aspect of genitalia. A rare variant, Buschke-Lowenstein giant tumour, can be seen in immunocompromised patients [89]. Urethral meatus involvement is less common in females compared to males. Instead, cervical warts may be encountered on per speculum examination [90].

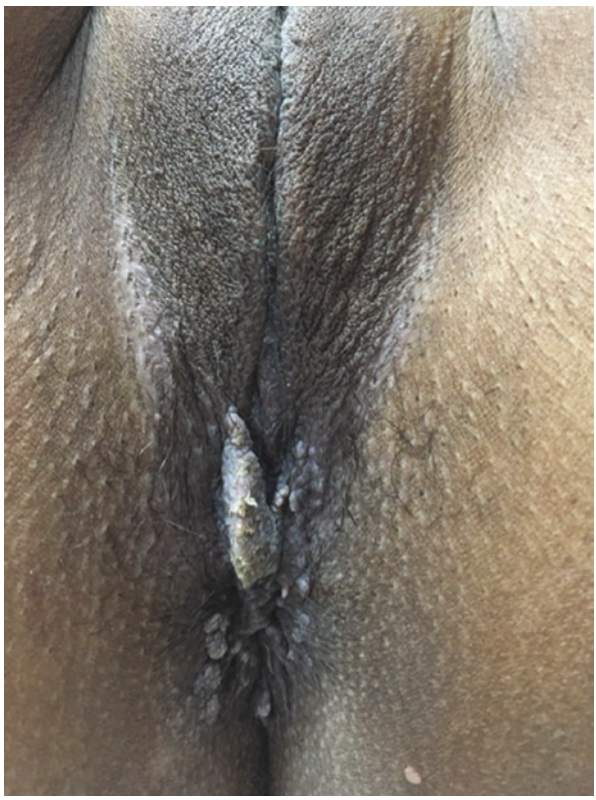

Fig. 18.5 Hyperkeratotic warts (image courtesy: Dr. Mahima Agarwal) over the vulva

About a third of the lesions regress spontaneously in a span of about 4 months [87]. While malignant transformation in a genital wart caused by low risk HPV type (6 and 11) is negligible, in situ carcinoma may occur in warts caused by high risk HPV (like 16 and 18). However, even this transformation is uncommon and may reflect immunosuppressed status of the patient [91].

18.3.2.3 Diagnosis

Genital warts are mainly diagnosed clinically. The doubtful lesions can be subjected to histology, which shows presence of hyperkeratosis, papillomatosis and koilocytosis, i.e. multiple perinuclear vacuoles within the infected cells, along with presence of irregular nuclei [92]. Acetowhite staining technique may be used to diagnose flat or macular warts [89]. Pap smear can be combined with Hybrid capture HPV DNA test 2 (HC2), which is FDA approved to detect HPV; as low as 1 pg HPV DNA/ml can be detected. In a study, its sensitivity for detection of lesions more severe than CIN 2 was 100%, specificity 64.8%, positive predictive value 66.7% and negative predictive value 100% [93]. PCR can also be performed. In a study comparing HC2 with PCR, the sensitivities of the HC2 assay and PCR for the detection of high grade squamous intraepithelial lesions (HSIL) were 85.2 and 74.0%, respectively, and the specificities were 67.2 and 64.1%, respectively [94].

18.3.2.4 Management

CDC has given recommendations to treat external anogenital warts, vaginal warts, urethral warts, cervical warts and intra-anal warts.

External anogenital warts can be treated with imiquimod 3.75% or 5% cream or with podofilox 0.5% solution or with sinecatechins 15% ointment. All these modalities are patient applied, reduce hospital visits and improve compliance. If the patient is willing to visit hospital, then provider administered modalities include trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90% solution or cryotherapy with liquid nitrogen or surgical excision by tangential scissor excision, curettage, laser, tangential shave excision or with electrosurgery [95].

Urethral meatal warts can be removed by cryotherapy or surgically. Vaginal, cervical and intra-anal warts can be treated with cryotherapy or surgically or using TCA/BCA 80–90% solution [95].

NACO recommendations for penile and perianal warts include 20% podophyllin, cryotherapy, electrocautery or surgical excision. Cryotherapy is modality of choice for cervical warts and vaginal warts can be treated with podophyllin 10–25% or TCA 50–75%, using vaginal speculum [16].

Partner Treatment Asymptomatic partners can be screened for presence of warts and other STDs [95].

Pregnancy Podophyllox, podophyllotoxin, imiquimod and sinecatechins are not to be used in pregnancy. Caesarean delivery is indicated only if pelvic outlet is obstructed or if vaginal delivery will lead to excessive bleeding [95].

18.3.3 Molluscum Contagiosum

Molluscum is caused by Molluscum contagiosum virus (MCV), belonging to Molluscipox family. Of the four genotypes, MCV 1 and 2 are encountered most commonly [96].

18.3.3.1 Epidemiology

Molluscum is more commonly seen in children than in adults and in men more than women. Worldwide, the prevalence of molluscum in children aged 0–16 is 8000 per 1,00,000 population [97].

18.3.3.2 Clinical Features

It is characterized by presence of single or multiple, clustered or discrete, skin coloured to pink coloured, firm, round, shiny and umbilicated papules of size about 2–5 mm (Fig. 18.6). In adults, lesions are mainly encountered on lower abdomen, thighs, and genitalia, as the transmission is usually sexual. Similar distribution in children is often from autoinoculation and thus is not always suspicious of abuse [98]. In about 9–47% cases, eczematous plaques may develop around 1–2 lesions, called molluscum dermatitis [99]. Beginning of the end (BOTE) phenomenon refers to development of inflammation around a lesion due to immune response and reflects imminent self-resolution of the lesion [100]. In immunocompromised patients, lesions are larger (giant molluscum), more numerous (>100), resolve slowly and don't respond well to treatment [101].

The lesions usually resolve in 6–9 months, but some lesions persist upto 3–4 years [102].

18.3.3.3 Diagnosis

It is mainly clinical diagnosis. However, it can be subjected to dermoscopy, which shows multilobular, white to yellowish, amorphous structureless areas with central umbilication and peripheral crown of vessels [103]. Histology reveals lobular proliferation of the affected epidermis with presence of eosinophilic intracytoplasmic inclusion bodies, called Henderson Paterson bodies [104].

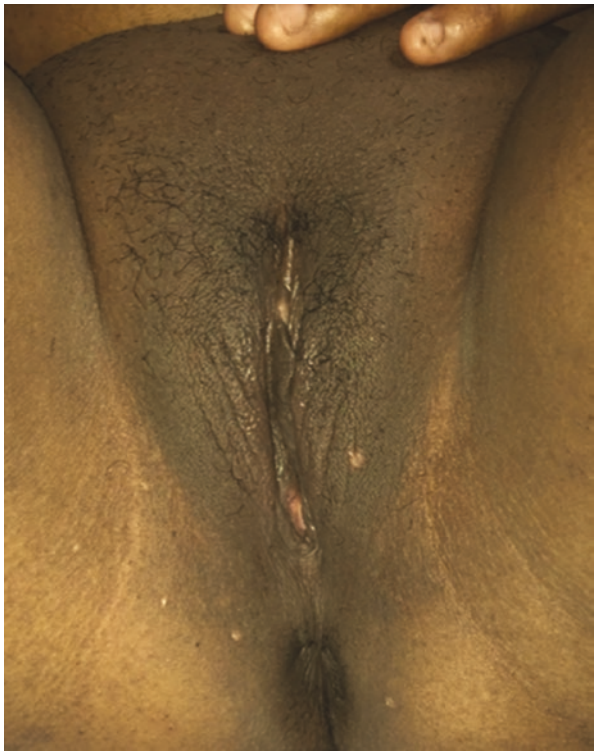

Fig. 18.6 Multiple molluscum contagiosum on the vulva

18.3.3.4 Management

NACO recommends that all the individual lesions should be laid open and their walls cauterized with 25% phenol solution or 30% TCA, after removal of central core [16].

Apart from the mechanical removal (evisceration) of the lesions, various other localized treatments like podophyllotoxin 0.5% cream, imiquimod 5% cream, cantharidin 0.9% solution, tretinoin 0.1% cream, 10% iodine solution, 10% potassium hydroxide solution and tape stripping can be tried. Cryotherapy, oral immunomodulators like ranitidine and zinc can be combined with local treatment [98].

18.3.4 Hepatitis Virus

Hepatitis B virus and hepatitis C virus are sexually transmitted. However, under certain circumstances, hepatitis A virus can also be transmitted sexually. As the name signifies, it primarily affects the liver; however, some non-specific cutaneous findings like polyarteritis nodosa, Gianotti-Crosti disease, lichen planus, porphyria cutanea tarda and prurigo can be seen. The diagnosis relies on seroconversion.

Table 18.3 Summary of clinical features of viral infections

Disease	Clinical features
Herpes genitalis	Multiple, painful, clear to turbid fluid filled vesicles that rupture to form coalescing, irregular and polycyclic erosions over external genitalia. Cervicitis may accompany
Genital warts	Single or multiple, painless, verrucous growths (may be flat or popular or acuminate in morphology) over genitalia
Molluscum contagiosum	Single or multiple, skin to pink coloured, firm, round and umbilicated papules of size about 2–5 mm

Table 18.4 Brief summary of diagnostic modalities and treatment of viral diseases

Disease	Diagnostic modalities	Treatment
Herpes genitalis	Tzanck smear; viral culture; antigen detection using immunofluorescence; serology and NAAT	Acyclovir 400 mg thrice a day for 7 days or valacyclovir 1 g twice a day for 7 days
Genital warts	Clinical diagnosis; histology and PCR	Imiquimod 5%; podofilox 0.5%; sinecatechins 15% ointment; TCA 80–90% and cryotherapy
Molluscum contagiosum	Clinical diagnosis; dermoscopy; crush smear and histology	Extirpation; chemical cautery using TCA 30% or phenol 25% solution; imiquimod 5% cream; podophyllotoxin 0.5% cream; cryotherapy and oral immunomodulators like ranitidine and zinc

Treatment is mainly symptomatic. However, antivirals like lamivudine, adefovir, tenofovir and emtricitabine have been tried [105].

Clinical features of the viral STIs are summarized in Table 18.3 with their diagnostic modalities and treatment summed up in Table 18.4.

18.4 Fungal and Protozoal STDs

18.4.1 Vulvovaginal Candidiasis (VVC)

Vulvovaginal candidiasis may or may not be sexually transmitted. *Candida albicans* (*C. albicans*) is the commonest species. Non-albican species include *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. guilliermondi* and *C. tropicalis* [106]. Approximately 75% women will have at least 1 episode of VVC in their lifetime with 40–45% developing 2 or more episodes [70].

CDC classifies VVC into uncomplicated (mild-moderate, sporadic or infrequent VVC in non-immunocompromised women, likely caused by *C. albicans.*) and complicated (recurrent or severe VVC or VVC in immunocompromised women or VVC caused by non-albicans candida) VVC. Recurrent VVC is defined as 4 or more episodes in a year [70].

18.4.1.1 Epidemiology

In an epidemiological study from India, out of 100 women with vaginal discharge, 27% had bacterial vaginosis, 25% had trichomoniasis and 22% had candidiasis [107]. According to statistics in the USA, 1.4 million women had vulvovaginal candidiasis [108].

18.4.1.2 Clinical Features

VVC is characterized by scanty to moderate, white, clumped, cheesy, adherent plaques of thick discharge (Fig. 18.7). This is accompanied by vaginal and vulval erythema and excoriations. Associated complaints like vulvar itching, external dysuria and dyspareunia are usually present. Per speculum examination shows adherent discharge over the vaginal walls. Cervicitis is usually not an accompaniment to vaginitis. Perianal involvement, satellite micropustules around labium majus and post thrush vestibulitis may also be present [106].

18.4.1.3 Diagnosis

Investigations including 10% potassium hydroxide (KOH) mount, culture, serological test and molecular diagnostic procedures can be employed to confirm the diagnosis.

10% KOH mount is POC test. After homogenizing with 10% KOH, the discharge is examined under microscope to visualize pseudohyphae (Fig. 18.8). Its sensitivity is only 30–45% [109]. Culture for VVC is performed only if clinical features are suggestive of VVC, but no organism can be visualized on microscopy or in patients with recurrent or persistent infection, in whom either the infecting

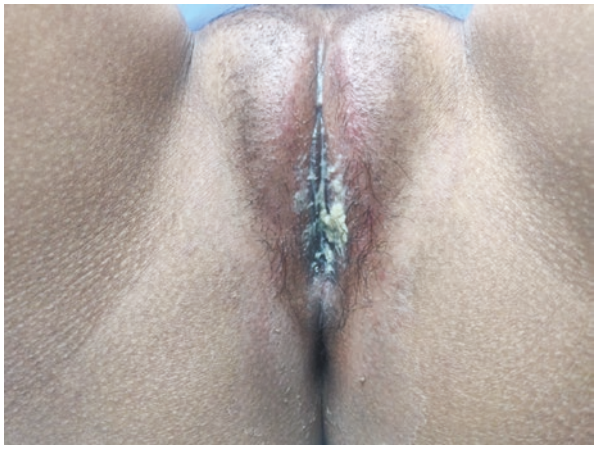

Fig. 18.7 Thick curdy white discharge of vulvovaginal candidiasis

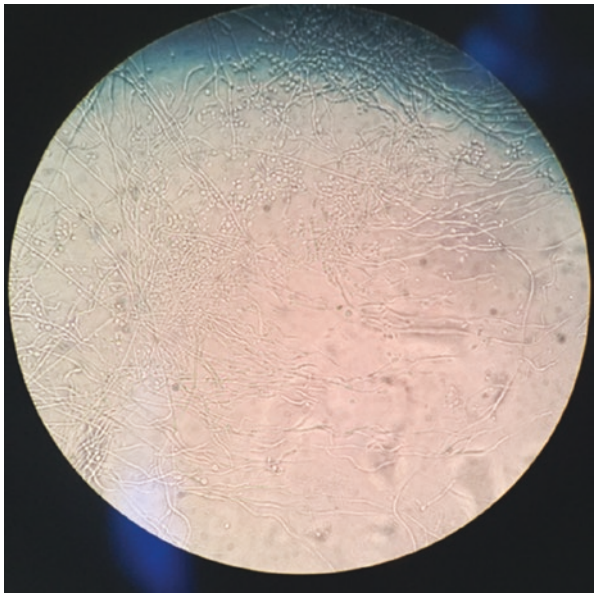

Fig. 18.8 Multiple pseudohyphae seen on 10% KOH examination (10×) from a case of vulvovaginal candidiasis

organism is suspected to be resistant to azoles or is one of the non-albicans species [70]. Various culture media include Sabouraud dextrose agar, Sabouraud brain heart infusion, Potato dextrose agar or broth, blood agar, Yeast nitrogen base and Yeast potato dextrose agar or broth [110]. CHROMagar can be used to detect *albicans* genome (40 fg of *C. albicans* genomic DNA) per 30 μl of serum [111]. Aptima CV/TV is approved by US Food and drug administration for identifying *C. albicans* [112]. Another molecular test, BD MAX, identifies not only candida species (sensitivity 90% and specificity 94%) but also organisms for BV and trichomoniasis [113].

18.4.1.4 Management

Topical formulations in a short course i.e. regimens for 1–3 days are effective for uncomplicated VVC. Clotrimazole 1% cream 5 g intravaginally for 7–14 days or miconazole 2% cream 5 g intravaginally for 7 days or tioconazole 6.5% ointment 5 g intravaginally in a single application can be given [70].

Severe VVC, i.e. presence of extensive vulvar erythema, edema fissures and excoriations, can either be treated with extended topical treatment for 7–14 days or 150 mg fluconazole can be sequentially re-administered after 72 h, i.e. on day 1 and 4 [22]. Recurrent VVC can be treated with either extended topical treatment over 7–14 days or with 100 mg, 150 mg or 200 mg fluconazole administered on day 1,4,7 for mycological remission followed by maintenance with same dose fluconazole weekly for 6 months [70].

Partner Treatment Only symptomatic partners are treated as uncomplicated VVC is generally not considered acquired sexually [70].

Pregnancy Pregnant females should be treated only with topical azoles for 7 days [70].

HIV HIV seropositive patients should be treated with same regimen as non-co-infected patients [70].

18.4.2 Trichomoniasis

It is caused by *Trichomonas vaginalis,* which is a flagellated protozoan parasite that survives in strictly anaerobic environment but in wide range of pH (3.5–8) [114].

18.4.2.1 Epidemiology

Prevalence of trichomoniasis in general population is about 5% in Indian community while it is about 60% in high risk groups [115]. According to statistics in the USA, 3.7 million patients were afflicted with trichomoniasis [116].

18.4.2.2 Clinical Features

It is characterized by profuse, frothy, greenish yellow discharge, along with vulval and vaginal erythema.

It is associated with intense itching or it may be asymptomatic. External dysuria may be present. Per speculum examination shows vaginal discharge and may show strawberry cervix with punctate hemorrhagic points [117].

Patients may also complain of irregular bleeding or post-coital bleeding and pelvic pain. Trichomoniasis may be further complicated by pelvic inflammatory disease, adverse pregnancy outcomes and cervical cancer [117].

18.4.2.3 Diagnosis

Wet mount is the POC test for trichomoniasis with sensitivity of about 60–70%. The organism remains motile in smears for about 10–20 min. Jerky and spinning motility can be observed [118]. Culture on Diamond's media was considered gold standard with sensitivity of upto 95% and specificity of >95%. It requires about 7 days. The InPouch TV culture technique requires about 3 days but has sensitivity of only 80%. However, culture has now been replaced by NAAT [119]. One of the most common PCR based tests, Aptima *T. vaginalis* assay has sensitivity and specificity of 95–100%. It is FDA approved [120]. Other available NAATs include Amplicore,

Xpert TV and NuSwab VG. BD MAX test also detects candida and bacterial vaginosis. It is FDA approved for the same [121]. Rapid antigen hybridization assays are useful mainly for vaginal swabs. AFFIRM VP III involves DNA hybridization and gives results in 45 min with sensitivity and specificity of about 95% [122]. OSOM Trichomonas rapid test uses immunochromatographic technology and gives result in 10 min with sensitivity of 82–95% and specificity of 97–100% [123].

18.4.2.4 Management

Recommended regimens include metronidazole or tinidazole 2 g orally in a single dose [70].

Persistent or recurrent trichomoniasis may be due to reinfection or drug resistance. If reinfection has been ruled out and patient was initially treated with metronidazole 2 g single dose orally, then patients and partner/s can be treated with metronidazole 500 mg orally twice a day for 7 days. Metronidazole or tinidazole 2 g orally daily for 7 days can be tried if the above fails. If the patient still does not respond, then susceptibility testing should be performed. In resistant cases, tinidazole 2–3 g for 14 days with intravaginal tinidazole usually brings about response.

Partner Treatment All concurrent sex partners should be treated presumptively to reduce the risk of reinfection in the patient [70]. NACO recommends treatment of all partners in last 30 days [16].

Pregnancy Pregnant patients should be treated with same regimen as non-pregnant patients [70]. Metronidazole can be safely used in first trimester. NACO recommends treating with metronidazole 400 mg twice a day for 7 days [16]. While screening in asymptomatic patients for trichomoniasis is not recommended, patients co-infected with HIV should be screened in first trimester to reduce vertical transmission of HIV [70].

HIV Single dose metronidazole regimen is insufficient for patients co-infected with HIV. They should thus be treated with metronidazole 500 mg orally twice daily for 7 days [70].

Clinical features of the fungal and protozoal STIs are summarized in Table 18.5, while the diagnostic modalities and treatment are summed in Table 18.6.

Table 18.5 Summary of clinical features of fungal and protozoal infections

Disease	Clinical features
Vulvovaginal candidiasis	Scanty to moderate, white, clumped, thick and curdy white discharge usually accompanied by external dysuria and vulvar itching
Trichomoniasis	Profuse, frothy, greenish yellow discharge, usually accompanied by vulval itching and external dysuria

Table 18.6 Brief summary of diagnostic modalities and treatment of fungal and protozoal diseases

Disease	Diagnostic modality	Management
Vulvovaginal candidiasis	10% KOH examination; culture; serology and molecular tests	Clotrimazole 1% cream 5 gm intravaginally for 7–14 days with fluconazole 150 mg single dose
Trichomoniasis	Wet mount; culture and NAAT	Metronidazole or tinidazole 2 g orally single dose

18.5 Pelvic Inflammatory Disease

Infection and inflammation of upper genital tract in women, i.e. uterus, fallopian tubes and ovaries, is referred to as PID. The commonest organisms responsible are *Neisseria gonorrhoeae* and *Chlamydia trachomatis.* Others include *Mycoplasma genitalium*, *Haemophilus influenzae*, *Streptococcus pneumonia*, *Staphylococcus aureus Escherichia coli*, *Bacteroides fragilis*, group B Streptococci and organisms causing BV [124].

18.5.1 Epidemiology

PID can lead to tubal infertility in upto 30% of the patients [125]. However, with increasing awareness, incidence of PID is showing declining trends. This was exemplified in data provided by National Disease and Therapeutic Index, according to which visits for PID in 2007–2016 declined by 38.3% [4].

18.5.2 Clinical Features

Lower back and abdominal pain, dyspareunia, post-coital or intermenstrual bleeding are main clinical features indicating PID. This may be accompanied by presence of vaginal discharge [124].

18.5.3 Diagnosis

While laparoscopy is the definitive diagnostic modality, it usually is not available and thus sole dependence on it may delay the diagnosis. Thus, ultrasonography can be performed. Presence of thickened and fluid filled tubes are 85% sensitive and 100% specific for PID. Doppler can demonstrate tubal hyperemia [126]. MRI can also be done for the same. However, it is expensive and is thus not performed very frequently [127].

18.5.4 Management

In mild to moderate PID, decision to hospitalize depends on the presence of factors like pregnancy, tubo-ovarian abscess, inability to tolerate oral regimens, or no response to oral regimens, as both parenteral and oral regimes have equal efficacy in this severity spectrum. Recommended parenteral regimes include: cefotetan 2 g IV every 12 h plus doxycycline 100 mg orally or IV every 12 h or cefoxitin 2 g IV every 6 h plus doxycycline 100 mg orally or IV every 12 h or clindamycin 900 mg IV every 8 h plus gentamicin loading dose IV or IM (2 mg/kg), followed by a maintenance dose (1.5 mg/kg) every 8 h. Alternative IM regimens include ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. If cephalosporins cannot be administered, then levofloxacin 500 mg orally once daily, ofloxacin 400 mg twice daily, or moxifloxacin 400 mg orally once daily with metronidazole for 14 days (500 mg orally twice daily) can be considered [127].

Partner Treatment All sexual partners who had sexual contact with the patient in past 60 days should be evaluated and presumptively treated for gonorrhoea and chlamydia [127].

Pregnancy All pregnant patients should be hospitalized and given parenteral treatment [127].

HIV HIV co-infected patients respond equally well to recommended parenteral and oral regimens as non-co-infected patients [127].

18.6 Conclusion

With female patients forming the bulk of patients attending STI clinics and due to their potential to transmit infection to newborn if infection is perinatal, they are the most important targets of adequate counselling and thus termination of chain of STIs. Adequate knowledge of commonly encountered STIs, POC to aid the clinical diagnosis and provision of appropriate treatment in agreement with latest guidelines is therefore of utmost importance.

References

1. Smith L, Angarone MP. Sexually transmitted infections. Urol Clin North Am. 2015;42(4):507–18.
2. Report on global sexually transmitted infection surveillance, 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO] https://www.who.int/reproductivehealth/publications/stis-surveillance-2018/en/.

3. Lukehart SA. Biology of treponemes Holmes. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, Cohen MS, Watts DH, editors. Sexually transmitted diseases. 4th ed. New York: The McGraw-Hill Companies; 2007. p. 647–61.
4. French P, Gupta S, Bhushan K. Infectious syphilis. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 429–57.
5. Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev. 1999;12:187–209. https://doi.org/10.1128/CMR.12.2.187.
6. Harrison LW. The Oslo study of untreated syphilis review and commentary. Sex Transm Infect. 1956;32:70–8.
7. Ratnam S. The laboratory diagnosis of syphilis. Can J Infect Dis Med Microbiol. 2005;16(1):45–51.
8. Spakling PF, Swartz MN, Musher DM, Healy BP. Clinical manifestations of syphilis. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, Cohen MS, Watts DH, editors. Sexually transmitted diseases. 4th ed. New York: The McGraw-Hill Companies; 2007. p. 661–84.
9. Quatresooz P, Piérard GE. Skin homing of *treponema pallidum* in early syphilis: an immunohistochemical study. Appl Immunohistochem Mol Morphol. 2009;17(1):47–50.
10. Shields M, Guy RJ, Jeoffreys NJ, Finlayson RJ, Donovan B. A longitudinal evaluation of *Treponema pallidum* PCR testing in early syphilis. BMC Infect Dis. 2012;12:353.
11. Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. Clin Infect Dis. 2020;71(Suppl_1):S21–42.
12. Henao-Martínez AF, Johnson SC. Diagnostic tests for syphilis: new tests and new algorithms. Neurol Clin Pract. 2014;4(2):114–22.
13. Castro AR, Esfandiari J, Kumar S, Ashton M, Kikkert SE, Park MM, et al. Novel point-of-care test for simultaneous detection of nontreponemal and treponemal antibodies in patients with syphilis. J Clin Microbiol. 2010;48(12):4615–9.
14. Ortiz DA, Shukla MR, Loeffelholz MJ. The traditional or reverse algorithm for diagnosis of syphilis: pros and cons. Clin Infect Dis. 2020;71(Suppl_1):S43–51.
15. National AIDS Control Organization. Ministry of Health and Family Welfare Government of India. National guidelines on prevention, management and control of reproductive tract infections and sexually transmitted infections. New Delhi, India; 2014.
16. Workowsky KA, Bolan GA. Syphilis. MMWR Recomm Rep. 2015;64(RR-3):34–48.
17. Centre of Disease Control and Prevention. Sexually transmitted disease surveillance. 2018. http://www.cdc.gov/std/stats18/other.htm. Accessed 27 Dec 2020.
18. Lewis DA. Chancroid: clinical manifestations, diagnosis, and management. Sex Transm Infect. 2003;79(1):68–71.
19. Al-Tawfiq JA, Thornton AC, Katz BP, et al. Standardization of the experimental model of Haemophilus ducreyi infection in human subjects. J Infect Dis. 1998;178:1684–7.
20. Nanda S, Reddy BV, Reddy BSN. Chancroid. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 522–31.
21. Workowsky KA, Bolan GA. Diseases characterized by genital, anal or perianal ulcers. MMWR Recomm Rep. 2015;64(RR-3):25–33.
22. Lewis DA. Diagnostic tests for chancroid. Sex Transm Infect. 2000;76(2):137–41.
23. Alfa M. The laboratory diagnosis of *Haemophilus ducreyi*. Can J Infect Dis Med Microbiol. 2005;16(1):31–4.
24. Glatz M, Juricevic N, Altwegg M, Bruisten S, Komericki P, Lautenschlager S, et al. A multicenter prospective trial to asses a new real-time polymerase chain reaction for detection of *Treponema pallidum, Herpes simplex*-1/2 *and Haemophilus ducreyi* in genital, anal and oropharyngeal ulcers. Clin Microbiol Infect. 2014;20(12):1020–7.
25. Elkins C, Yi K, Olsen B, Thomas C, Thomas K, Morse S. Development of a serological test for *Haemophilus ducreyi* for seroprevalence studies. J Clin Microbiol. 2000;38(4):1520–6.
26. Spaargaren J, Schachter J, Moncada J, de Vries HJ, Fennema HS, Peña AS, Coutinho RA, Morré SA. Slow epidemic of lymphogranuloma venereum L2b strain. Emerg Infect Dis. 2005;11(11):1787–8.

27. Ceovic R, Gulin SJ. Lymphogranuloma venereum: diagnostic and treatment challenges. Infect Drug Resist. 2015;8:39–47.
28. De Vries HJC, Reddy BSN, Khandpur S. Lymphogranuloma venereum. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 506–21.
29. Ballard RC. Genital ulcer adenopathy syndrome. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, Cohen MS, Watts DH, editors. Sexually transmitted diseases. 4th ed. New York: The McGraw-Hill Companies; 2007. p. 1177–98.
30. Harrison T, Som M, Stroup J. Lymphogranuloma venereum proctitis. Proc (Bayl Univ Med Cent). 2016;29(4):418–9.
31. Mabey D, Peeling RW. Lymphogranuloma venereum. Sex Transm Infect. 2002;78:90.
32. Bachmann LH, Johnson RE, Cheng H, Markowitz L, Papp JR, Palella FJ, et al. Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* and *chlamydia trachomatis* rectal infections. J Clin Microbiol. 2010;48(5):1827–32.
33. Morré SA, Spaargaren J, Fennema JS, de Vries HJ, Coutinho RA, Peña AS. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum. Emerg Infect Dis. 2005;11(8):1311–2.
34. Lister NA, Tabrizi SN, Fairley CK, Garland S. Validation of roche COBAS Amplicor assay for detection of *chlamydia trachomatis* in rectal and pharyngeal specimens by an omp1 PCR assay. J Clin Microbiol. 2004;42(1):239–41.
35. O'Farrell N. Donovanosis. Sex Transm Infect. 2002;78(6):452–7.
36. Velho PE, Souza EM, Belda Junior W. Donovanosis. Braz J Infect Dis. 2008;12(6):521–5.
37. O'Farrell N. Donovanosis: an update. Int J STD AIDS. 2001;12(7):423–7.
38. Richens J. Donovanosis (granuloma inguinale). Sex Transm Infect. 2006;82(Suppl 4):21–2.
39. Carter JS, Kemp DJ. A colorimetric detection system for *Calymmatobacterium granulomatis*. Sex Transm Infect. 2000;76(2):134–6.
40. Centre of Disease Control and Prevention. Sexually transmitted disease surveillance 2018. https://www.cdc.gov/std/stats18/gonorrhea.htm. Accessed 16 Jan 2021.
41. Centre of Disease Control and Prevention. Sexually Transmitted disease surveillance 2018. https://www.cdc.gov/std/stats18/chlamydia.htm. Accessed 16 Jan 2021.
42. Reddy BSN, Khandpur S, Sethi S, Unemo M. Gonococcal infections. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 473–93.
43. Chan PA, Robinette A, Montgomery M, Almonte A, Cu-Uvin S, Lonks JR, et al. Extragenital infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: a review of the literature. Infect Dis Obstet Gynecol. 2016;2016:5758387.
44. Theofanakis CP, Kyriakidis AV. Fitz-Hugh–Curtis syndrome. Gynecol Surg. 2011; 8(2):129–34.
45. Steedman N. *Chlamydia trachomatis* infections. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 494–505.
46. Papp JR, Schachter J, Gaydos CA, Van Der Pol B. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*—2014. MMWR Recomm Rep. 2014;63:1.
47. Knox J, Tabrizi SN, Miller P, Petoumenos K, Law M, Chen S, et al. Evaluation of self-collected samples in contrast to practitioner-collected samples for detection of *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Trichomonas vaginalis* by polymerase chain reaction among women living in remote areas. Sex Transm Infect. 2002;29(11):647–54.
48. Goldenberg SD, Finn J, Sedudzi E, White JA, Tong CY. Performance of the GeneXpert CT/NG assay compared to that of the Aptima AC2 assay for detection of rectal *chlamydia trachomatis* and *Neisseria gonorrhoeae* by use of residual Aptima samples. J Clin Microbiol. 2012;50(12):3867–9.
49. Van Der Pol B, Taylor SN, Mena L, Lebed J, McNeil CJ, Crane L, et al. Evaluation of the performance of a point-of-care test for chlamydia and gonorrhea. JAMA Netw Open. 2020;3(5):e204819.
50. Gaydos CA, Van Der Pol B, Jett-Goheen M, Barnes M, Quinn N, Clark C, et al. Performance of the cepheid CT/NG Xpert rapid PCR test for detection of *chlamydia trachomatis* and *Neisseria gonorrhoeae*. J Clin Microbiol. 2013;51(6):1666–72.

51. US Food and Drug Administration. 510(k) Substantial equivalence determination decision summary: Binx health io CT/NG Assay.
52. Workowsky KA, Bolan GA. Gonococcal infections. MMWR Recomm Rep. 2015;64(RR-3):60–8.
53. Workowsky KA, Berman S. Gonococcal infections. MMWR Recomm Rep. 2010;59(RR-12):49–56.
54. St. Cyr S, Barbee L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1911–6.
55. Golden MR, Whittington WL, Handsfield HH, Hughes JP, Stamm WE, Hogben M, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med. 2005;352(7):676–85.
56. Workowsky KA, Bolan GA. Chlamydial infections. MMWR Recomm Rep. 2015;64(RR-3):55–9.
57. Hay P, Chandeying V. Bacterial vaginosis. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 542–56.
58. Centre of Disease Control and Prevention. Sexually transmitted disease surveillance 2018. https://www.cdc.gov/std/bv/stats.htm. Accessed 16 Jan 2021.
59. Vijaya D, Patil Sunil S, Sambarey Pradip W. Clinical and microscopic correlation of vaginal discharge. Int J Contemp Med Res. 2016;3(5):1328–31.
60. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74(1):14–22.
61. Landers DV, Wiesenfeld HC, Heine RP, Krohn MA, Hillier SL. Predictive value of the clinical diagnosis of lower genital tract infection in women. Am J Obstet Gynecol. 2004;190(4):1004–10.
62. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol. 1991;29(2):297–301.
63. Chawla R, Bhalla P, Chadha S, Grover S, Garg S. Comparison of Hay's criteria with Nugent's scoring system for diagnosis of bacterial vaginosis. Biomed Res Int. 2013;2013:365194.
64. Money D. The laboratory diagnosis of bacterial vaginosis. Can J Infect Dis Med Microbiol. 2005;16(2):77–9.
65. Bradshaw CS, Morton AN, Garland SM, Horvath LB, Kuzevska I, Fairley CK. Evaluation of a point-of-care test, BVBlue, and clinical and laboratory criteria for diagnosis of bacterial vaginosis. J Clin Microbiol. 2005;43(3):1304–8.
66. Briselden AM, Hillier SL. Evaluation of affirm VP microbial identification test for *Gardnerella vaginalis* and *trichomonas vaginalis*. J Clin Microbiol. 1994;32(1):148–52.
67. Schwebke JR, Taylor SN, Ackerman R, Schlaberg R, Quigley NB, Gaydos CA, et al. Clinical validation of the Aptima *Bacterial Vaginosis* and Aptima *Candida/trichomonas* vaginitis assays: results from a prospective multicenter clinical study. J Clin Microbiol. 2020;58(2):e01643–19.
68. Evaluation of Automatic Class III Designation for BD MAX Vaginal Panel. Deci son Summary. US Food and Drug Administration. www.accessdata.fda.gov/cdrh_docs/reviews/DEN160001.pdf. Accessed 16 Nov 2018.
69. Workowsky KA, Bolan GA. Diseases characterized by vaginal discharge. MMWR Recomm Rep. 2015;64(RR-3):69–78.
70. Bunge KE, Beigi RH, Meyn LA, Hillier SL. The efficacy of retreatment with the same medication for early treatment failure of bacterial vaginosis. Sex Transm Dis. 2009;36(11):711–3.
71. Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. Am J Obstet Gynecol. 2006;194(5):1283–9.
72. Reichman O, Akins R, Sobel JD. Boric acid addition to suppressive antimicrobial therapy for recurrent bacterial vaginosis. Sex Transm Dis. 2009;36(11):732–4.
73. McClelland RS, Richardson BA, Hassan WM. Improvement of vaginal health for Kenyan women at risk for acquisition of human immunodeficiency virus type 1: results of a randomized trial. J Infect Dis. 2008;197(10):1361–8.

74. Groves MJ. Genital herpes: a review. Am Fam Physician. 2016;93(11):928–34.
75. Satterwhite CL, Torrone E, Meites E, Dunne EF, Mahajan R, Ocfemia MC, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sex Transm Dis. 2013;40(3):187–93.
76. Looker KJ, Magaret AS, Turner KM, Vickerman P, Gottlieb SL, Newman LM. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. PLoS One. 2015;10(1):e114989.
77. https://www.cdc.gov/std/stats18/other.htm#herpes.
78. Sauerbrei A. Herpes genitalis: diagnosis, treatment and prevention. Geburtshilfe Frauenheilkd. 2016;76(12):1310–7.
79. Johnston C, Magaret A, Selke S, Remington M, Corey L, Wald A. *Herpes simplex virus* viremia during primary genital infection. J Infect Dis. 2008;198(1):31–4.
80. Corey L, Wald A. Genital herpes. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, Cohen MS, Watts DH, editors. Sexually transmitted diseases. 4th ed. New York: The McGraw-Hill Companies; 2007. p. 399–438.
81. LeGoff J, Péré H, Bélec L. Diagnosis of genital *Herpes simplex virus* infection in the clinical laboratory. Virol J. 2014;11:83.
82. Yaeen A, Ahmad QM, Farhana A, Shah P, Hassan I. Diagnostic value of Tzanck smear in various erosive, vesicular, and bullous skin lesions. Indian Dermatol Online J. 2015;6(6):381–6.
83. Sam SS, Caliendo AM, Ingersoll J, Abdul-Ali D, Kraft CS. Performance evaluation of the Aptima HSV-1 and 2 assay for the detection of HSV in cutaneous and mucocutaneous lesion specimens. J Clin Virol. 2018;99(100):1–4.
84. Al-Shobaili H, Hassanein KM, Mostafa MS, Al Duways AS. Evaluation of the HerpeSelect express rapid test in the detection of *Herpes simplex virus* type 2 antibodies in patients with genital ulcer disease. J Clin Lab Anal. 2015;29(1):43–6.
85. Al-Shobaili H, Hassanein KM, Mostafa MS, Al Duways AS. Evaluation of the HerpeSelect Express rapid test in the detection of *Herpes simplex virus* type 2 antibodies in patients with genital ulcer disease. J Clin Lab Anal. 2015;29(1):43–6.
86. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012;5(6):25–36.
87. McQuillan G, Kruszon-Moran D, Markowitz LE, et al. Prevalence of HPV in adults aged 18–69: United States, 2011–2014. NCHS data brief, no 280. Hyattsville, MD: National Center for Health Statistics; 2017.
88. Fox P, Rowen D. Anogenital warts, intraepithelial neoplasia, and their clinical management. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 366–74.
89. Chae JY, Bae JH, Yoon CY, et al. Female urethral condyloma causing bladder outlet obstruction. Int Neurourol J. 2014;18:42.
90. Gormley RH, Kovarik CL. Human papillomavirus-related genital disease in the immunocompromised host: part I. J Am Acad Dermatol. 2012;66:867.e1.
91. Vyas NS, Pierce Campbell CM, Mathew R, Abrahamsen M, Van der Kooi K, Jukic, et al. Role of histological findings and pathologic diagnosis for detection of human papillomavirus infection in men. J Med Virol. 2015;87(10):1777–87.
92. Lin CT, Tseng CJ, Lai CH, Hsueh S, Huang HJ, Law KS. High-risk HPV DNA detection by Hybrid Capture II. An adjunctive test for mildly abnormal cytologic smears in women > or = 50 years of age. J Reprod Med. 2000;45(4):345–50.
93. Kulmala SM, Syrjänen S, Shabalova I, et al. Human papillomavirus testing with the hybrid capture 2 assay and PCR as screening tools. J Clin Microbiol. 2004;42(6):2470–5. https://doi.org/10.1128/JCM.42.6.2470-2475.2004.
94. Anogenital warts CDC.
95. Zorec TM, Kutnjak D, Hošnjak L, et al. New insights into the evolutionary and genomic landscape of molluscum contagiosum virus (MCV) based on nine MCV1 and six MCV2 complete genome sequences. Viruses. 2018;10(11):586.

96. Olsen JR, Gallacher J, Piguet V, Francis NA. Epidemiology of molluscum contagiosum in children: a systematic review. Fam Pract. 2014;31(2):130–6.
97. Meza-Romero R, Navarrete-Dechent C, Downey C. Molluscum contagiosum: an update and review of new perspectives in etiology, diagnosis, and treatment. Clin Cosmet Investig Dermatol. 2019;12:373–81.
98. Berger EM, Orlow SJ, Patel RR, Schaffer JV. Experience with molluscum contagiosum and associated inflammatory reactions in a pediatric dermatology practice: the bump that rashes. Arch Dermatol. 2012;148(11):1257–64.
99. Butala N, Siegfried E, Weissler A. Molluscum BOTE sign: a predictor of imminent resolution. Pediatrics. 2013;131(5):e1650–3.
100. Vora RV, Pilani AP, Kota RK. Extensive giant molluscum contagiosum in a HIV positive patient. J Clin Diagn Res. 2015;9(11):Wd01–wd02.
101. van der Wouden JC, Menke J, Gajadin S, et al. Interventions for cutaneous molluscum contagiosum. Cochrane Database Syst Rev. 2017;5:CD004767.
102. Ianhez M, Cestari Sda C, Enokihara MY, Seize MB. Dermoscopic patterns of molluscum contagiosum: a study of 211 lesions confirmed by histopathology. An Bras Dermatol. 2011;86(1):74–9.
103. Brown J, Janniger CK, Schwartz RA, Silverberg NB. Childhood molluscum contagiosum. Int J Dermatol. 2006;45(2):93–9.
104. Brook G, Chawla Y. Hepatitis viruses. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 380–99.
105. Janet Say P. Genital candida infections. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 591–601.
106. Venugopal S, Gopalan K, Devi A, Kavitha A. Epidemiology and clinico-investigative study of organisms causing vaginal discharge. Indian J Sex Transm Dis AIDS. 2017;38(1):69–75.
107. Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of direct healthcare costs of fungal diseases in the United States. Clin Infect Dis. 2019;68(11):1791–7.
108. Carlson P, Richardson M, Paavonen J. Evaluation of the Oricult-N dipslide for laboratory diagnosis of vaginal candidiasis. J Clin Microbiol. 2000;38(3):1063–5.
109. Alwakeel SS, Nasser LA. Bacterial and fungal contamination of Saudi Arabian paper currency and cell phones. Asian J Biol Sci. 2011;4(7):556–62.
110. Madhavan P, Jamal F, Chong PP, Ng KP. Identification of *Candida* species using CHRO Magar Candida. In: Proceedings of 1st Joint Workshop of OGACH and OGMM Med Mycmedical mycology: from basic science to clinical needs, Vienna, Austria. 2009:54.
111. 510(k) substantial equivalence determination decision summary. https://www.accessdata.fda.gov/cdrh_docs/reviews/K190472.pdf.
112. Gaydos CA, Beqaj S, Schwebke JR, Lebed J, Smith B, Davis TE, et al. Clinical validation of a test for the diagnosis of vaginitis. Obstet Gynecol. 2017;130(1):181–9.
113. Pol BVD. *Trichomonas vaginalis* infection. In: Gupta S, Kumar B, editors. Sexually transmitted infections. 2nd ed. New Delhi: Elsevier; 2012. p. 602–9.
114. Muthusamy S, Elangovan S. A study on the prevalence of genital trichomoniasis among female outpatients attending sexually transmitted infection clinic in a tertiary care hospital. J Lab Physicians. 2017;9(1):16–9.
115. Centre of Disease Control and Prevention. Sexually Transmitted disease surveillance 2018. https://www.cdc.gov/std/trichomonas/stats.htm. Accessed 16 Jan 2021.
116. Kissinger P. Trichomonas vaginalis: a review of epidemiologic, clinical and treatment issues. BMC Infect Dis. 2015;15:307.
117. Krieger JN, Tam MR, Stevens CE, Nielsen IO, Hale J, Kiviat NB, et al. Diagnosis of trichomoniasis: comparison of conventional wet-mount examination with cytologic studies, cultures, and monoclonal antibody staining of direct specimens. JAMA. 1988;259(8):1223–7.
118. Borchardt KA, Zhang MZ, Shing H, Flink K. A comparison of the sensitivity of the InPouch TV, Diamond's and Trichosel media for detection of *Trichomonas vaginalis*. Sex Transm Infect. 1997;73(4):297–8.

119. Chapin K, Andrea S. APTIMA® *trichomonas vaginalis*, a transcription-mediated amplification assay for detection of *trichomonas vaginalis* in urogenital specimens. Expert Rev Mol Diagn. 2011;11(7):679–88.
120. Schwebke JR, Gaydos CA, Nyirjesy P, Paradis S, Kodsi S, Cooper CK. Diagnostic performance of a molecular test versus clinician assessment of vaginitis. J Clin Microbiol. 2018;56(6):e00252-18.
121. Andrea SB, Chapin KC. Comparison of Aptima *trichomonas vaginalis* transcription-mediated amplification assay and BD affirm VPIII for detection of T. vaginalis in symptomatic women: performance parameters and epidemiological implications. J Clin Microbiol. 2011;49(3):866–9.
122. Gaydos CA, Klausner JD, Pai NP, Kelly H, Coltart C, Peeling RW. Rapid and point-of-care tests for the diagnosis of *Trichomonas vaginalis* in women and men. Sex Transm Infect. 2017;93(S4):S31–5.
123. Mitchell C, Prabhu M. Pelvic inflammatory disease: current concepts in pathogenesis, diagnosis and treatment. Infect Dis Clin N Am. 2013;27(4):793–809. https://doi.org/10.1016/j.idc.2013.08.004.
124. Tsevat DG, Wiesenfeld HC, Parks C, et al. Sexually transmitted diseases and infertility. Am J Obstet Gynecol. 2017;216(1):1–9.
125. Cacciatore B, Leminen A, Ingman-Friberg S, Ylostalo P, Paavonen J. Transvaginal sonographic findings in ambulatory patients with suspected pelvic inflammatory disease. Obstet Gynecol. 1992;80(6):912–6.
126. Tukeva TA, Aronen HJ, Karjalainen PT, Molander P, Paavonen T, Paavonen J. Mr imaging in pelvic inflammatory disease: comparison with laparoscopy and us. Radiology. 1999;210(1):209–16.
127. Workowsky KA, Bolan GA. Pelvic inflammatory disease. MMWR Recomm Rep. 2015;64(RR-3):78–82.

Chapter 19
Challenges faced by women Dermatologists and Training Programs available to them

Isha Narang and Rashmi Sarkar

"I want to have clear skin like yours," said a patient. "I usually tan even darker than you" said another one. I hear these two phrases and their many paraphrases very frequently in my practice. While the former one was more popular during my training and practice in India, the latter is staple in my practice in the United Kingdom. Now as contrasting these as these two statements are, essentially their essence is the same. It is a huge challenge when a female dermatologist is judged not just for her knowledge and patient management skills but also the way she looks. While in India, I can imagine the women dermatologist do feel the pressure to have their "best face forward," in the UK the paraphrases of the latter statement also give racial connotations and one must chuckle and rest it there. So, I believe I belong to Fitzpatrick skin type 4, and I presume there must have been thoughts like "I want to be lighter than you." I would say I have not heard it but have clearly sensed it. This is just one challenge that we face apart from experiences of misogyny from patients and colleagues. Most of us women dermatologists have stories of being in a disadvantageous position due to gender bias which supersedes merit at various occasions, and I am no exception. Work–life balance is another tussle. But, even after all this, we wake up every morning to put our "best foot forward" and want nothing but the best for our patients.

There is no doubt that women understand each other the best. The cohort of women dermatologists is a special one due to some of the aforementioned reasons. There have been many initiatives nationally and internationally to bring the women dermatologist together. Women dermatologists are the flag bearer of our specialty

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and this is indicated by women leadership in various dermatological societies of the world. These initiatives have started a new era for women dermatologists.

The unique relationship of women and dermatology also encompasses dermatological problems specially pertaining to females. This may include a whole spectrum from pigmentary, connective tissue disorders to vulval disorders. Few international organizations like Women's dermatological Society are active towards supporting personal and professional development of women dermatologists. The Indian arm of this organization "Indian Women's Dermatology Society" aims to do similar nationally.

Mentorship programs offered by various organizations can be instrumental in molding and supporting a young dermatologist. Mentorship is defined as guidance received from a mentor who is generally a more experienced person in the same field. I have personally learnt a lot from my mentors, majority of them being women and have evolved professionally and personally (Figs. 19.1, 19.2, and 19.3). I have

Fig 19.1 Dr Sarkar and me, she is my first mentor in dermatology. I was her student during my dermatology training in Delhi, India. She still remains a mentor for me and for many across the world

Fig 19.2 Here I am with Dr Carmen Cantisani, my mentor at Sapienza University, Rome, Italy. This is the first time I practically realized dermatology depends on geography and Fitzpatrick skin type! I learnt complex concepts of skin cancer and dermoscopy from her

Fig 19.3 This is me with Dr Kid Wan Shum, my mentor in the UK. She gave me the confidence that all my aspirations can be achieved in a country that was new to me. I believe she has brought out the best in me and I have grown as a person both personally and professionally with her

inculcated many qualities from such driven women that make you believe that there is no limit in what you could achieve. Here is an outline of various similar opportunities nationally and internationally (Table 19.1). This is not an exhaustive list and some of these opportunities may be affected by the Covid-19 pandemic. The criteria

Table 19.1 National and International opportunities in dermatology for dermatologists/trainees

Society	Programs for development	Additional information
Women's Dermatology Society https://www.womensderm.org/	Mentorship programs available No funding available	Resident membership is free
International Society of Dermatology https://www.intsocderm.org/	Mentorship programs available with funding Maria-Duran Fellowship with funding	Concessionary fee for residents
Skin of color Society https://skinofcolorsociety.org	Mentorship programs No funding available	Free for resident members
European Academy of Dermatology Venereology https://www.eadv.org	Grants and Scholarships (including the ones offering free membership and EADV meeting registration) Courses and e-learning for residents	Reduced membership fee for residents
Indian Association of Dermatology Venereology and Leprosy (IADVL)	Travel grants Observership grants International dermatopathology scholarship grant IADVL Postgraduate Thesis Research Grants	Highly recommended for Indian trainees and dermatologists
Association of Cutaneous Surgeons of India https://acsinet.net	Observership in dermatosurgery	Usually 4 weeks observership. No financial support
All India Institute of Medical Sciences, New Delhi	Observership available in various disciplines Contact dermatitis, Dermatosurgery, Lasers, etc.	Usually 4 weeks. No financial support
Rajiv Gandhi University of Health Sciences (RGUHS),India [BMCRI, St John's Medical college, Cutis academy, Venkat Charmalya, Kempegowda Institute of medical sciences]	Fellowship available in various disciplines like Dermatosurgery, Aesthetic dermatology, Paediatric dermatology	Usually one year fellowships. Each institute has different application process
Maharashtra University of Health Sciences (MUHS), India	King Edward Memorial-Diagnostic dermatology Institute of skin cosmetology and Lasers-Basic phototherapy and lasers in clinical dermatology	Usually one year fellowships
St John's Derm Academy, United Kingdom https://www.stjohnsdermacademy.com/ A part of Guy's and St Thomas' Hospital	Fellowships, observership, and MSC Clinical Dermatology (Mostly fees based)	Sometimes funding can be sought from other organizations

Table 19.1 (continued)

Society	Programs for development	Additional information
The University of Manchester, United Kingdom	PhD/MPhil Dermatological Sciences (Fees based)	For ones interested in research
Society of Pediatric Dermatology https://pedsderm.net	Non-ABD Pediatric Dermatology Fellowship Programs (No funding) Grants and Awards	Free membership for residents/fellows
Medical Dermatology Society https://www.meddermsociety.org	Mentorships (Funding available)	Free membership for residents/fellows
National University Health System, Singapore https://www.nuhs.edu.sg/	Fellowship and Observership available No funding available (admin fee to be paid)	This is quite popular amongst Indian dermatologists as the demography and practice of dermatology is quite close to that in India
NYU Langone Health, New York https://med.nyu.edu/departments-institutes/dermatology/	International Observership Program (Fee based)	This can be utilized to understand the US system better
Trialect (Various programs internationally)	Traineeship, fellowship, and grants (Funding and scholarship available)	It is preferable to do check language requirements as mode of training in teaching may not be English in many of the programs offered

for these are dynamic, please check their website for details to see if this is suitable for you and your career goals. Also, every country has its own rules for International medical graduates, and you will need to comply by them.

Apart from these formal opportunities some mentors are happy to make arrangements locally if they think one is enthusiastic and passionate to learn from them. You may express your interest through meetings in conferences, courses and sometimes just an email can do wonders.

There is plethora of training opportunities available and it is great to learn from a group of diverse dermatologists, especially women. From my experience there are somethings you should not forget having faith in yourself and your training system is one, the other is making sure your choices have a positive impact on your career goals. Eventually your choices will have impact on patients and the whole dermatology community.

Part II
Aesthetic Dermatology

Chapter 20
Treatment of the Aging Face

Gulhima Arora, Sandeep Arora, and V. Sandeep Lal

20.1 Introduction

Aging is inevitable and progressive, starting in the third decade of life. Contributory factors are both intrinsic and extrinsic and hence both uncontrollable and controllable. Chronological aging encompasses involutional and structural changes and biological aging encompasses genetics as well as extrinsic factors such as ultraviolet radiation, pollution, and lifestyle habits. The two may, however, be asynchronous. The face is considered as one of the most important interfaces between the self and the outer world. Evident signs of aging pull back on one's self-esteem and image, making people seek treatment for the same [1]. This is more so with an increase in the elderly population cohort and an increase in awareness regarding the remedies for aging. There is a need for earlier interventions in aging skin in our population as Asian Indian population has been proposed to age earlier than the reported ages in Caucasian population [2].

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20.2 Pathophysiology of Aging

The complex biological process of aging influenced by extrinsic and intrinsic factors leads to cumulative physiological and structural changes in the face (Fig. 20.1). Senescent aging versus premature photoaging is on account of deeper structural changes as well, while the latter is confined only to skin changes.

Slower rate of epidermal cell turnover and the increase in cell cycle time, with a slower wound healing and less effective desquamation in older adults results in thin, atrophic, finely wrinkled, and intrinsically dry aged skin. Collagen production gradually reduces at the rate of 1% per year per unit area of the skin, with an enhanced rate seventh decade onwards. An altered ratio of collagen 3 to collagen 1 results from reduced, disorganized, and broken down collagen 1 [3, 4]. Elastin loss further results in reduced elasticity, wrinkling, and sagging of skin. Hyaluronic acid content in the epidermis reduces dramatically, while in the dermis remains stable. Alterations in matrisome interaction with extracellular matrix proteins underlines most of the changes in either type of aging skin, while genomic alterations may further predispose an individual to these changes [5, 6].

Photoaged skin has marked collagen and elastin degradation caused by the metalloproteinases and proteases which along with ineffective glycosaminoglycan reduces water binding. However, marked depletion of serine proteases, increase in pro-inflammatory proteases, and elastic fiber-associated proteins in photodamaged skin result in elastosis. Overall a reduction in functional elastin fibers versus an

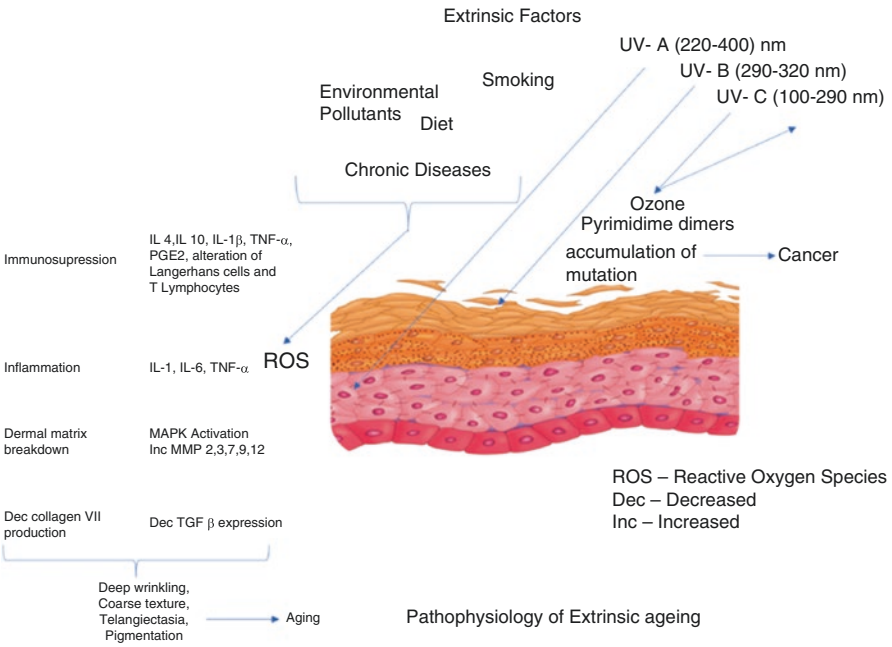

Fig. 20.1 Pathophysiology of aging

increase in non-functional elastin results in a thick mottled epidermis with deep wrinkles and a lax, dull, and rough skin.

20.2.1 Anatomy of Aging

The bones, mimetic muscles, ligaments, subcutaneous fat, epidermal and dermal layers of skin with appendages make up the facial anatomy. The progressive and accumulated changes in their shape, texture, and color result in aging of skin.

20.2.1.1 Bones

The framework of the face is provided by bones which acts as a scaffold for attachment of muscles and supporting structures. There are mainly five facial bones: skull (calvaria), nasal bone, zygoma (cheek bone), maxilla (upper jawbone), and mandible (lower jawbone). Osteoporotic changes and the loss of teeth may be the main factors resulting in the age-related effects in skull (Fig. 20.2) [7].

In old age the facial height decreases which is marked in mandible and maxilla, there is a modest increase in facial width and a minimal increase in facial depth [8].

20.2.1.1.1 Orbit

Volume of bony orbit increases with age and the curvilinear shape is distorted. Supra-medial orbital rim recedes with age in both sexes and infraorbital rim recedes laterally in women while the entire infraorbital rim recedes in men (Fig. 20.2). This loss of volume and lateral projection of orbit causes loss of support of soft tissues causing its descent and bunching. This is the reason for lateral orbital hooding and

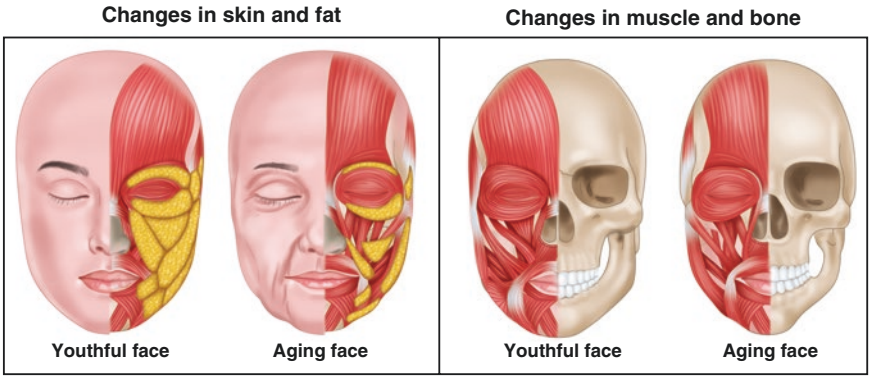

Fig. 20.2 Changes in face with aging

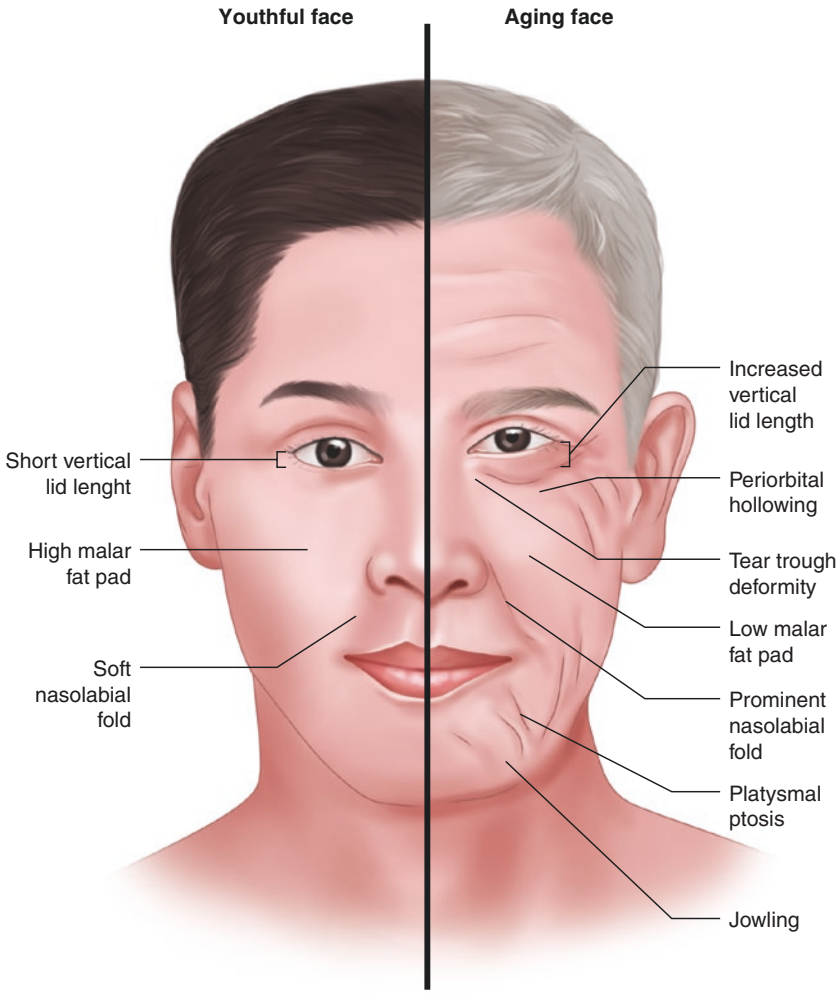

Fig. 20.3 Aging changes on the face

crow's feet. Glabellar crease is formed due to the glabellar angle being more acute with age and thereby leading to descent of medial brow. These changes give an appearance of descending brows, lateral orbital hooding of upper eye lid, and the descent of the lower lid and its junction with the cheek with deepening of the naso-jugular groove (Fig. 20.3).

20.2.1.1.2 Maxilla

The loss of teeth and bone resorption is most evident in the maxilla. The reduction in height of retrusion of lower maxillary skeleton at pyriform area causes the malar fat pad to slide downwards and forwards contributing to the prominence of nasolabial folds.

20.2.1.1.3 Mandible

The loss of teeth and associated resorption causes reduction in alveolar height. This resorption along with the depository effects leads to a change in the contour giving an appearance of "witch's chin." The prejowl sulcus (genio-mandibular) and increased labio-mental fold are the recognized features of aging in the lower face (Fig. 20.3).

20.2.1.2 Mimetic Muscles and Ligaments

The muscles of facial expression that are affected by aging are the frontalis, corrugators, procerus, orbicularis oculi, levator labii superioris alaeque nasi, nasalis, depressor septi nasi, masseter, orbicularis oris, mentalis, and depressor anguli oris (Table 20.1). The declining number of functional motor units and decreasing efficiency of muscles are the factors contributing to aging. Hypertrophy of orbicularis oculi is the most established reason for aging in the periorbital region. The aged periorbital region reveals progressive descent of the lid-cheek junction and lid lag with an increased scleral show, an evident nasojugal groove, malar bags, and tear trough formation.

The ligamentous attachments of face are divided into osteocutaneous and fasciocutaneous ligaments. Main osteocutaneous ligaments are the zygomatic and mandibular which originate from periosteum of malar and mandibular bones and are inserted into the dermis, the masseteric and parotid ligaments are fascial coalescence, the attenuation of these results in descent of the malar and buccal pad of fat augmenting the nasolabial fold and exacerbating the jowls (Fig. 20.4).

The SMAS described first by Mitz and Peyronie is an upward extension of superficial cervical fascia [9].

In the neck the main signs of aging are the development of platysmal bands associated with enlargement and ptosis of glands. These age-related changes cause increase of cervicomental angle and deposition of subplatysmal fat (Fig. 20.5).

Table 20.1 Mimetic muscles and their action

Muscle	Function	Result
Frontalis	Elevator of the medial and lateral brow	Horizontal ridges and frown lines
Procerus, corrugator supercilii, and the medial aspect of the orbicularis oculi	Depressors along the medial brow	Glabellar lines
Lateral half of the orbicularis oculi	Lateral depressor of the brow	Crow's feet
Nasalis	Flares and constricts the nostrils	Bunny lines

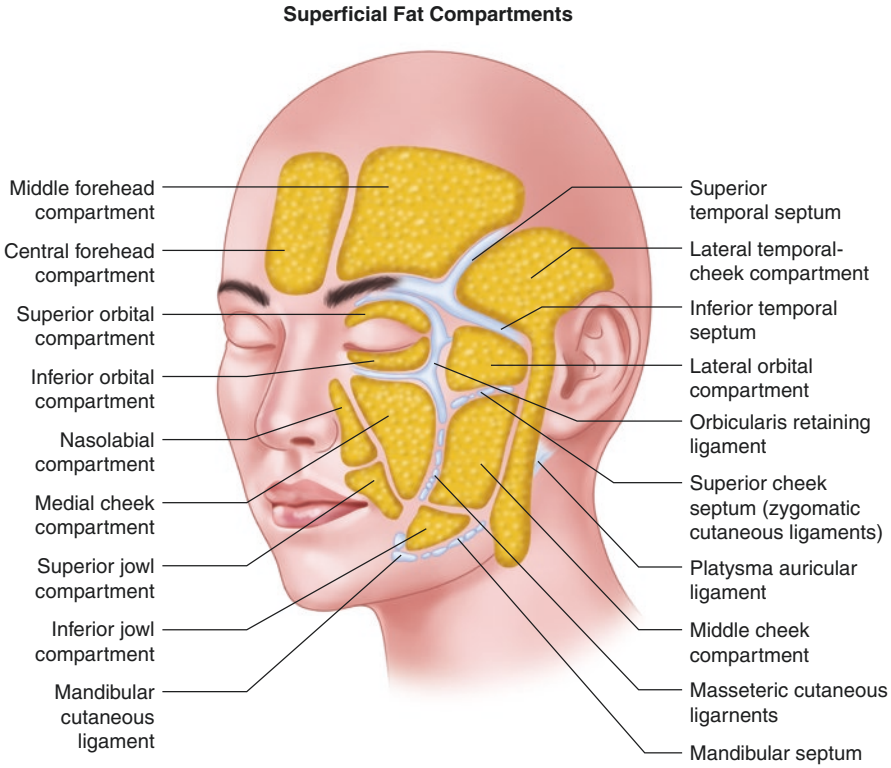

Fig. 20.4 Ligaments of the face

20.2.1.3 Subcutaneous Fat

Loss of fat plays a major role in facial aging. Rodrich and Pessa characterized subcutaneous fat compartments of face and postulated the theory of differential affection of aging in these groups [10].

The uniform diffuse and balanced distribution of fat in young is lost with aging, especially particularly around the orbit, forehead, glabella, mandible, malar, mental, and perioral regions. Dynamic rhytids which later turn into static wrinkles are due to loss of subcutaneous fat which gives prominence to contraction of the underlying muscle.

There is hypertrophy of superficial fat pads and atrophy of deep fat pads with age. Buccal pad of fat increases the marionette fold and the jowls, while malar fat pad causes prominence of the nasolabial fold and unmasking orbital fat pad.

Aging also causes reduction in hair, change in texture of skin, and pigmentary changes.

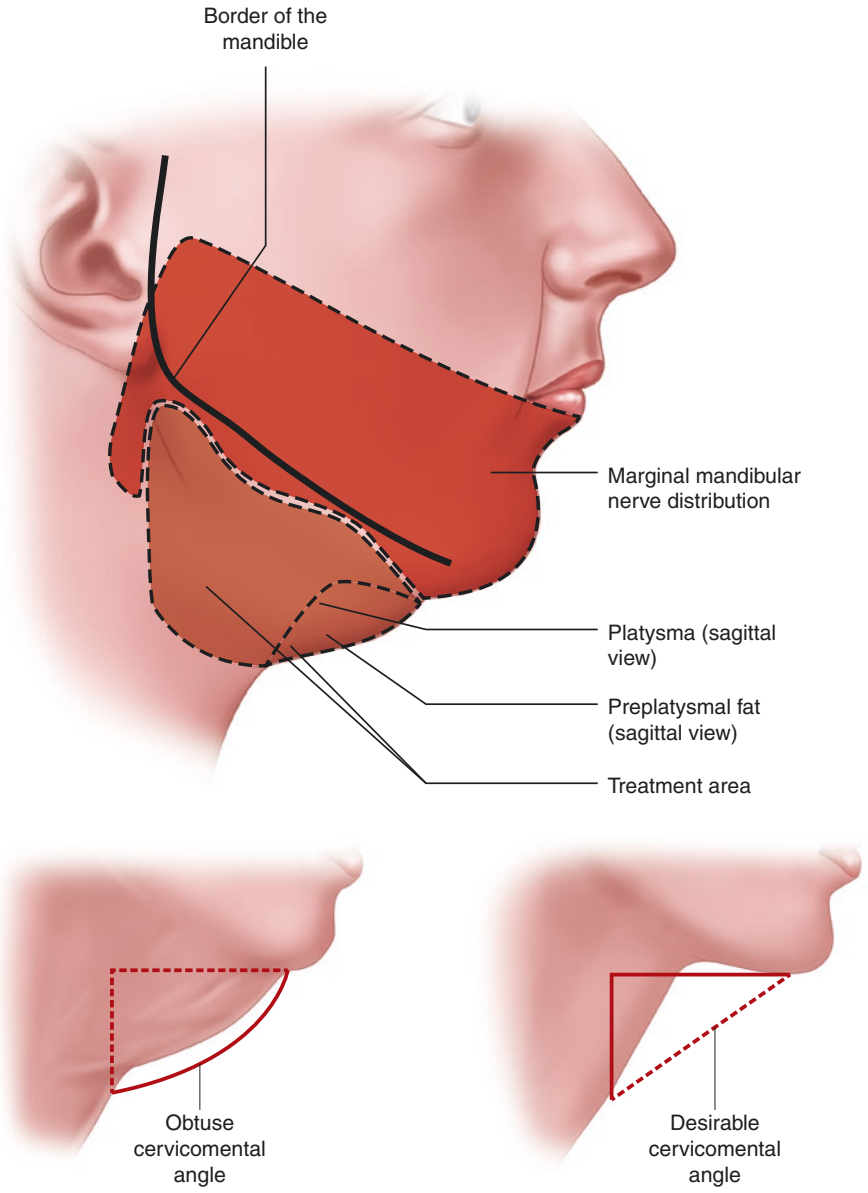

Fig. 20.5 Age-related changes of the neck

20.2.2 Clinico-Pathological Features of Aging

Aging of skin is a complex multisystem degenerative process in which the environmental changes are superimposed on the chronological senescence. These changes affect the skin, the support system and the appendages by altering its shape, texture and color. As a process aging is more pronounced and appears early in the photo-exposed areas and is of two types mainly intrinsic or extrinsic. Chronological or intrinsic aging is influenced by the genetic factors we inherit and depends on the passage of time. Intrinsic aging manifest mainly as fine wrinkles, thin transparent skin, hollow cheeks, dry skin with reduced sweating, and hair loss. This is due to progressive atrophy of skin and appendages along with the osteoporotic changes resulting from progressive senescence, defects in autophagy, and telomere shortening. The extrinsic aging, also called photoaging, is caused by environmental factors such as UV radiations, smoking, and pollutants which results in the production of reactive oxygen species (ROS) and DNA damage. This predominantly affects the photo-exposed areas manifesting as coarse wrinkling, roughness, pigmentary changes, loss of elasticity, telangiectasias, and rarely skin cancers.

Clinical	Histological
Textural changes/ roughness	Increased compaction of stratum corneum, increased thickness of granular layer, reduced epidermal thickness, and reduced epidermal mucin content
Irregular pigmentation	
Freckles	Reduced or increased number of hypertrophic, strongly dopa-positive melanocytes
Solar lentigines	Elongation of epidermal rete ridges; increases in number and melanization of melanocytes
Guttate hypomelanosis	Decreased dopa oxidase-positive, KIT+, and melanocyte sand reduction in melanocytes
Wrinkles	Thinned epidermis as well as less elastotic changes, tropoelastin, and collagen VII when compared to the surrounding photoaged skin
Sagging	Loss of elastic tissue in the dermis and the remaining fibers were disorganized, shortened, and fragmented
Inelasticity	Accumulated large amounts of homogenization and a dark blue amorphous elastotic material in the dermis, the so-called solar elastosis
Vascular changes	
Telangiectasia	Ectatic vessels often with atrophic walls
Senile purpura	Extravasated erythrocytes and increased perivascular inflammation

20.2.3 Assessment Tools for Objective Improvement of Aging

Objective assessment along with patient satisfaction is essential in esthetic practice [11–13]. A number of tools are available to assess the treatment outcome and to assess the degree of aging. The most essential among these are pre-procedural and post-procedural photographs taken with uniform lighting, patient posture, and similar photography equipment. The validated subjective scoring systems include the

wrinkle severity rating scale (WSRS), the medicis midface volume scale (MMFVS), the global aesthetic score (GAIS) and patient satisfaction score using the face visual scale. Objective assessments use instruments such as the cutometer for skin deformation, mexameter or chromatometer for color changes, sebumeter to assess sebum production, tewameter to determine the transepidermal water content, and visiometer to assess the skin topography [14]. Dermoscopy, reflectance confocal microscopy, and 3D imaging with or without projection systems are increasingly being used [15]. Histopathology remains the gold standard for assessment of tissue changes; however, it is cumbersome. Overall a combination of physician's tool along with patient satisfaction index provides the most comprehensive assessment.

20.3 Female Facial Esthetics

20.3.1 Signs of Aging

The aged skin shows the signs of photodamage pertaining to skin texture, pigmentation, and structure like atrophic, dry skin, loss of skin elasticity, uneven skin tone, pigmentation, blotchiness and telangiectasis, fine lines, and wrinkles.

Soft tissue aging gives the appearance of dynamic static wrinkles and folds, volume depletion, and ptosis of the facial tissues with sagging [8, 16].

20.4 Preventative Treatment of Aging

Beauty and youthfulness are intricately related to health. Taking care of the facial skin from the early years has proved to be beneficial in prolonging biological aging to a great extent. The authors describe a few treatments which they describe as "preventative," which can delay aging to an extent.

20.4.1 Skin Care

Dermaceuticals which involve the use of SPFs and barrier retaining creams would logically be the first-line preventative treatments in the second and third decades. Maintaining a healthy skin barrier protects against dehydration, harmful effects of environmental insults, allergens, and microbes. The use of creams with ceramides, neutral lipids, and natural moisturizing factors proves useful.

The use of sun protection factors both chemical and physical is also preventative in causing premature photoaging and the initial molecular damage by the reactive oxygen species (ROS) and the cascade of chronic photodamage that follows [17].

"Prejuvenation" is the term that is used to delay the onset of photodamage of the skin by the harmful effects of ultraviolet radiation.

Alpha hydroxy acids can be added to the skin care regime in the fourth decade, and retinoids in the late fourth and fifth decades. Their mechanism of actions are to regulate the growth and differentiation of the epithelial cells, improving the epidermal barrier and evening the skin tone [18], acting as an antioxidant, reducing fine lines and inflammation [19], especially in combination with vitamin E [20], maintaining under-eye pigmentation, and suppressing the effect of collagenase following UV radiation, respectively [21]. Preventative injectables are also being used to maintain the early signs of aging.

Botulinum toxin is used for treating motor wrinkles in the early stages before they become static, and hence can be used preventatively.

Collagen induction therapies to maintain skin elasticity can also be done. Monofilament polydioxanone threads can also be used for rejuvenation by increasing the vascularization and collagen production.

The use of regenerative medicine procedures like platelet rich plasma or injectable platelet rich fibrin are also done to maintain the biological skin health. Autologous micrograft transplant using multipotent progenitor cells can also be used.

Lifestyle modifications such as avoidance of smoking, managing stress, and weight reduction are of equal value in slowing down the aging process.

Systemic antioxidants which scavenge the free radicals, neutralize and decrease ROS by quenching iron are also used as preventative and antiaging treatment options. Oral vitamin C, vitamin E, trace elements like selenium which increases glutathione peroxidase, carotenoids, and copper are a few of them [22–24].

Chemical peels are also preventative in delaying and reversing the early signs of photodamage.

20.4.2 Topical Antiaging Agents

Antioxidants in different formulations can be used as antiaging applications. They quench and reduce the free radicals in the skin and thus reduce collagen degradation. Polyphenols and flavonoids along with topical vitamins are the most commonly used antioxidants.

The power of topical vitamins to skin care is beneficial when started at any age. The commonly used topical vitamins are vitamins A, B, C, E, and K and Co-enzyme Q10. Vitamin C is used in the concentration of 5–15%. Studies have proved that in combination with vitamin E it acts as a stronger antioxidant. Vitamin B3 or niacinamide is used in the concentration of 5%, and vitamin E in 2–20% as antiaging agents. Vitamin A or retinol and its derivatives, retinaldehyde, and tretinoin are among the most powerful antiaging agents. In the concentration of 0.05% tretinoin is approved as an antiaging treatment in the USA. It has also been shown to reduce the early signs of photodamage [25]. Their mechanism of actions are to regulate the growth and differentiation of the epithelial cells, improving the epidermal barrier and evening the skin tone [18], acting as an antioxidant, reducing fine lines and inflammation [19, 20], maintaining under-eye pigmentation, and suppressing the effect of collagenase following UV radiation, respectively [21].

Other antiaging agents such as polypeptides and growth factors can induce the production of collagen and decrease the effect of matrix metalloproteinases [26].

20.4.3 Minimally Invasive Antiaging Treatments

20.4.3.1 Treatment of Structural Changes

20.4.3.1.1 Treatment of Wrinkles

The facial expression lines are usually tackled with botulinum toxin. It is not completely therapeutic for static wrinkles, but it does soften them. The injections are intramuscular, relaxing the muscles responsible for rhytid formation by preventing the release of acetylcholine at the neuromuscular junction. The number of units needed depend on the muscle bulk. Females need lesser units compared to males.

Static wrinkles need filling with hyaluronic acid, biologic materials, or other synthetic fillers.

Energy-based devices like radiofrequency can also be used to soften wrinkles.

20.4.3.1.2 Treatment of Folds

Direct filing of folds can be done with the use of biodegradable or synthetic fillers. Autologous lipofilling can also be done. A retrograde or antegrade technique can be used. Direct filling can also be achieved with the use of "filler" or "broom" threads, which stimulate collagenization. Platelet rich fibrin when done over sessions, can also stimulate collagen, thus making them shallow.

Indirect softening of the nasolabial or marionette lines can be done by repositioning the soft tissues in vectors opposite to the aging vectors with injections of fillers on the lateral side of the face.

Sutures or thread lifts can also cause attenuation of the folds by lifting and stretching the tissues adjacent to them.

Energy-based devices like high intensity focused ultrasound for lifting the facial tissues also soften them.

20.4.3.1.3 Volume Restoration

Biodegradable or non-biodegradable synthetic fillers can be used to restore volume that gets depleted with age. Instant volumization occurs with the use of these cross-linked gels. Natural fillers like biofillers, which are platelet poor plasma gels, can also be used with short-term longevity. Collagen induction with threads, platelet rich plasma, or bioactive hyaluronic acid gels can also be done, but the process takes several sittings along with minimal stimulation.

Injections can be supraperiosteal for structural support and greater longevity or in the deep atrophic fat pads for contouring and filling. The former requires gels with a high cohesivity, and the latter can be done with gels having greater viscosity and tissue integration.

20.4.3.1.4 Treatment of Sagging

Lifting of ptotic tissues against the vectors of aging is best done with thread lifts. Usually threads with barbs or cones are used as lifting threads. The insertion is in vectors perpendicular to the ptosis of the tissue. Insertion is always in the subcutaneous plane.

Peripheral injections of fillers can also stretch and lift the face against the aging vectors. Injecting in the lateral zygoma, for example, lifts the face and softens the nasolabial fold.

Energy-based devices are also very useful to lift sagging tissues. The use of high intensity focused ultrasound (HIFU) when used in the depths of 4.5 and 3 mm can target the SMAS and the deep dermis, respectively. Monopolar and some good bipolar radiofrequency devices can also tighten the sagging skin, but they do not penetrate as deep as HIFU. These work on the principle of stimulating the extracellular matrix proteins and improving collagenization and elastogenesis.

20.4.3.2 Laser and Energy-Based Devices

With the demand for non-aggressive, non-invasive, non-surgical procedures with minimal downtime increasing lasers and energy-based devices have a special place in management of the aging skin.

The lasers used may be of differing wavelengths as ablative or non-ablative in fractionated or non-fractionated forms. These lasers function to target pigmentation, erythema, irregular vessels, sebaceous changes, rhytids, and other senescent changes.

Ablative lasers are more aggressive with a longer downtime e.g., carbon dioxide, erbium YAG laser. They function by causing skin resurfacing by epidermal removal and dermal remodeling by dermal heating causing collagen denaturation and subsequent resynthesis. They are best suited for severe facial rhytids and pigmentary changes. The superficial rhytids are targeted directly while the deeper ones improve with subsequent dermal remodeling.

Non-ablative lasers cause the above dermal remodeling without or minimal epidermal damage, e.g., erbium glass, pulse dye laser, Nd: YAG, diode, and intense pulse light.

Ablative and non-ablative lasers may be fractionated or non-fractionated wherein the laser beam is fractionated into columns. This prevents excessive epidermal damage and dermal overheating.

Ablative lasers generally have been reported to have a better clinical response compared to non-ablative lasers.

20.5 Conclusion

Treatment of the aging face is a part of "successful aging." It boosts the self-esteem of an individual and hence the overall well-being. Preventative and restorative esthetic dermatology thus play a convincing role in healthy aging. Preventative anti-aging strategies can even prevent certain cutaneous malignancies. Treatment of the aging face is not just to look younger, but to look better with an even tone and a good skin texture, free from pigmentary conditions. Antiaging encompasses a holistic and combination approach from lifestyle modification to targeted treatments.

References

1. Baker L, Gringart E. Body image and self-esteem in older adulthood. Ageing Soc. 2009;29:977–95.
2. Shome D, Vadera S, Khare S, Ram MS, Ayyar A, Kapoor R, et al. Aging and the Indian face: an analytical study of aging in the Asian Indian face. Plast Reconstr Surg Glob Open. 2020;8:e2580.
3. Varani J, Dame MK, Rittie L, Fligiel SEG, Kang S, Fisher GJ, et al. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Pathol. 2006;168:1861–8.
4. Oikarinen A. Aging of the skin connective tissue: how to measure the biochemical and mechanical properties of aging dermis. Photodermatol Photoimmunol Photomed. 1994;10:47–52.
5. Kołodziej-Wojnar P, Borkowska J, Wicik Z, Domaszewska-Szostek A, Połosak J, Cąkała-Jakimowicz M, et al. Alterations in the genomic distribution of 5hmC in in vivo aged human skin fibroblasts. Int J Mol Sci. 2020;22:78.
6. McCabe MC, Hill RC, Calderone K, Cui Y, Yan Y, Quan T, et al. Alterations in extracellular matrix composition during aging and photoaging of the skin. Matrix Biol Plus. 2020;8:100041.
7. Ozturk CN, Ozturk C, Bozkurt M, Uygur HS, Papay FA, Zins JE. Dentition, bone loss, and the aging of the mandible. Aesthet Surg J. 2013;33:967–74.
8. Coleman S, Grover R. The anatomy of the aging face: volume loss and changes in 3-dimensional topography. Aesthet Surg J. 2006;26:S4–9.
9. Mitz V, Peyronie M. The superficial musculo-aponeurotic system (SMAS) in the parotid and cheek area. Plast Reconstr Surg. 1976;58:80–8.
10. Rohrich RJ, Pessa JE. The fat compartments of the face: anatomy and clinical implications for cosmetic surgery. Plast Reconstr Surg. 2007;119:2219–27.
11. Day DJ, Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol. 2004;5:49–52.
12. Shoshani D, Markovitz E, Monstrey SJ, Narins DJ. The modified Fitzpatrick Wrinkle Scale: a clinical validated measurement tool for nasolabial wrinkle severity assessment. Dermatol Surg. 2008;34:S85–91.
13. Sen S, Choudhury S, Gangopadhyay A, Halder C, Biswas P, Jain A. A clinical rating scale for the assessment of facial aging in Indian population. Indian J Dermatol Venereol Leprol. 2016;82:151.

14. Hersant B, Abbou R, SidAhmed-Mezi M, Meningaud JP. Assessment tools for facial rejuvenation treatment: a review. Aesthet Plast Surg. 2016;40:556–65.
15. Verhulst A, Hol M, Vreeken R, Becking A, Ulrich D, Maal T. Three-dimensional imaging of the face: a comparison between three different imaging modalities. Aesthet Surg J. 2018;38:579–85.
16. Kaur M, Garg RK, Singla S. Analysis of facial soft tissue changes with aging and their effects on facial morphology: a forensic perspective. Egypt J Forensic Sci. 2015;5:46–56.
17. Baumann L. Skin ageing and its treatment. J Pathol. 2007;211:241–51.
18. Bissett DL, Oblong JE, Berge CA. Niacinamide: a B vitamin that improves aging facial skin appearance. Dermatol Surg. 2006;31:860–6.
19. Gaspar L, Campos P. Photostability and efficacy studies of topical formulations containing UV-filters combination and vitamins A, C and E. Int J Pharm. 2007;343:181–9.
20. Lin F-H, Lin J-Y, Gupta RD, Tournas JA, Burch JA, Angelica Selim M, et al. Ferulic acid stabilizes a solution of vitamins c and e and doubles its photoprotection of skin. J Invest Dermatol. 2005;125:826–32.
21. Choi CM, Berson DS. Cosmeceuticals. Semin Cutan Med Surg. 2006;25:163–8.
22. Terada A, Yoshida M, Seko Y, Kobayashi T, Yoshida K, Nakada M, et al. Active oxygen species generation and cellular damage by additives of parenteral preparations: selenium and sulfhydryl compounds. Nutrition. 1999;15:651–5.
23. Fusco D, Colloca G, Lo Monaco MR, Cesari M. Effects of antioxidant supplementation on the aging process. Clin Interv Aging. 2007;2:377–87.
24. Marini A. Beauty from within: does it really work? Hautarzt. 2011;62:614–7.
25. Ascenso A, Ribeiro H, Marques H, Oliveira H, Santos C, Simões S. Is tretinoin still a key agent for photoaging management? Mini-Rev Med Chem. 2014;14:629–41.
26. Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol. 2007;8:221–33.

Chapter 21
The Sensitive Skin: Do's and Don'ts

Surabhi Sinha and Neha Meena

21.1 Introduction

Sensitive skin is characterized by predominantly subjective abnormal sensations of burning or pricking of the skin without persistent visible signs of erythema, though there is no universally accepted definition of sensitive skin [1]. Most patients present with unpleasant sensations like burning, tingling, smarting or pricking, sometimes accompanied with transient redness, tightness or dryness of skin, after coming in contact with routinely used skin products or cosmetics. In some cases, various environmental, chemical, physical, hormonal or psychological factors may be associated with the onset of sensitive skin [1–3].

Muizzuddin et al. defined sensitive skin on the basis of primary pathology, skin reactivity and stinging capacity. Delicate skin is the one with easy penetration of irritants due to disrupted barrier function, but shows only mild inflammatory response. On the other hand, reactive skin is less permeable to irritants but shows strong inflammatory response. Stingers have exaggerated neurosensory response to cutaneous stimuli [4]. Pons-Guiraud classified sensitive skin into very sensitive (a strong psychological impact as it may present with both acute and chronic symptoms and shows reactivity with both endogenous and exogenous factors), environmentally sensitive (dry, clear and thin, more prone to blushing or flushing and more reactive to environmental factors such as ultraviolet radiation, wind, cold and heat) and cosmetically sensitive (reactive to cosmetics or toiletries) [5]. Sensitive skin may be

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present in partially treated dermatoses such as rosacea (heightened neurosensory perception), atopic dermatitis (barrier disruption), seborrheic dermatitis, contact dermatitis (immune hyperreactivity), psoriasis, etc. In such cases, mild or transient erythema or scaling may be present and is termed visible sensitive skin, in contrast to invisible sensitive skin which shows no perceptible signs and is more difficult to discern [6]. Status cosmeticus or cosmetic intolerance of the face is a situation where intolerance to cosmetics persists even after resolution of skin diseases [7].

21.2 Pathophysiology of Sensitive Skin

Although the exact pathophysiology of sensitive skin is still unknown, the common consensus is that sensitive skin is the result of a low skin tolerance threshold. There is abnormal penetration of potential irritant agents into the skin due to defective skin barrier function [8]. Impaired barrier function may be due to altered intercellular lipids with increased neutral lipids and decreased sphingolipids, thinned stratum corneum, increased permeability leading to increased trans-epidermal water loss [1]. Abnormal neurosensory interaction between nerve growth factors, endothelin receptors and transient receptor potential receptors may lead to exaggerated sensitivity response [9].

21.3 General Skin Care of Sensitive Skin

The first step for sensitive skin care is to identify and avoid the causative agent or agents so as to prevent further sensitivity. This is often the most challenging step as myriad constituents in make up routine skin care and cosmetic products. The next step is to rule out or treat any underlying or accompanying cutaneous disorders like atopic dermatitis or rosacea. Finally, attempts should be made to repair the disrupted cutaneous barrier function. Basic key to cure or prevent sensitive skin is to use minimal cosmetic products with fewer ingredients with skin-friendly pH (5.5) so as to keep the skin intact and well hydrated [10]. Frequent use of moisturizers also helps in maintaining healthy skin (Fig. 21.1).

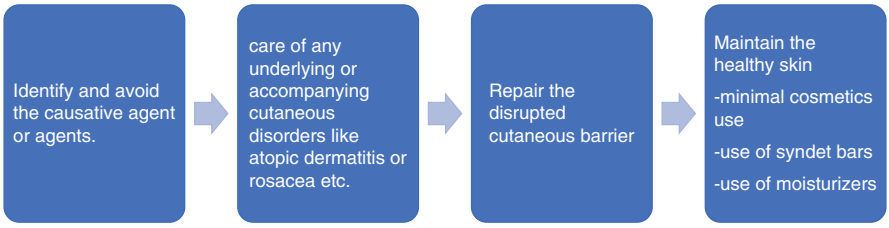

Fig. 21.1 Basic steps for sensitive skin care

21.4 Step 1: Identify and Avoid the Potential Source

1. In order to identify and avoid the potential source or cause of sensitive skin, Draelos suggested that all skin products like cosmetics, toiletries, over the counter or prescription topical medications like tretinoin should be stopped for 2 weeks [11]. Any potential source of friction is to be avoided for 2 weeks. This washout period also helps in revealing any underlying cutaneous diseases like rosacea or seborrheic dermatitis, which can be treated symptomatically [11]. Any product that causes discomfort and irritation should be stopped immediately.
2. During this washout period, use of syndet bars is recommended. Syndet bars are synthetic detergents that have synthetic surfactants like sulfosuccinic acid, sodium cocoyl isethionate, stearic acid, sodium stearate, etc. They have skin-friendly pH (neutral or slightly acidic), so their use causes minimal or no skin irritation along with preservation of cutaneous protein, natural moisturizing factor and lipid content. Charge density of protein bound surfactant aggregates of syndet bars causes minimal protein denaturation. High free fatty acid concentration also helps in hydration of skin [12, 13]. Hence, syndet bars help in recovery of sensitive skin and prevent further damage to skin. Simultaneously, their use also helps in management of the underlying cutaneous diseases like atopic dermatitis by providing a moisturizing effect [14, 15].
3. Body washes or liquid cleansers can be used in sensitive skin. They tend to both cleanse and moisturize the skin by using the two stages of cleansing depending upon the concentration gradient of water and the cleanser. Body washes have water as the primary ingredient along with syndets and moisturizers like vegetable oils, shea butter, petrolatum, etc. [15]
4. Water used for rinsing or washing should be lukewarm (and not hot).
5. Thermal spring water spritzers reduce skin sensitivity and erythema by calming, soothing and hydrating the skin. They repair skin by maintaining the superficial biomechanical and cutaneous ultrastructure [16]. Thermal spring water has a unique mineral composition and contains prebiotics and trace elements as well [16, 17].
6. For individuals like health care workers, frequent handwashing may lead to subjective irritation and sensitive skin of hands. Hand sanitizers, with either ethanol or quaternary ammonium compounds like benzalkonium chloride or benzethonium chloride can be used. In addition to this, frequent use of moisturizers or incorporation of emollients into the formulation helps in maintaining the skin healthy and hydrated.
7. No-rinse cleansers that can be applied and removed without the use of water are preferred for use in elderly patients with sensitive perianal or genital skin due to ageing or incontinence [18].

8. Cosmetics can be removed from the skin by use of special cleansers like micellar water cleansers, cleansing milk, cleansing balms, cleansing oils, cold cream cleansers and non-foaming cleansers. Micellar water cleansers are good for water soluble cosmetic products, while cleansing milk is used for eye makeup removal. For waterproof cosmetics, cleansing oils can be used. Cold cream cleansers are good for facial cosmetic removal and have additional moisturizing effect on skin [15].
9. Micellar water may be used as face cleanser and it uses the concept of micelle formation during interaction of surfactant and water. The hydrophobic end of micelle attaches itself to the dirt on skin and the hydrophilic end helps in rinsing with water. It can be applied gently by rubbing or dabbing on skin with the help of a cotton ball and rinsed off with water.
10. Skin should be gently pat dried after washing. This prevents the skin irritation that can be caused by rubbing and also keep the moisture intact.
11. Hair cosmetics—pH of shampoos should be neutral or slightly acidic in nature like syndet bars [19]. Shampoos contain various ingredients like a surfactant, conditioner, fragrances and preservatives. Various potential allergens are balsam of Peru, formaldehyde, Kathon CG, captan, FM1, FM2, cocamidopropyl betaine, etc. [20] Hence, care must be taken to identify if a shampoo is the contributory agent towards causation of sensitive skin. Products with irritating tensioactive surfactants should be avoided. Hair straightening products with formaldehydes must be avoided as they are not just irritant but are potentially carcinogenic in nature.
12. Baby shampoos usually are "tear free" as they contain betaine-like mild amphoteric detergents which have more favourable pH while the mild detergent action minimizes the skin irritation. However, care should be taken to decrease the contact time of skin care products to prevent any skin sensitivity.
13. Baby wipes are routinely considered as mild products but they contain methylisothiazolinone as preservative. This may lead to allergic sensitization in baby and/or in the caregiver [21].
14. Cosmetics with various irritants like propylene glycol, butylene glycol, alcohol, resorcinol, triethanolamine, cocamidopropyl betaine, etc. should be avoided [2].

21.5 Step 2: Care of Any Underlying or Accompanying Cutaneous Disorders

1. Any topical formulation that causes discomfort or burning sensation should be discontinued.
2. Sensitive skin due to underlying cutaneous diseases like rosacea can be precipitated by irritants like alcohol, astringents, toner, eucalyptus oil, camphor, fragrances, clove oils, etc. Hence, such products are to be avoided.

3. Products with sodium lauryl sulphate should be avoided due to their irritant potential.
4. Avoid intake of hot spicy food, chocolates, wine, tea and caffeine as they may exacerbate symptoms due to high vascular reactivity in sensitive skin and rosacea [22].
5. For sensitive skin with underlying diseases like atopic dermatitis or seborrheic dermatitis, non-foaming cleansers are useful. They can be applied on skin and then either wiped off or rinsed off.
6. Combination skin care regime that includes use of micellar water cleanser in morning, non-tinted cream with sunscreen in afternoon and serum in night can help in reduction of sensitivity and erythema in rosacea (Figs. 21.2 and 21.3) [23].

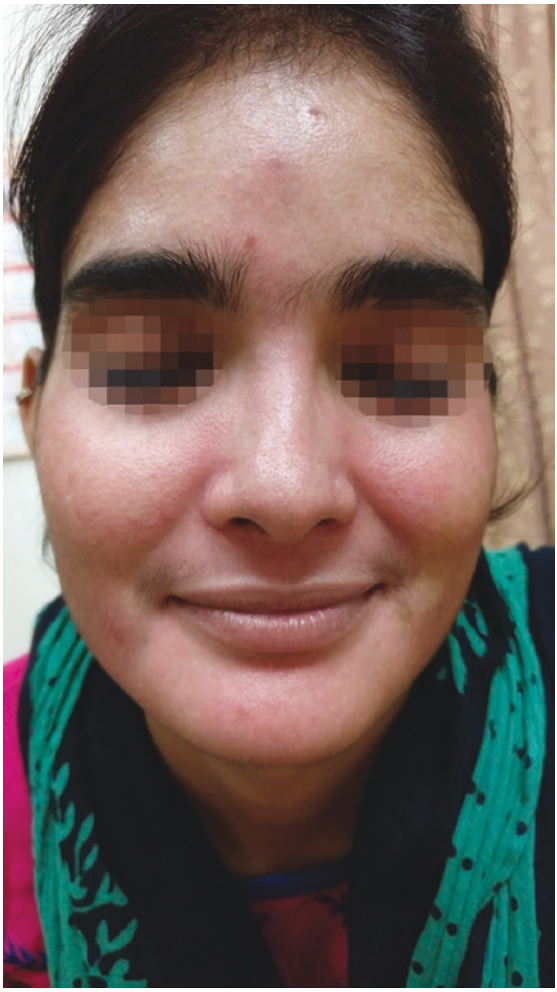

Fig. 21.2 Topical tretinoin induced sensitive skin

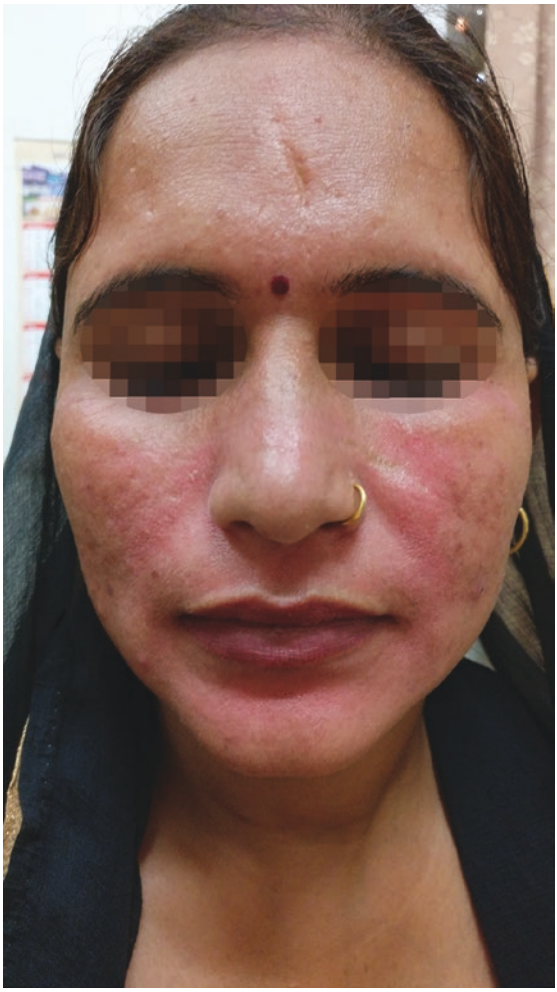

Fig. 21.3 Iatrosacea following topical steroid abuse

7. Skin care is needed in case of excess sun exposure, cold wind and sudden temperature variations. Most important triggering factors for sensitive skin after cosmetics are dry air, air conditioning, heat and wind [24].
8. Inorganic sunscreens like zinc oxide or titanium oxide are inert, non-sensitizing and non-irritant in nature and are preferred in sensitive skin [25, 26].
9. Individuals with sensitive skin should avoid use of chemical peelings with keratolytic or exfoliating agents as salicylic acid, retinols, resorcinol, trichloroacetic acid and alpha hydroxy acids like glycolic acid and lactic acid. They can precipitate the sensitivity or irritation of skin depending upon their formulation, pH, concentration and contact time [2, 27].
10. Rigorous post-operative care is needed after dermatosurgical procedures like ablative laser resurfacing, chemical peels, dermabrasion, micro needling, etc. as

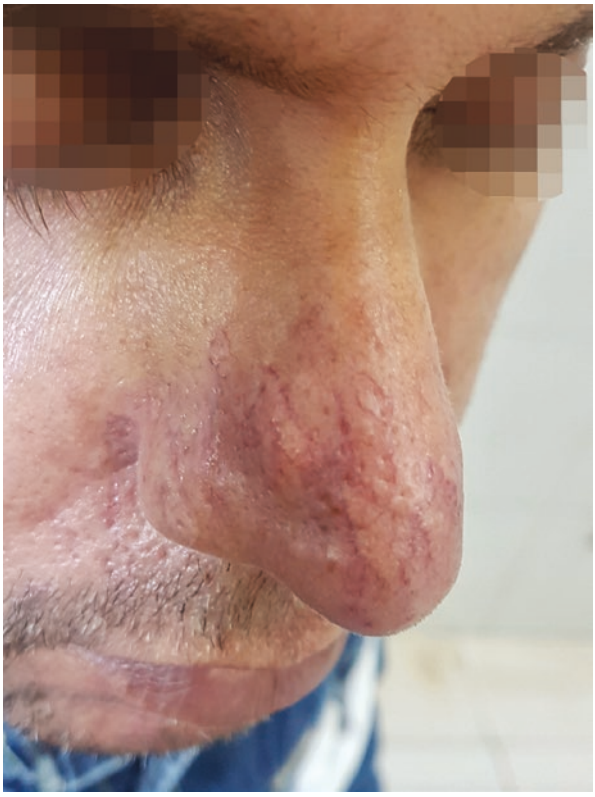

Fig. 21.4 Erythematotelangiectatic rosacea on the nose showing telangiectasias and persistent erythema

they cause breach in continuity of skin and lead to sensitization and exacerbation of sensitive skin [5].

11. Patient counselling to be done for adequate and proper application of topical drugs with irritant or sensitivity potential. For example, tretinoin should be applied only on acne lesions with dab action in night only. Any rubbing or excess use may cause irritation and redness of skin (Fig. 21.4).
12. Topical corticosteroid abuse is very common in some countries, including India, due to their availability as over-the-counter drugs. Patients with various dermatological condition buy the steroid directly from chemist without visiting any dermatologist. This corticosteroid abuse leads to cutaneous changes like erythema, telangiectasia, photosensitivity, increased fragility and irritation of skin. Such skin is more prone for sensitization after use of cosmetics (Fig. 21.5) [7].
13. Specially formulated anti-ageing creams containing sodium salicylates (1%), polyhydroxy and bionic acids are preferred in sensitive skin in contrast to the standard use of salicylic acid and hydroxy acids, respectively [28, 29].

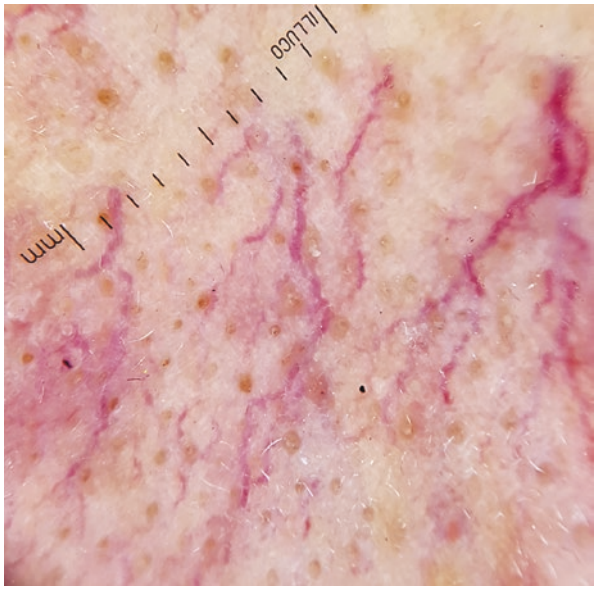

Fig. 21.5 Dermoscopy of the earlier patient with rosacea with a better demonstration of the network-like telangiectasias

Commonly used polyhydroxy acid in anti-ageing creams is gluconolactone. It also acts as antioxidant, moisturizer and repairs the skin barrier [29].

14. Benzoyl peroxide induced erythema and irritation can be reduced by gluconolactone-based formulations [29].
15. Bionic acids like lactobionic acid, cellobionic acid and maltobionic acid are hygroscopic in nature, so they form a gel like matrix with water at room temperature. This aqueous gel provides soothing and protecting effect on sensitive skin especially post dermatosurgical procedures like chemical peels and also inhibits further oxidative damage to skin [29].
16. Silicone-based gels can also be used for post-operative care and wound dressing after laser resurfacing [30].
17. Facial moisturizers containing niacinamide improve the skin barrier function, decrease trans-epidermal water loss, reduce inflammation and hydration of sensitive skin in rosacea [31].
18. Mild topical corticosteroids and topical calcineurin inhibitors can be used for brief duration for symptomatic treatment.
19. Topical crisaborole ointment (2%) can be used in sensitive skin to reduce symptoms. It acts as non-steroidal agent with anti-inflammatory and phosphodiesterase 4 inhibitor action [32, 33].
20. Elderly females may have sensitive skin of the vulva due to age-related structural and functional epidermal changes in genital skin. Secondly, hormonal changes may lead to dry and sensitive skin of genitalia [34]. Elderly women with urinary incontinence may also have sensitive skin of genitalia; however, they often ascribe the symptoms to their incontinent state [35].

21.6 Step 3: Repair the Disrupted Cutaneous Barrier—Moisturizers and Novel Formulations

1. Restoration of structural, chemical and physiological integrity of cutaneous barrier is necessary for resolution of sensitive skin. Products for repair of skin barrier should ideally contain bland cream-based moisturizers with humectants, occlusive and emollient properties, pH neutral or slightly acidic ingredients, additional microbiota with or without pre- or probiotics [17].
2. Moisturizers should be applied on the skin when it is still moist just after the pat drying. This helps in better maintaining the hydration of skin by locking the water in the skin.
3. White soft paraffin is inert and bland moisturizer but can lead to greasy or messy look.
4. Repeated application of moisturizers after exposure to air conditioning or change in temperature is advisable.
5. Moisturizers help in the restoration of damaged skin barrier function and homeostasis, maintain hydration, softness and repair the dry skin. So, they reduce the risk of irritation or onset of symptoms of sensitive skin.
6. Kinetin 0.1% lotion can be applied twice a day in rosacea for its moisturizing and skin repair functions [36].
7. Damaged skin barrier due to loss of intercellular lipids like fatty acids, cholesterol and ceramides can lead to increased trans-epidermal water loss, increased penetration of irritants and thus may lead to dry and sensitive skin [37].
8. Different types of moisturizers include humectants, emollients, occlusive and protein rejuvenators. Emollients help in replenishing the intercellular lipids like fatty acids (linoleic, lauric, oleic, stearic acids), cholesterol, ceramides, squalene and so, lead to restoration of barrier function and improve cell signalling. Thus, they help in reducing the symptoms of sensitive skin.
9. Essential fatty acids like alpha linolenic acids and linoleic acid help in maintaining the skin barrier intact and active.
10. Moisturizers that contain ceramides, cholesterol and fatty acid in the optimal ratio of 3:1:1 lead to faster restoration of skin barrier. They all are non-irritant in nature and help in replacing the lost natural ceramides of damaged skin. Natural ceramides are costly so synthetic pseudo-ceramides can be used [38].
11. Squalene is found in sebum secretions. Its saturated form is known as Squalane. Squalane is an odourless, anti-bacterial, non-comedogenic, non-irritant moisturizer safe for sensitive skin.
12. Various botanical substances can be added in moisturizers to enhance their efficiency like oatmeal, aloe, allantoin and flavonoids. Aloe vera has shown wound healing properties, acts as anti-inflammatory and anti-pruritic agent. Shea butter is obtained from *Vitellaria paradoxa* (formerly called *Butyrospermum parkii)* or shea tree kernel. Shea butter also has anti-inflammatory properties [37].

13. Oatmeal (*Avena sativa*) contains various phenols that possess antioxidant, anti-inflammatory properties. Other contents of oatmeal are protein, lipid, fibres, starch and beta glucans. Colloidal oatmeal is added in moisturizers and syndet bars to reduce the symptoms and sooth the sensitive skin. Colloidal oatmeal acts as potent hydrating and moisturizing agent for sensitive skin due to its high concentration of beta glucan and starch [37–39].
14. However, an eye should be kept out for any sensitive skin symptoms with these "natural" products.
15. Canola oil can help in reducing the inflammation and irritation caused by sodium lauryl sulphate.
16. Bakuchiol is a meroterpene extracted from the seed of *Psoralea corylifolia* or babchi herb. Bakuchiol acts via regulation of retinol-like gene expression in skin and so also leads to retinol-like anti-ageing effects. Recently, Draelos et al. demonstrate the effectiveness and safety of this natural bakuchiol-based anti-ageing moisturizer in sensitive skin [40].
17. A topical gel formulation containing nicotinamide, witch hazel, oat kernel extract and disodium lauriminodipropionate tocopheryl phosphates (DLTP) was found to be safe and effective in sensitive skin. It decreased the erythema and trans-epidermal water loss, and also induced in vitro new collagen formation. This formulation was also found to be non-comedogenic, non-irritating, non-sensitizing and non-stinging in nature [41].
18. Skin products containing 4-t-butylcyclohexanol provide calming and fast soothing effect on sensitive skin. 4-t-butylcyclohexanol decreases the sensory symptoms like burning, pricking, stinging of sensitive skin by counteracting the hyperresponsiveness of the nerve fibres by blocking the TRPV1 receptor [42, 43].
19. Licochalcone A is an anti-inflammatory agent, synthesized from the reversely constructed chalcone removed from *Glycyrrhiza inflata* species of licorice. Topical application of licochalcone A along with 4-t-butylcyclohexanol has shown to reduce erythema and stinging [43, 44].

21.7 Step 4: Restart of Cosmetics (If Needed) and Cosmetics for Sensitive Skin

1. Use of cosmetics should be avoided if possible or used in very minimal quantity for short duration.
2. Cosmetics with inert, hypoallergic, fragrance free, pure ingredients, specially formulated for sensitive skin should be used if at all needed.
3. Ingredients should be less than 10 in number so as to minimize the risk of sensitivity or irritation in sensitive skin.

4. Always check and highlight the date of expiry on skin care and cosmetic products. Post-dated products should be discarded at once to prevent any inadvertent use that can cause induction of symptoms of sensitive skin.
5. Water soluble cosmetics should be preferred over waterproof cosmetics as increased contact time with waterproof cosmetics may lead to irritation on skin. Also, they need specialized cleansing oils for removal [45].
6. Powder or mineral based cosmetics like powder foundation, talcum powder, eye shadow, blush, dry shampoo, etc. are preferred in sensitive skin. They contain talc, titanium dioxide, silicates or aluminium oxides that have no or minimal irritant or allergic potential. Secondly, these mineral-based products usually do not have additional ingredients like binders that can stuck to skin, so these are easily removable and doesn't last longer on skin. However, care must be taken to choose products with fewer number of ingredients, minimal to no fragrance, bland and no added colour, etc. [7]
7. Microfine zinc oxide or titanium oxide-based powder products are preferred for inert nature and added sun protection.
8. If powder-based or cream-based products are not available, then second preference is silicone (dimethicone, cyclomethicone) based products.
9. Dimethicone is water insoluble, non-comedogenic and hypoallergic. It also acts as emollient and makes skin soft to touch. So, it is used in facial foundation and oil free moisturizers [46].
10. For eye makeup, black coloured pencil eye liner and eyebrow pencil, black mascara should be preferred over the colour ones. Eye shadow should be light coloured.
11. After a washout period of 2 weeks, cosmetics can be incorporated back one by one in the chronological order of lipstick, face powder and blush [47]. If there is no sign of exacerbation or recurrence of sensitive skin after the use of newly added product, then that particular product can be continued.
12. Nail polish contains toluenesulfonamide-formaldehyde resin (TSFR) to increase their durability, adhesiveness and contrast. This allergen leads to allergic contact dermatitis and sensitivity of skin of face, lips, neck and in few cases periungual or perianal region. So, use of nail polish with TSFR should be avoided [48, 49].
13. Other newer potential allergens in nail polish are acrylates, especially the acrylic monomers, hydroxyethyl methacrylate, hydroxypropyl methacrylate, polyester resins and formaldehydes [50, 51].
14. Newer longer lasting nail polish like shellac, gel and porcelain nail lead to increased risk of allergic contact dermatitis and skin sensitivity [50, 51].
15. "Hypo-allergenic nail polish" available in market may also lead to allergic contact dermatitis due to presence of at least one of the potent allergens like epoxy resins, formaldehyde, sulfonamides, toluene or even TSFR. Hence, in sensitive skin individuals, nail polish is better avoided [52].
16. Fragrance free lipstick should be used.
17. Summers have been noted as a triggering factor for individuals with sensitive skin [53].

21.8 Emotional and Psychological Support

1. Individuals with sensitive or very sensitive skin may have impaired self-perception of social, physical and mental health. This psychological impairment in quality of life was found to be directly proportional to the degree of sensitivity of skin [53].
2. If the symptoms of sensitive skin persist even after the proper care of skin as advised, psychological aspect of sensitive skin should be assessed. Neuropsychiatric illnesses like anxiety, somatization, interpersonal sensitivity, hostility or depression may masquerade or present as hypersensitivity of skin. So, timely intervention may help the patient [54].
3. Differential diagnosis of body dysmorphic disorder should be kept in mind in cases where subjective symptoms of sensitive skin can't be explained or non-responsive to therapy.
4. In recurrent or recalcitrant cases of sensitive skin, psychological counselling may be needed.

21.9 The COVID-19 Pandemic and Care of Sensitive Skin

During the COVID-19 pandemic, frequent handwashing with soaps, frequent and liberal use of alcohol-based sanitizers and almost universal use of face masks have led to increase skin sensitivity and redness, dryness and irritation at the site of contact of skin with these personal protective equipment (PPE) items. Skin care during the COVID-19 pandemic thus would require judicious use of disinfectants and more frequent application of moisturizers. Some tips are as follows:

1. Use of mild skin cleanser with skin-friendly pH is recommended.
2. Regular use of moisturizers with humectant like urea and occlusive emollient like petroleum jelly are preferred to prevent dryness of skin and to keep skin well hydrated.
3. Hypoallergic and fragrance free products should be used to minimize the risk of sensitivity [55].
4. Anti-ageing creams may contain retinoids and further exacerbate skin irritation so they should be avoided. Use of moisturizer at bed time may be advised.
5. Overheated water should be avoided for baths and showers [56].
6. Alcohol-based hand sanitizers can cause hand dryness and erythema (Fig. 21.6), irritant or allergic contact dermatitis and urticaria. Alcohol-based hand sanitizers which contain at least 60% alcohol and no added surfactants, fragrances or preservatives are of low allergenic potential. An additional moisturizer in the alcohol-based sensitizers will further reduce the risk of hand dermatitis and sensitivity [57, 58].
7. Prolonged and repeated use of PPE may lead to exacerbation of pre-existing skin diseases.
8. Face mask should be of adequate fit and not too tight.

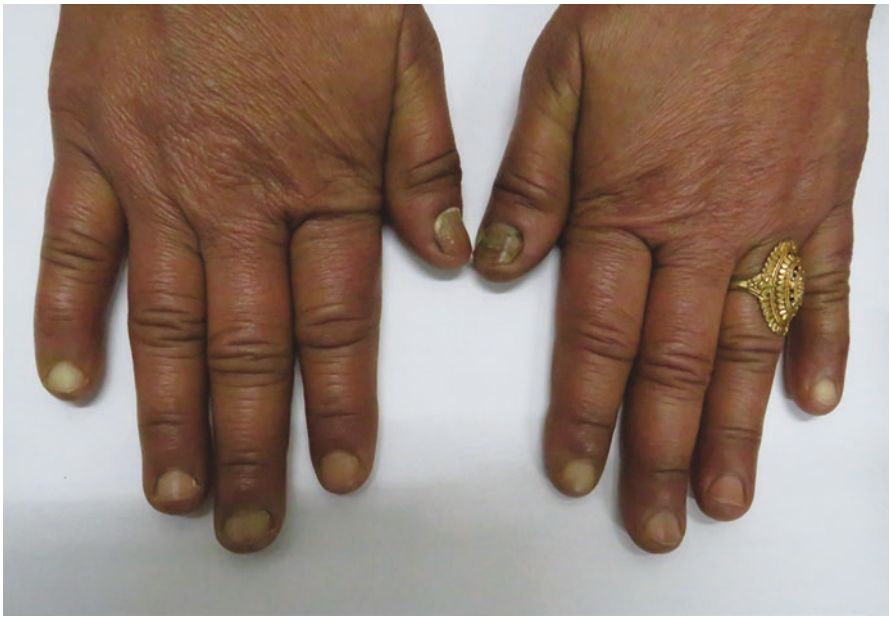

Fig. 21.6 Sensitive hands due to frequent handwashing during the COVID-19 pandemic

9. Skin reactions due to N95 masks are more common than surgical masks, due to the greater impermeability of N95 masks, a tighter fit and the different constituents [59]. Masks may cause skin sensitivity and irritation due to metal clips, rubber straps and adhesives among others [60]. In case of skin irritation due to mask, layering with gauze can help [56]. Also, different brand or material of face mask can be tried.
10. Before donning the mask at work, skin barrier wipes can be used to dry and clean face. Use of ample moisturizer 30 min prior to wearing the mask can help in keeping the facial skin supple and reduces the friction due to mask. However, petroleum-based moisturizers should be avoided as they may impede the integrity of N95 masks. Additionally, silicone cover protectors can also be used to prevent friction [60].
11. Disinfectant wipes meant for surface cleaning contain potent irritants like N-alkyl dimethyl benzyl ammonium chloride. Such wipes should not be used for hand-sanitizing as they may lead to skin sensitivity or irritant contact dermatitis [57].
12. The glove manufacturing process involves the use of rubber accelerators which can lead to skin sensitization and allergies [60]. Use of a different brand or material of gloves may help in such cases. Mild topical corticosteroid can be added for faster relief.

References

1. Inamadar AC, Palit A. Sensitive skin: an overview. Indian J Dermatol. 2013;79(1):9–16.
2. Escalas-Taberner J, Gonzalez-Guerra E, Guerra-Tapia A. Sensitive skin: a complex syndrome. Actas Dermosifiliogr. 2011;102(8):563–71.
3. Meena N, Sinha S, Sarkar R. Sensitive skin care: general measures—Do's and Don'ts. In: Sarkar R, Sinha S, editors. The sensitive skin: treatment modalities and cosmeceuticals. 1st ed. New Delhi: Jaypee Bros; 2019. p. 14–8.
4. Muizzuddin N, Marenus KD, Maes DH. Factors defining sensitive skin and its treatment. Am J Contact Dermat. 1998;9(3):170–5.
5. Pons-Guiraud A. Sensitive skin: a complex and multifactorial syndrome. J Cosmet Dermatol. 2004;3(3):145–8.
6. Sinha S, Sarkar R. What is sensitive skin? In: Sarkar R, Sinha S, editors. The sensitive skin: treatment modalities and cosmeceuticals. 1st ed. New Delhi: Jaypee Bros; 2019. p. 1–13.
7. Fisher AA. "Status cosmeticus": a cosmetic intolerance syndrome. Cutis. 1990;46(2):109–10.
8. Dieamant Gde C, Velazquez Pereda Mdel C, Eberlin S, Nogueira C, Werka RM, Queiroz ML. Neuroimmunomodulatory compound for sensitive skin care: in vitro and clinical assessment. J Cosmet Dermatol. 2008;7(2):112–9.
9. Ständer S, Schneider SW, Weishaupt C, Luger TA, Misery L. Putative neuronal mechanisms of sensitive skin. Exp Dermatol. 2009;18(5):417–23.
10. Duarte I, Silveira J, Hafner MFS, Toyota R, Pedroso DMM. Sensitive skin: review of an ascending concept. An Bras Dermatol. 2017;92(4):521–5.
11. Draelos ZD. Sensitive skin: perceptions, evaluation, and treatment. Am J Contact Dermat. 1997;8(2):67–78.
12. Abbas S, Goldberg JW, Massaro M. Personal cleanser technology and clinical performance. Dermatol Ther. 2004;17(1):35–42.
13. Ananthapadmanabhan KP, Moore DJ, Subramanyan K, Misra M, Meyer F. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. Dermatol Ther. 2004;17(1):16–25.
14. Mukhopadhyay P. Cleansers and their role in various dermatological disorders. Indian J Dermatol. 2011;56(1):2–6.
15. Draelos ZD. The science behind skin care: cleansers. J Cosmet Dermatol. 2018;17(1):8–14.
16. Mias C, Maret A, Gontier E, Carrasco C, Satge C, Bessou-Touya S, et al. Protective properties of avène thermal spring water on biomechanical, ultrastructural and clinical parameters of human skin. J Eur Acad Dermatol Venereol. 2020;34(5):15–20.
17. Strugar TL, Kuo A, Seité S, Lin M, Lio P. Connecting the dots: from skin barrier dysfunction to allergic sensitization, and the role of moisturizers in repairing the skin barrier. J Drugs Dermatol. 2019;18(6):581.
18. Hodgkinson B, Nay R, Wilson J. A systematic review of topical skin care in aged care facilities. J Clin Nurs. 2007;16(1):129–36.
19. Tarun J, Susan J, Suria J, Susan VJ, Criton S. Evaluation of pH of bathing soaps and shampoos for skin and hair care. Indian J Dermatol. 2014;59(5):442–4.
20. Lazzarini R, Costa LL, Suzuki NM, Hafner MFS. Allergic contact dermatitis by shampoo components: a descriptive analysis of 20 cases. An Bras Dermatol. 2020;95(5):658–60.
21. Schlichte MJ, Katta R. Methylisothiazolinone: an emergent allergen in common pediatric skin care products. Dermatol Res Pract. 2014;2014:132564.
22. Chen SY, Yin J, Wang XM, Liu YQ, Gao YR, Liu XP. A new discussion of the cutaneous vascular reactivity in sensitive skin: a sub-group of SS? Skin Res Technol. 2018;24(3):432–9.
23. Guertler A, Jøntvedt NM, Clanner-Engelshofen BM, Cappello C, Sager A, Reinholz M. Efficacy and safety results of micellar water, cream and serum for rosacea in comparison to a control group. J Cosmet Dermatol. 2020;19(10):2627–33.

24. Brenaut E, Barnetche T, Le Gall-Ianotto C, Roudot A-C, Misery L, Ficheux A-S. Triggering factors in sensitive skin from the worldwide patients' point of view: a systematic literature review and meta-analysis. J Eur Acad Dermatol Venereol. 2020;34(2):230–8.
25. Grivet-Seyve M, Santoro F, Lachmann N. Evaluation of a novel very high sun-protection-factor moisturizer in adults with rosacea-prone sensitive skin. Clin Cosmet Investig Dermatol. 2017;10:211–9.
26. Chintaginjala A, Kamcharla L, Kolalapudi S. Sunscreens. J NTR Univ Health Sci. 2012;1(4):210–6.
27. Ehnis-Perez A, Torres-Alvarez B, Cortes-Garcia D, Hernandez-Blanco D, Fuentes-Ahumada C, Castanedo-Cazares JP. Relationship between transient receptor potential vanilloid-1 expression and the intensity of sensitive skin symptoms. J Cosmet Dermatol. 2016;15(3):231–7.
28. Merinville E, Byrne AJ, Rawlings AV, Muggleton AJ, Laloeuf AC. Three clinical studies showing the anti-aging benefits of sodium salicylate in human skin. J Cosmet Dermatol. 2010;9(3):174–84.
29. Green BA, Yu RJ, Van Scott EJ. Clinical and cosmeceutical uses of hydroxyacids. Clin Dermatol. 2009;27(5):495–501.
30. Yeh LC, Gonzalez N, Goldberg DJ. Comparison of a novel wound dressing vs current clinical practice after laser resurfacing. J Cosmet Dermatol. 2019;18(4):1020–4.
31. Draelos ZD, Ertel K, Berge C. Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. Cutis. 2005;76(2):135–41.
32. Zane LT, Hughes MH, Shakib S. Tolerability of crisaborole ointment for application on sensitive skin areas: a randomized, double-blind, vehicle-controlled study in healthy volunteers. Am J Clin Dermatol. 2016;17(5):519–26.
33. Zane LT, Chanda S, Jarnagin K, Nelson DB, Spelman L, Gold LS. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Immunotherapy. 2016;8(8):853–66.
34. Farage MA. Sensitive skin in the genital area. Front Med. 2019;6:96.
35. Farage MA. Perceptions of sensitive skin: women with urinary incontinence. Arch Gynectol Obstet. 2009;280(1):49–57.
36. Culp B, Scheinfeld N. Rosacea: a review. P T. 2009;34(1):38–45.
37. Sethi A, Kaur T, Malhotra S, Gambhir M. Moisturizers: the slippery road. Indian J Dermatol. 2016;61(3):279–87.
38. Purnamawati S, Indrastuti N, Danarti R, Saefudin T. The role of moisturizers in addressing various kinds of dermatitis: a review. Clin Med Res. 2017;15(3-4):75–87.
39. Pazyar N, Yaghoobi R, Kazerouni A, Feily A. Oatmeal in dermatology: a brief review. Indian J Dermatol. 2012;78(2):142–5.
40. Draelos ZD, Gunt H, Zeichner J, Levy S. Clinical evaluation of a nature-based bakuchiol anti-aging moisturizer for sensitive skin. J Drugs Dermatol. 2020;19(12):1181–3.
41. Heinicke IR, Adams DH, Barnes TM, Greive KA. Evaluation of a topical treatment for the relief of sensitive skin. Clin Cosmet Investig Dermatol. 2015;8:405–12.
42. Schoelermann AM, Jung KA, Buck B, Grönniger E, Conzelmann S. Comparison of skin calming effects of cosmetic products containing 4-t-butylcyclohexanol or acetyl dipeptide-1 cetyl ester on capsaicin-induced facial stinging in volunteers with sensitive skin. J Eur Acad Dermatol Venereol. 2016;30(S1):18–20.
43. Sulzberger M, Worthmann A-C, Holtzmann U, Buck B, Jung KA, Schoelermann AM, et al. Effective treatment for sensitive skin: 4-t-butylcyclohexanol and licochalcone A. J Eur Acad Dermatol Venereol. 2016;30(S1):9–17.
44. Kolbe L, Immeyer J, Batzer J, Wensorra U, Dieck K, Mundt C, et al. Anti-inflammatory efficacy of Licochalcone A: correlation of clinical potency and in vitro effects. Arch Dermatol Res. 2006;298:23–30.
45. Draelos ZD. Cosmetics in acne and rosacea. Semin Cutan Med Surg. 2001;20(3):209–14.
46. Draelos ZD. Active agents in common skin care products. Plast Reconstr Surg. 2010;125(2):719–24.

47. Lev-Tov H, Maibach HI. The sensitive skin syndrome. Indian J Dermatol. 2012;57(6):419–23.
48. Hausen BM, Milbrodt M, Koenig WA. The allergens of nail polish. (I). Allergenic constituents of common nail polish and toluenesulfonamide-formaldehyde resin (TS-F-R). Contact Dermat. 1995;33(3):157–64.
49. Lazzarini R, Duarte I, de Farias DC, Santos CA, Tsai AI. Frequency and main sites of allergic contact dermatitis caused by nail varnish. Dermatitis. 2008;19(6):319–22.
50. Lee S, Maor D, Palmer A, Nixon RL. Declining prevalence of allergic contact dermatitis caused by toslyamide/formaldehyde in nail polish. Contact Dermat. 2018;79(3):184–5.
51. Le Q, Cahill J, Palmer-Le A, Nixon R. The rising trend in allergic contact dermatitis to acrylic nail products. Australas J Dermatol. 2015;56(3):221–3.
52. Lazzarini R, Hafner MFS, Lopes ASA, Oliari CB. Allergy to hypoallergenic nail polish: does this exist? An Bras Dermatol. 2017;92(3):421–2.
53. Misery L, Myon E, Martin N, Consoli S, Boussetta S, Nocera T, et al. Sensitive skin: psychological effects and seasonal changes. J Eur Acad Dermatol Venereol. 2007;21(5):620–8.
54. Zafiriou E, Angelopoulos NV, Zintzaras E, Rallis E, Roussaki-Schulze AV. Psychiatric factors in patients with sensitive skin. Drugs Exp Clin Res. 2005;31:25–30.
55. Beiu C, Mihai M, Popa L, Cima L, Popescu MN. Frequent hand washing for COVID-19 prevention can cause hand dermatitis: management tips. Cureus. 2020;12(4):e7506.
56. Masood S, Tabassum S, Naveed S, Jalil P. COVID-19 pandemic & skin care guidelines for health care professionals. Pak J Med Sci. 2020;36(4):S115–7.
57. Rundle CW, Presley CL, Militello M, Barber C, Powell DL, Jacob SE, et al. Hand hygiene during COVID-19: Recommendations from the American Contact Dermatitis Society. J Am Acad Dermatol. 2020;83(6):1730–7.
58. Araghi F, Tabary M, Gheisari M, Abdollahimajd F, Dadkhahfar S. Hand hygiene among health care workers during COVID-19 pandemic: challenges and recommendations. Dermatitis. 2020;31(4):233–7.
59. Hu K, Fan J, Li X, Gou X, Li X, Zhou X. The adverse skin reactions of health care workers using personal protective equipment for COVID-19. Medicine. 2020;99(24):e20603.
60. Desai SR, Kovarik C, Brod B, James W, Fitzgerald ME, Preston A, et al. COVID-19 and personal protective equipment: treatment and prevention of skin conditions related to the occupational use of personal protective equipment. J Am Acad Dermatol. 2020;83(2):675–7.

Chapter 22
A Guide to Botulinum Toxin and Fillers

Richa Ojha Sharma

22.1 Introduction

The desire to improve aesthetic appeal and to efface the signs of ageing is innate human nature. History abounds with evidence of how humans have explored sundry methods to enhance beauty. Ancient Egyptians would make face packs of milk with incense cake, wax, fresh olive oil and cypress and leave it on the face for 6 days in an earnest effort to erase wrinkles. Ancient Greeks on the other hand would apply an overnight concoction comprising bread and milk, to be wiped off the next morning with beans cooked in butter. This, rather smelly business, they believed, would preserve their beauty. All through history, various oils, animal fats and plant distillates have been used for the rather elusive goal of erasing wrinkles [1].

In recent times, with better understanding of the ageing process, facial anatomy and technological advancement, anti-ageing treatments have been refined to include topicals, injectables and energy-based devices. These help not just to erase the effects of vagaries of time on a face, but to enhance features and correct undesirable facial attributes. In this chapter, we shall be focussing on two of the most effective, popular and gratifying treatments in aesthetic medicine—Cosmetic Injectables—more specifically—Botulinum Toxin and Dermal Fillers.

The process of ageing leads to changes in facial structure like collagen loss, fat pad atrophy, laxity of ligaments and bone resorption. These culminate in dynamic wrinkles due to muscular contracture, static wrinkles due to volume loss and wrinkle folds due to sagging. The dynamic lines produced due to muscle contraction can be smoothed with injecting a neuromodulator—Botulinum Toxin. Static lines and folds can be minimised with dermal fillers.

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Table 22.1 Commercially used botulinum toxin serotypes and brands available

Type	Brands
BTX/A	OnabotulinumtoxinA (Botox; Allergan, Irvine, CA), Nabota (Daewoong, Republic of Korea, Mkt by Dr. Reddy's Lab Ltd. in India) AbobotulinumtoxinA (Dysport; Galderma Laboratories, Fort Worth, TX) IncobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Greensboro, NC), PrabotulinumtoxinA (Jeuveau; Evolus, Inc., Santa Barbara, CA)
BTX/B	RimabotulinumtoxinB (Myobloc; Solstice Neurosciences, Louisville, KY)

22.2 Botulinum Toxin

Botulinum toxin (BTX) is manufactured from a toxin produced by the anaerobic bacterium *Clostridium botulinum*. Since the 1970s, BTX has been used in ophthalmology. Jean Carruthers, a Canadian ophthalmologist specialising in treating strabismus with BTX, noted that her patients would appreciate the improvement in expression after each session of BTX. This piqued her interest and she, along with her dermatologist husband, Alastair Carruthers wrote the first published paper on the cosmetic use of neuromodulators in 1992 [2]. They can be credited with discovering the aesthetic use of neuromodulators, culminating in the launch of the now popular neuromodulator brand—BOTOX from Allergan. As per The American Society for Aesthetic Plastic Surgery, over 1.7 million BTX treatments were carried out in the USA in 2019, making it the most common non-surgical aesthetic treatment [3]. There are seven BTX serotypes (BTX/A-G), types A (BTA) and B (BTB) are commercially produced for clinical use. Currently four BTX/A and one BTX/B preparations are FDA approved for use (Table 22.1).

22.3 Mechanism of Action

Botulinum toxin (BTX) binds to presynaptic neurons and inhibits acetylcholine release at the neuromuscular junction, thus preventing the nerve impulses that cause muscle contraction [4]. This flaccid paralysis of the injected muscles occurs immediately, but clinical effect shows after up to 3–7 days of injection [5]. Typically, the effect of BTX injections lasts for 3–4 months. The duration of effect depends upon the dose, injection technique, and patient immune response [6]., BTX inhibits the release of acetylcholine in the sympathetic fibres to sweat glands and effectively reduces sweat production [7]. BTX also inhibits release of mediators of pain and inflammation, including substance P and cGRP (calcitonin gene-related peptide) from sensory nerves. Thus, it has a role in amelioration of pain and neural inflammation in conditions like migraine [8].

22.4 Handling, Storage and Dilution

BTX is supplied in vials in powder form and must be reconstituted before use. Although FDA guidelines recommend BTX to be reconstituted with preservative free 0.9% saline, it has been seen that diluting with saline preserved with benzalkonium alcohol, or with lidocaine leads to better pain tolerance, with comparable efficacy [9, 10]. One BTX vial can be used for more than one patient. Several studies have shown that BTX is not as delicate as company package instructions suggest. BTX retains its efficacy even after 6 weeks of reconstitution, even if reconstitution was done by vigorous shaking, and even if stored in a refrigerator and not a freezer [11–13].

Effects of BTX injections are observed within 3 days and last for up to 3–4 months [14].

22.5 Indications of Use

Botulinum toxin is approved by FDA for injections to correct rhytids in the glabellar region and for axillary hyperhidrosis. Botulinum toxin is one of the most common aesthetic treatments worldwide and is used to reduce rhytids on forehead, glabella, around eyes and lips. Facial sculpting, treatment of dimpled chin and rejuvenation of ageing neck are other uses of botulinum toxin. In dermatology, various off-label uses such as for sweating disorders like Hailey Hailey Disease, pompholyx and inverse psoriasis; as well as other conditions like facial erythema, flushing and oily skin have been reported. But larger trials are needed to confirm the efficacy of BTX for such conditions [15].

The technique of injecting BTX is a continuously evolving process. While earlier, the focus would be to target individual area muscles using larger doses to smoothen out wrinkles, current practice is to soften the lines and focus on improving the aesthetics of the entire zone being treated. For instance, chasing forehead wrinkles, aiming at a shiny, smooth forehead was practised earlier. Now, subtle improvements in forehead length and brow position while keeping intact some mobility of muscle is the preferred treatment approach. This gives a subtler, alert and brighter look, improving the overall aesthetics of the person.

22.6 Common Indications of Botox

1. Glabellar lines—Frown lines or glabellar lines that appear upon frowning, cause an unduly angry, frustrated, and tired look. BTX is approved by FDA for injection into the corrugator and procerus muscles to relax them and reduce the appearance and depth of these lines. The preferred technique is to inject between

20–40 U in a 5-point V pattern—the central point into the procerus and 2 points each for the corrugator on either side (Fig. 22.1a). In order to avoid ptosis, care should be taken to palpate the orbital rim and inject at least 1 cm above it, in order to avoid diffusion into the levator palpebrae superioris muscle [6].

2. Horizontal forehead lines—Although one of the most common indications, BTX injections in the frontalis muscle can still be challenging. In every patient, a careful assessment of frontalis strength, its unique orientation and brow position helps determine the best injection sites. In general, 10–20 U are injected in 5–10 points, in a V pattern or staggered pattern, starting 3–4 cm above the orbital rim to avoid lid and brow ptosis (Fig. 22.1b). Spocking, or undue elevation of brows, can be avoided by injecting 1 U on each side in the lateral fibres of the frontalis [16].
3. Crow's feet—Contraction of the lateral fibres of orbicularis oculi muscle causes bunching up of skin upon smiling, called crow's feet or smile lines. Three points of injection consisting of 3–4 U each in the lateral fibres of each side softens these lines. Care should be taken to stay above the zygoma so as not to inadvertently inject into the fibres of the zygomaticus muscle, as this could cause difficulty in smiling. Lateral fibres of the orbicularis can be injected just below the eyebrow tail to achieve a lateral flare of the eyebrows too (Fig. 22.1c) [17].
4. Bunny lines—Contraction of the lateral nasalis muscle causes rhytids on the upper dorsal part of the nose while smiling. 2–4 U of BTX on each side improves the appearance markedly [18].
5. Droopy corners of mouth—The downturn of mouth corners is due to an overactive depressor anguli oris. This muscle can be weakened by injecting 2–5 U BTX in its belly [19].
6. Dimply chin—An overactive mentalis causing a rugged chin appearance can be made to relax by injecting 5–10 U BTX.

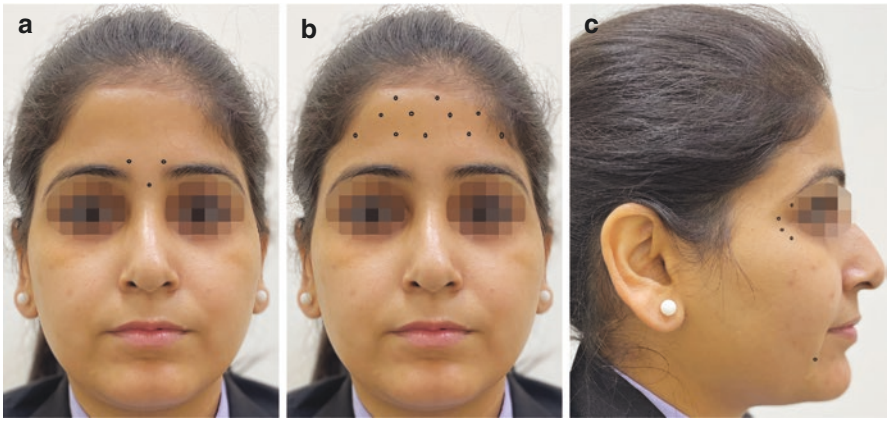

Fig. 22.1 (**a**) Injection points for BTX for glabellar lines. (**b**) Injection points for BTX for forehead. (**c**) Injection points for BTX for crow's feet, DAO and eyebrow flare

7. Masseter hypertrophy—A hypertrophic masseter lends heaviness to the lower face and a square jaw, which may not be appealing especially to women. The masseter can be injected with up to 30 U BTX on each side to reduce the hypertrophy of this muscle [20].
8. Platysmal bands—With ageing, contraction of the platysma muscle can cause vertical bands in the neck, especially in thin individuals. 2–4 U of BTX injected at gaps of 2 cm superficially into each platysmal band, beginning just below the mandible, is the preferred technique to treat these bands. A total of 3–5 injection points per side is recommended [21].
9. Botox for hyperhidrosis—For the distressing condition of axillary or palmoplantar hyperhidrosis, BTX injections may be used when topical agents fail to give satisfactory improvement. BTX is injected intradermally to target the sweat glands. 50 U of Botox is used for each axilla, divided into 10–15 sites spaced 1–2 cm apart. Higher doses are needed for palms and soles [22].

22.7 Side Effects and Contraindications

BTX is a safe, office procedure with minimal side effects like swelling, erythema and slight pain at the injection site. Rarely, diffusion of toxin to adjacent muscles can cause their paresis resulting in unwanted effects such as ptosis of eyelids or brow. Headache may be caused by forehead BTX at times. BTX should not be used in pregnant or lactating women. It is contraindicated in patients with hypersensitivity to any of the components in the Botox formulation, and if there is infection at the injection site. Individuals with amyotrophic lateral sclerosis, peripheral neuropathy and neuromuscular junctional disorders like myasthenia gravis must not be treated with Botox. Drugs like aminoglycosides, calcium channel blockers, can modify the metabolism of BTX [23].

There are reports that rarely, some patients may develop neutralising antibodies to the 150 kDa core of Botox, thus leading to treatment failure [24].

Formation of these antibodies depends on factors such as large doses, short injection intervals [25] and the individual characteristics of a patient's immune system [26].

22.8 Dermal Fillers

Dermal fillers are products injected in the skin to fill folds, to volumise areas of deflation, to sculpt and contour facial features, and to rejuvenate dull and dehydrated skin.

The desire to augment and enhance facial features has led to experimentation with sundry substances like paraffin, vegetable oil, mineral oil, lanolin, and beeswax, with disastrous consequences in many cases [1]. In 1981, bovine collagen

[Zyderm (Allergan, Dublin, Ireland)] was the first agent to be approved by the FDA for cosmetic injection. With these, hypersensitivity reactions were common; thus, skin tests were required. Human collagens were marketed as CosmoDerm (Allergan) in 2003 to eliminate hypersensitivity but never gained as much popularity. Synthetic hyaluronic acid (HA), resembling the extracellular matrix, was launched in 2003 as Restylane (Galderma S.A., Lausanne, Switzerland) in the United States.

22.9 Types of Dermal Fillers

There are three major types of dermal fillers (Table 22.2) [27].

Semi-permanent and permanent fillers are associated with more frequent complications because they are very resistant to degradation and linger in tissue for much longer than temporary fillers.

In this chapter, the focus is on HA fillers as they are the most used fillers worldwide.

Table 22.2 Types of dermal fillers

Type	Mechanism of Action	Duration of effect	Brands
Temporary	Hyaluronic acid—It is hydrophilic and absorbs water, thus volumising tissue	6–18 months	• Restylane, Restylane Silk, Restylane Lyft (Galderma, Upsala, Sweden) • Juvederm Ultra Plus, Voluma, Volite, Volift, Volbella, Vollure (Allergan Inc Irvine, CA) • Belotero Hydro, Soft, Balance, Intense, and Volume (marketed by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) • Princess fillers (produced by Austrian company Croma-Pharma GmbH) • Definisse Touch, Definisse Restore, Definisse Core (Croma-Pharma GmbH, Leobendorf, Austria)
Semi-permanent	Biodegradable particles that stimulate the body to produce its own collagen	1–2 years	• Poly-L-lactic acid—Sculptra (Dermik Laboratories) • Calcium hydroxylapatite—Radiesse (Merz Pharma)
Permanent	Nonbiodegradable particles that provoke a foreign body reaction that stimulates a fibroblastic deposition of collagen around the nonabsorbable microspheres	At least 5 years	• Polymethylmethacrylate—Bellafill (Suneva Medical Inc.) • Liquid silicone

22.10 HA Fillers

Hyaluronic acid (HA) filler injections are popular, non-surgical treatments carried out to add volume in deficient areas, in order to produce aesthetic appeal, to rejuvenate and to provide youthfulness of the face. According to The American Society for Aesthetic Plastic Surgery report, there has been an increment of 26.4% in HA filler treatments from 2015 to 2019 [28].

The reasons for the popularity of this treatment are many, including visible, reliable and instant change in aesthetics, minimal downtime and relative safety. HA fillers can be dissolved using hyaluronidase if there is a need, such as in case of inadvertent intra-arterial injection of HA, persistent lumps or aesthetically undesirable effects.

Hyaluronic acid (HA) is a glycosaminoglycan consisting of repeating units of D-glucuronic acid and DN-acetylglucosamine disaccharide. To increase the longevity and stiffness of HA gel, cross-linking of the HA chains is carried out. After the cross-linking, the gel is sized by either sieving or homogenisation. This makes the gel consistency just right for injection into the skin.

Different brands of HA fillers use different patented technologies for manufacturing.

The first-generation Restylane gels were developed with the patented Non-Animal Stabilized Hyaluronic Acid (NASHA) technology and have an HA concentration of 20 mg/mL with 1% of cross-linking. The second-generation products, Refyne and Defyne, launched in 2016 have the same HA concentration, but are formulated by a patented XpresHAn technology. Juvederm (Allergan) line of HA fillers were approved by FDA in 2006. The first-generation Juvederm products—Ultra and Ultra Plus—were created with a patented Hylacross technology. The second-generation of fillers Voluma, Vollure, Volift, Volite and Volbella were created with a patented Vycross technology. Juvederm range or products have HA concentration ranging from 15 to 24 mg/ml.

The Belotero range of fillers are formulated by a patented technology called cohesive polydensified matrix. HA content of this range varies from 22.5 to 26 mg/mL [29].

22.11 Rheology

The study of flow related properties is called Rheology [30].

There are various grades of fillers available, with different rheological properties. These properties of a filler depend upon the process of manufacturing, the HA concentration, degree of cross-linking and particle sizing. Understanding rheology of gels helps in making informed choices regarding product selection for different indications, thereby improving treatment outcome.

G′: Also known as elastic or storage modulus, G′ is a measure to describe the firmness or hardness of a gel and represents the ability of a gel to resist deformation under force. Gels with higher *G′* can resist dynamic forces better. They are best suited for areas where deep placement is needed for volumising and support.

G″: This is the viscous modulus and measures the inability of the gel to recover the original shape after being subjected to shear forces.

Cohesivity—The cohesivity of a gel is its tendency to retain its form or shape under stress [31]. Fillers having low cohesivity are those that have lesser degree of cross-linking and lesser HA concentration. They are easier to mould and must be used for superficial rhytides. Fillers having high cohesivity are preferred where lifting and volumising are required.

22.12 Assessment of the Patient

Before any aesthetic procedure, the aspirations of the patient and the improvement possible must be aligned. This is particularly important before injecting fillers. Very often, patients have unrealistic expectations from the treatment and may end up unhappy with the outcome. This can be avoided by first spending time to explain the treatment goals. Assessment must be done in sitting position to allow for the full effect of gravity in causing sagging and folds. Patients must be told about the type of filler that will be used, what the potential side effects are and the longevity of the product. Preprocedure photographs are a must. Any asymmetries or natural aberrations must be recorded before the injection sessions. Postprocedure photographs and discussion are also necessary. Written informed consent before the procedure is a legal requirement.

Before proceeding to practise filler injections, it is imperative to get oneself thoroughly acquainted with facial anatomy. Special attention to facial vasculature must be paid in order to minimise risk of intra-arterial injections which can have serious consequences.

22.13 Common Indications of HA Fillers

Broadly speaking, the following points can be used as a guide:

- For contouring, volumising and lifting—a high G′, more viscous and higher concentration HA filler is used. This must be injected deep onto the supraperiosteum.
- For treating medium depressions like nasolabial and mental folds, a filler with moderate elasticity and cohesivity is preferred.

- For treating the periorbital area, where projection is to be avoided at all costs, an HA preparation with low G′ and cohesivity is needed.
- Less viscous fillers are placed in subdermal or intradermal planes where fine lines need to be effaced and when superficial hydration and rejuvenation is the goal [19].

Common injection techniques include linear threading, serial puncture, linear threading, cross-hatching, fanning and depot placement.

1. Upper face—In the upper face, regions that can be filled with HA fillers are temples, lateral eyebrows, glabella and horizontal forehead creases.
    a. Temple hollowing is one of the first signs of ageing. Supraperiosteal bolus injections placed superior and lateral to the orbital rim and tapering to the hairline with a filler having a high G′ help in revolumising this area. The frontal branch of the superficial temporal artery and the middle temporal vein lie in this zone and must be avoided [32].
    b. Forehead lines—Botulinum toxin is first used to relax the dynamic forehead lines. Those grooves that persist, can be treated with low G' fillers injected superficially into them.
    c. Glabellar lines—In older patients as well as in some younger individuals, static glabellar lines persist despite botulinum injection into the depressors of the medial brow. These can be softened by placing low viscosity HA fillers subdermally in them. This area is to be treated with great caution as the supraorbital and supratrochlear vessels appear superficially from beneath the corrugators into the forehead. Inadvertent intra-arterial injection in this area can lead to blindness [33]. Aspiration before injection is advised.
    d. Lateral brow—Ptosis of the lateral brow occurs with fat atrophy and bone resorption. A high viscosity HA gel is placed deep, just below the brow, bringing about elevation of this region.
    e. Crow's feet—Although rarely needed, the static laugh lines remaining despite botulinum toxin injections can be treated with a moderate G' filler.
2. Midface—Deep fat pad atrophy and laxity of retaining ligaments occurring with ageing lead to midface deflation and descent [34, 35]. These changes lead to several changes such as tear trough deformity, depressed malar prominence, nasolabial fold development and lengthening of the upper lip.
    a. Tear trough—Moderate G′ fillers are placed deep on the orbital bone to reduce the appearance of tear troughs. Lumps can be gently massaged to integrate with the skin. Undercorrection is always advised in this area (Fig. 22.2).
    b. Malar area—A high viscosity and cohesive filler is introduced through a cannula to fill the medial cheek fat pads. Lateral areas and anterior cheek can be filled with bolus placement on the zygomatic arch. The infraorbital vascular

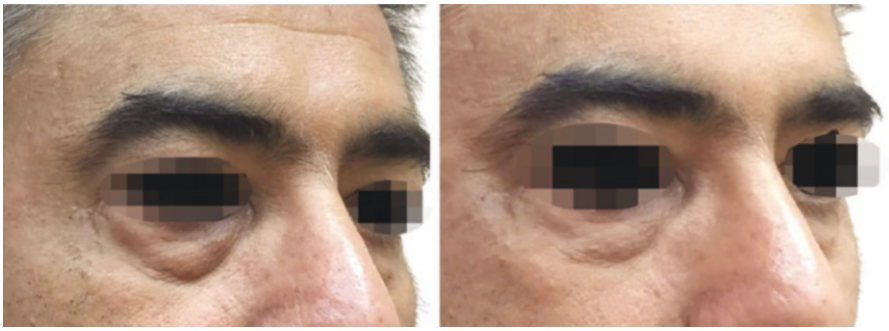

Fig. 22.2 Improvement in tear troughs after injection of moderate G′ HA filler

bundle lies a finger breadth below the inferior orbital margin at the level of medial limbus and injections should be away from this spot. Submalar areas are treated with subcutaneous fanning injections of moderate G′ HA fillers [36].

c. Nasolabial folds—Correcting malar and temple deflation with filler leads to a lift in the midface, improvement in the ligament laxity and pull to the superficial musculoaponeurotic system, indirectly causing reduction in the depth of nasolabial folds. Yet, it may be necessary, at times, to fill the medial end of the nasolabial fold, with a deep bolus injection of a moderate G′ HA filler. In the lower two-thirds, the filler is injected in the subcutaneous plane.
d. Nose—Mild deformities in nose can be corrected with moderate G′ HA fillers. The nose is highly vascular, and connections of nasal vessels are with vessels that feed the retina. Additionally, even small amounts of filler in the ala or tip of the nose can cause compression and necrosis. Hence, nasal fillers must be attempted with great caution.

3. Lower face—Thinning of lips may be a facial feature or a result of ageing. With advancement of age, there is resorption of the mandible and maxillary bones, as well as fat atrophy and soft tissue loss. Hyperactivity of the depressor anguli oris muscle also adds to this. As a result, there is a downturn of mouth corners, mentolabial or Marionette lines, jowls and a loss of jawline definition [37]. All these can be corrected with the use of HA fillers.

   a. Lips—Women of all age groups regard lips as an important attribute of beauty. At the same time, they are wary of lip injections causing an unnatural pout or “duck lips”. Balancing the upper and lower lip volume proportion, projection of the upper lip and maintaining the length of the mouth, are all important points to be remembered when seeking to beautify the lips with HA Fillers. Moderate G′ is always preferred. Definition of the vermillion

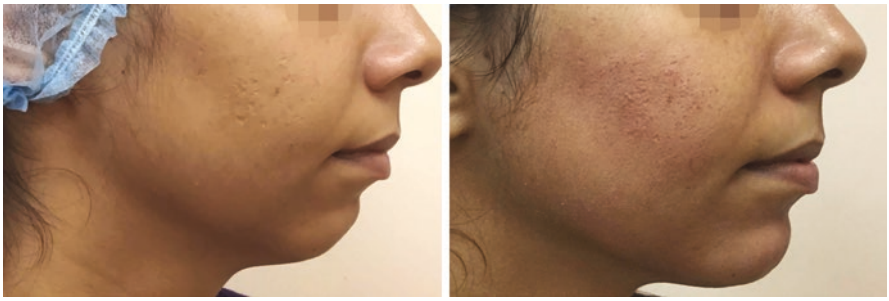

Fig. 22.3 Chin augmentation with high G′ HA filler

body, cupid's bow and small boluses into the body of the upper and lower lip is needed along with slight elevation of the corners of the lips. More than 1 ml of HA gel is rarely ever needed at one session. Perioral lip lines must be first relaxed with botulinum toxin and then treated with superficial linear threads of low G′ HA filler [38].

b. Marionette lines—A moderate G′ filler is injected in the marionette lines as well as medial to them, using a cannula and cross-hatching technique.
c. Chin—Highly viscous and dense fillers are injected in the chin area to address retrognathia. The goal, in males, is to align the chin height with the lower lip, and in females, it is to maintain the chin height 2 mm behind the lower lip (Fig. 22.3). A bolus in the midline and one each on either side of the midline, is the preferred technique. Avoid injecting too low [39].
d. Pre- and postjowl sulcus—Deep subcutaneous injections of high G′ filler using a cannula is spread by fanning technique in the prejowl sulcus, and by linear retrograde technique in the postjowl sulcus. The facial artery runs over the mandible in this area. The product should be placed in the deep subcutaneous plane after pinching and lifting the skin in order to avoid the facial artery.
e. Mandible angle—Deep supraperiosteal bolus injection of high G′ HA Filler is injected in males to give a chiselled jaw look. In females, the plane of injection is not as deep [38].

22.14 Complications

Table 22.3 elaborates the early and late onset complications of dermal filler injections [40]. Management of adverse effects must be early and aggressive. Vascular compromise is the most dreaded complication and a thorough knowledge of the use of hyaluronidase is imperative even before beginning filler injections.

Table 22.3 Complications of dermal fillers

Onset of complication	Events
Early onset (up to weeks after filler injections)	Injection site reactions—bruising, pain, redness, swelling Infection—reactivation of herpes simplex, abscess, and cellulitis due to staphylococcus and streptococcus Hypersensitivity reactions (usually Type I) Injection technique complications—palpable nodules, visible product, tyndall effect, contour irregularities Vascular occlusion—skin necrosis, retinal embolism leading to blindness, internal carotid artery embolism leading to cerebral ischemia
Late-onset (weeks to years after procedure)	Type IV Hypersensitivity reactions Hyperpigmentation Infection—mycobacteria or biofilm-related Foreign body granulomas Malar oedema Migration of filler material

22.15 Conclusion

Real, reliable and tangible aesthetic improvement is no longer just an aspiration of patients. Dermatologists are now able to deliver these effects with the help of botulinum toxin and dermal fillers.

- Dynamic rhytides that occur due to muscle contraction can be eased by relaxing the target muscles with botulinum toxin injections.
- The effect of botulinum toxin lasts for 3–5 months.
- The upper face dynamic wrinkles respond best to botulinum toxin injections.
- Static rhytides, folds and sagging can be corrected using dermal fillers.
- HA fillers are the most favoured as their effects are temporary, predictable and reversible if needed.
- Understanding of fluid properties or rheology of fillers helps in making correct choice of product for specific indications.
- Vascular compromise is the most sinister of all complications of fillers. To minimise this risk, a thorough knowledge of facial anatomy and vasculature is necessary for injectors.

References

1. Parish LC, Crissey JT. Cosmetics: a historical review. Clin Dermatol. 1988;6(3):1–4.
2. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. J Dermatol Surg Oncol. 1992;18(1):17–21.
3. Source: The Aesthetic Society. https://www.surgery.org/sites/default/files/Top-5.pdf
4. Schiavo G, Matteoli M, Montecucco C. Neurotoxins affecting neuroexocytosis. Physiol Rev. 2000;80(2):717–66.
5. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med. 1991;324(17):1186–94.

6. Gart MS, Gutowski KA. Overview of botulinum toxins for aesthetic uses. Clin Plast Surg. 2016;43(3):459–71.
7. Bhidayasiri R, Truong D. Evidence for effectiveness of botulinum toxin for hyperhidrosis. J Neural Transm. 2008;115:641–5.
8. Wenzel RG. Pharmacology of botulinum neurotoxin serotype A. Am J Health Syst Pharm. 2004;61(6):5–10.
9. Liu A, Carruthers A, Cohen JL, et al. Recommendations and current practices for the reconstitution and storage of botulinum toxin type A. J Am Acad Dermatol. 2012;67(3):373–8.
10. Gulec AT. Dilution of botulinum toxin A in lidocaine vs. in normal saline for the treatment of 429 primary axillary hyperhidrosis: a double-blind, randomized, comparative preliminary study. J Eur Acad Dermatol Venereol. 2012;26(3):314–8.
11. Hexsel DM, De Almeida AT, Rutowitsch M, et al. Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted up to six consecutive weeks before application. Dermatol Surg. 2003;29:523–9.
12. Sloop RR, Cole BA, Escutin RO. Reconstituted botulinum toxin type A does not lose potency in humans if it is refrozen or refrigerated for 2 weeks before use. Arch Facial Plast Surg. 2008;10:273–9.
13. Shome D, Nair AH, Kapoor R, et al. Botulinum toxin A: is it really that fragile a molecule? Dermatol Surg. 2010;36:2106–10.
14. Flynn TC. Botulinum toxin: examining duration of effect in facial aesthetic applications. Am J Clin Dermatol. 2010;11(3):189–99.
15. Campanati A, Martina E, Giuliodori K, et al. Botulinum toxin off-label use in dermatology: a review. Skin Appendage Disord. 2017;3(1):39–56.
16. Ascher B, Talarico S, Cassuto D, et al. International consensus recommendations on the aesthetic usage of botulinum toxin type A (Speywood Unit): part I. Upper facial wrinkles. J Eur Acad Dermatol Venereol. 2010;24(11):1278–84.
17. Frankel AS, Kamer FM. Chemical browlift. Arch Otolaryngol Head Neck Surg. 1998;124(3):321–3.
18. Carruthers J, Carruthers A. Aesthetic botulinum A toxin in the mid and lower face and neck. Dermatol Surg. 2003;29(5):468–76.
19. Alam M, Tung R. Injection technique in neurotoxins and fillers: indications, products, and outcomes. J Am Acad Dermatol. 2018;79(3):423–35. https://doi.org/10.1016/j.jaad.2018.01.037.
20. Cheng J, Hsu SH, McGee JS. Botulinum toxin injections for masseter reduction in East Asians. Dermatol Surg. 2019;45(4):566–72.
21. Sepehr A, Chauhan N, Alexander AJ, et al. Botulinum toxin type A for facial rejuvenation: treatment evolution and patient satisfaction. Aesthet Plast Surg. 2010;34(5):583–6.
22. Nawrocki S, Cha J. Botulinum toxin: pharmacology and injectable administration for the treatment of primary hyperhidrosis. J Am Acad Dermatol. 2020;82(4):969–79.
23. Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta547 analysis. Curr Med Res Opin. 2004;20(7):981–90.
24. Dressler D, Hallett M. Immunological aspects of botox, dysport and myobloc/neurobloc. Eur J Neurol. 2006;13(1):11–5.
25. Atassi MZ. Basic immunological aspects of botulinum toxin therapy. Mov Disord. 2004;19(8):68–84.
26. Dressler D, Dirnberger G, Bhatia KP, et al. Botulinum toxin antibody testing: comparison between the mouse protection assay and the mouse lethality assay. Mov Disord. 2000;15(5):973–6.
27. Liu MH, Beynet DP, Gharavi NM. Overview of deep dermal fillers. Facial Plast Surg. 2019;35(3):224–9.
28. Source: The Aesthetic Society. https://www.surgery.org/sites/default/files/2019-Trends.pdf.

29. Rohrich RJ, Bartlett EL, Dayan E. Practical approach and safety of hyaluronic acid fillers. Plast Reconstr Surg Glob Open. 2019;7(6):e2172.
30. Stocks D, Sundaram H, Michaels J, et al. Rheological evaluation of the physical properties of hyaluronic acid dermal fillers. J Drugs Dermatol. 2011;10(9):974–80.
31. Kablik J, Monheit GD, Yu L, et al. Comparative physical properties of hyaluronic acid dermal fillers. Dermatol Surg. 2009;35:302–12.
32. Lee JG, Yang HM, Hu KS, et al. Frontal branch of the superficial temporal artery: anatomical study and clinical implications regarding injectable treatments. Surg Radiol Anat. 2015;37(1):61–8.
33. Beleznay K, Carruthers JD, Humphrey S, Jones D. Avoiding and treating blindness from fillers: a review of the world literature. Dermatol Surg. 2015;41(10):1097–117.
34. Rohrich RJ, Pessa JE. The fat compartments of the face: anatomy and clinical implications for cosmetic surgery. Plast Reconstr Surg. 2007;119(7):2219–27.
35. Mendelson BC. Anatomic study of the retaining ligaments of the face and applications for facial rejuvenation. Aesthet Plast Surg. 2013;37(3):513–5.
36. de Maio M, DeBoulle K, Braz A, et al. Facial assessment and injection guide for botulinum toxin and injectable hyaluronic acid fillers: focus on the midface. Alliance for the Future of Aesthetics Consensus Committee. Plast Reconstr Surg. 2017;140(4):540–50.
37. Zimbler MS, Kokoska MS, Thomas JR. Anatomy and pathophysiology of facial aging. Facial Plast Surg Clin North Am. 2001;9(2):179–87.
38. de Maio M, Wu WTL, Goodman GJ, Monheit G. Facial assessment and injection guide for botulinum toxin and injectable hyaluronic acid fillers: focus on the lower face. Plast Reconstr Surg. 2017;140(3):393–404.
39. Vanaman Wilson MJ, Jones IT, et al. Role of nonsurgical chin augmentation in full face rejuvenation: a review and our experience. Dermatol Surg. 2018;44(7):985–93.
40. Kassir M, Gupta M, Galadari H, et al. Complications of botulinum toxin and fillers: a narrative review. J Cosmet Dermatol. 2020;19(3):570–3. https://doi.org/10.1111/jocd.13266.

Chapter 23
Chemical Peels: Special Considerations

Rashmi Sarkar, Akhilesh Thole, and Surabhi Sinha

23.1 Introduction

Chemical peeling is one of the commonly employed method of resurfacing the skin in which there is controlled wounding of the epidermis and dermis which may lead to collagen remodelling for medical and aesthetic improvement [1]. Chemical peels when used in appropriate concentration and indication are assumed to induce all three stages of tissue replacement, viz. destruction, elimination and regeneration all accompanied by controlled stages of inflammation [2].

23.2 Male Versus Female Skin: What We Should Know Prior to Peels

The biophysical properties of the skin between men and women have been studied by various studies. When it comes to various cutaneous disorders, although infectious diseases are presented more in men but psychosomatic problems, pigmentary disorders, some hair disorders and autoimmune and allergic diseases are more common in women [3]. In literature and in general, significantly more female

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sex-associated dermatoses have been identified than in male [3]. Despite best efforts, the causes of gender differences in skin diseases remain largely unknown.

The thickness and mass of stratum corneum appear to be gender independent in most studies [4, 5]. But at all ages skin thickness in males is slightly more than in females especially at forearm, forehead, cheeks and back. According to some authors skin thickness gradually decreases with age in men starting by the age of 20, whereas it remains constant in women until the age of 50 or so and then starts decreasing [6]. Leveque et al. suggested that in both sexes, skin thickness starts decreasing at the age of 45 [7].

Sebum maintains the flexibility and the extensibility of the stratum corneum. It is also an excellent lubricant. Excess sebum leads to pore enlargement and acne which are aesthetically undesirable [5]. According to an earlier report, men produce a significantly more amount of sebum than women especially after puberty [8]. Researchers have found a positive correlation between male sex, pore size and sebum excretion in a Korean study with 30 males and 30 females [9].

Skin colour is regulated by vascularity, melanin and other pigments. In most of the reports no difference in melanin distribution has been reported between men and women [10, 11]. But according to some reports, in ethnic groups, men seem to have darker and less reflective complexions. After sun exposure, men's skin pigments more intensely than women and they also retain it longer, and women's skin have a speedy recovery after pigment darkening [12, 13],

.In the available literature, there is no standard method for determining skin pH. Hence studies determining gender difference in skin surface pH fail to come at a consensus regarding skin surface pH in both genders [5].

23.2.1 Classification

Chemical peels are often divided on the basis of the histologic depth of penetration into superficial, medium and deep peels [14]. Superficial peels, subdivided into very light and light peels, penetrate epidermis only reaching up to stratum spinosum and stratum basale, respectively.[iv] Medium depth peels penetrate up to the upper reticular dermis, whereas deep peels may wound to the level of the mid-reticular dermis.[iv] Classification of various peeling agents is described in Table 23.1, while mechanism of action is described in Table 23.3.

Indications of chemical peels are listed in Table 23.2.

Table 23.1 Classification of chemical peels

Classification	Histological depth of penetration	Agents available	Interval between sessions
Superficial, very light	Wounding to the level of stratum spinosum	Trichloroacetic acid (TCA) 10–20% Low potency AHAs and BHAs Tretinoin	1–2 weeks

Table 23.1 (continued)

Classification	Histological depth of penetration	Agents available	Interval between sessions
Superficial, light	Wounding through entire epidermis up to stratum basale	TCA 20–30% Jessner's solution 70% glycolic acid	2–4 weeks
Medium	Wounding through the level of upper reticular dermis	35–40% TCA 88% phenol(unoccluded) Solid CO2 plus TCA Jessner's solution plus TCA 35% 70% Glycolic acid plus 35% TCA	1–2 months
Deep	Wounding to mid-reticular dermis	Baker Gordon Phenol peel	Single to two monthly sessions

Table 23.2 Various indications of chemical peels [15]

Pigmentary	Acne	Aesthetics	Epidermal growths
Post-inflammatory hyperpigmentation Freckles Lentigines Melasma	Post-acne hyperpigmentation Mild scarring Acne vulgaris grade 2/3 Comedonal acne	Fine wrinkles Photoageing Dilated pores Superficial scars	Actinic keratoses Seborrheic keratoses DPN Milia Warts

Beta-Hydroxy Acid Salicylic acid also known as 2-hydroxybenzonic acid is a crystalline carboxylic acid and classified as a beta-hydroxy acid [16]. Salicylic acid is a lipophilic compound which acts by removing intercellular lipids, thus producing exfoliation [15]. It also has anti-inflammatory and anti-microbial properties [15]. It functions as a keratolytic agent at concentrations of 3% to 5%, but it functions as a peel at ethanol solutions of 20–30% [17].

As demonstrated by work from Grimes and Bari et al. salicylic acid peel is considered safer in ethnic skin with skin types IV–VI [18, 19]. According to the studies conducted by Lee and Kim [20] and Ahn and Kim [21] salicylic acid leads to reduction of both inflammatory and noninflammatory acne lesions, along with some amount of lightening (Fig. 23.1).

Some other advantages of salicylic acid peels are uniformity of application as a white precipitate is quite conspicuous [15]. Also the patient tolerance is quite increased after few minutes due to anaesthetic effect of salicylic acid [15]. Some disadvantages are minimal efficacy in significant photodamage and limited depth of peeling [15] (Table 23.3).

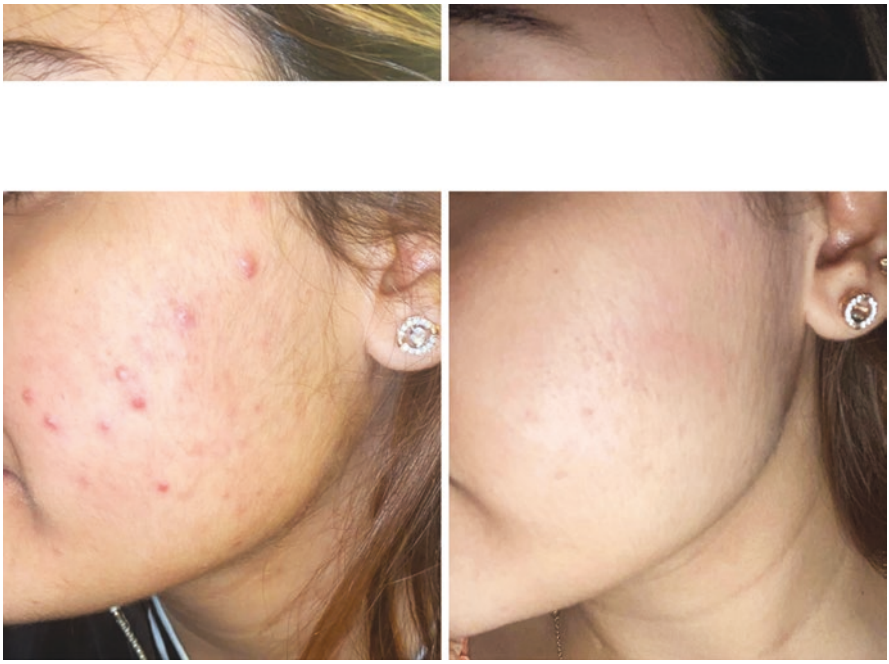


Fig. 23.1 Four sessions of salicylic acid peel done in a patient with acne once in 2 weeks

Table 23.3 Mechanism of action of various peeling agents

Peeling agent	Mechanism of action
Glycolic acid	1. At epidermal level: Corneolysis (lysis of corneo-desmosomes)—Low concentration and acidic pH, moisturising effects—Higher pH 2. At dermal level: Causes stimulation of fibroblasts and synthesis of collagen, elastin and gags
Lactic acid	1. Desquamation of stratum corneum: Dissolves intercellular desmosomes 2. Humectant effect: It increases hyaluronic acid content of skin 3. Anti-microbial and anti-inflammatory properties
Pyruvic acid	1. At epidermal level: 40% concentration causes keratinocyte detachment, epidermolysis and thinning of epidermis 2. At dermal level: Increases collagen and glycoproteins 3. Lipophilic nature results in sebostatic and anti-microbial nature
Salicylic acid	1. Comedolytic effect: Lipophilic nature results in dissolution intercellular bonds 2. Anti-inflammatory and anti-microbial effects
TCA	1. Caustic action due to coagulation of proteins
Jessner's peel	1. Corneolysis 2. Increases effects of other keratolytic agents
Phenol	1. Coagulation of epidermal and dermal proteins

23.2.2 Alpha Hydroxy Acids

It is a group of acids which includes glycolic acid (derived from sugar cane), lactic acid (from sour milk), citric acid (from citrus fruits), phytic acid (from rice), tartaric acid (from grapes) and malic acid (from apples) [17].

Glycolic acid: It is the smallest AHA by way of molecular weight and chemical structure and is also a highly hydrophilic molecule with the greatest bioavailability of all the AHAs [22]. As with all AHA's glycolic acid functions as peel by causing epidermolysis within minutes of application, gradually followed by desquamation and the dispersion of epidermal melanin [21]. Glycolic acid is readily available and comes in preparations ranging from 10% to 70%. It is popular at 10–50% concentration for most purposes and effective in dark-skinned patients [23]. Glycolic acid requires to be neutralised with cold water or sodium bicarbonate to prevent undesired effects [24]. It is considered chemical peel of choice for treatment of melasma which is far more common in women [25] (Figs. 23.2 and 23.3).

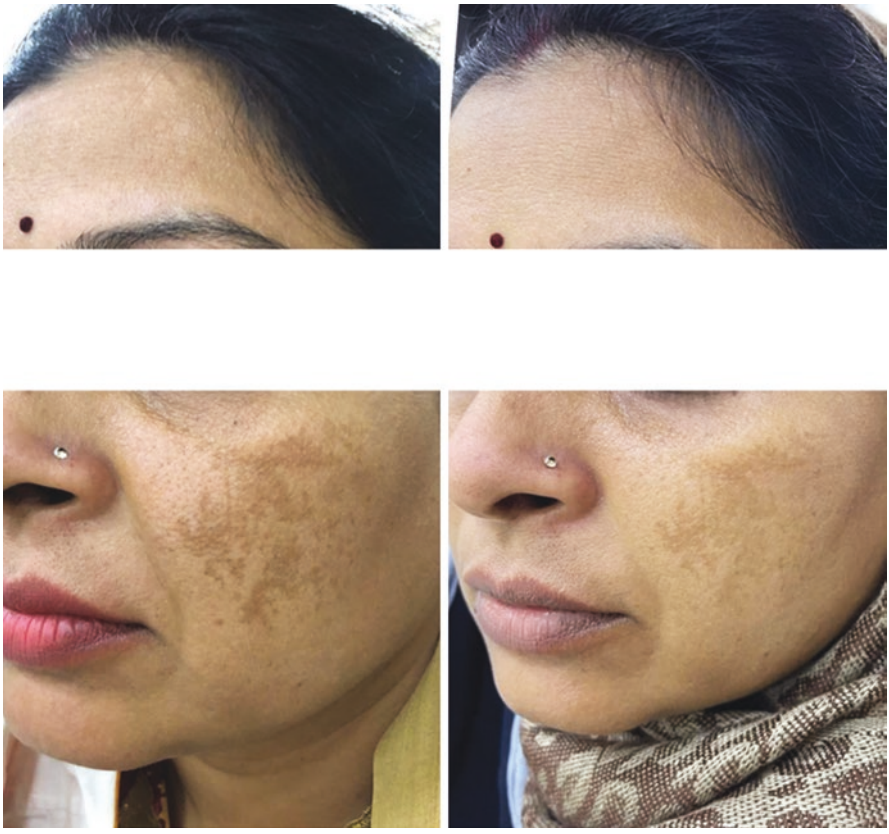


Fig. 23.2 Four sessions of glycolic acid 30% peel done once in 3 weeks. Priming was done with hydroquinone 2% 2 weeks prior

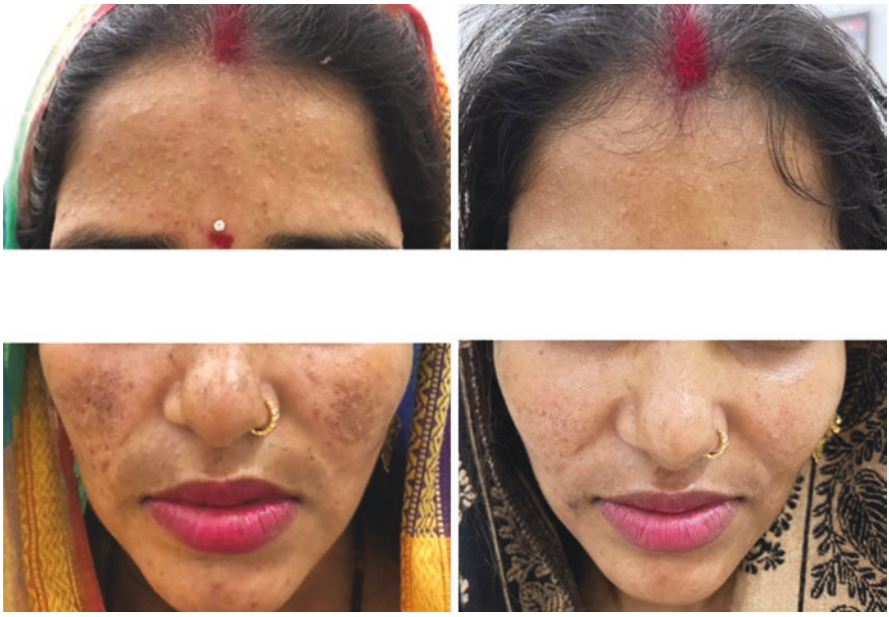


Fig. 23.3 Three sessions of glycolic acid peel 50% done, once in 3 weeks

Lactic acid: It inhibits tyrosinase enzyme activity directly in a dose-dependent manner [26].

According to a report lactic acid at 92% concentration may be used for the treatment of acne scarring with minimal risk of any adverse events [27]. Sharquie et al. reported improvement in the Melasma Area and Severity Index (MASI) with pure lactic acid and results were comparable to Jessner's solution [28].

Jessner's Solution It is a combination of three keratolytic agents which also have skin-lightening properties: salicylic acid (14 g), resorcinol (14 g) and lactic acid (85%) in ethanol (95%). These agents act synergistically to provide superficial chemoexfoliation with some lightening [29] (Fig. 23.4). Important aspects of Jesner's solution have been enumerated in Table 23.4.

23.2.3 Trichloroacetic Acid (TCA)

TCA is a crystalline inorganic compound and exerts caustic action through coagulative necrosis of cells by extensive protein denaturation and resultant structural cell death [21].The concentration of solution applied determines the degree of necrosis tabulated in Table 23.5 [33].

TCA is considered as a benchmark medium depth peel [34]. TCA at 35% concentration is used for focal treatment to avoid complications such as dyschromia and scars which are common with use over large areas [31]. Frosting witnessed with TCA is due to epidermal and dermal protein denaturation [31].

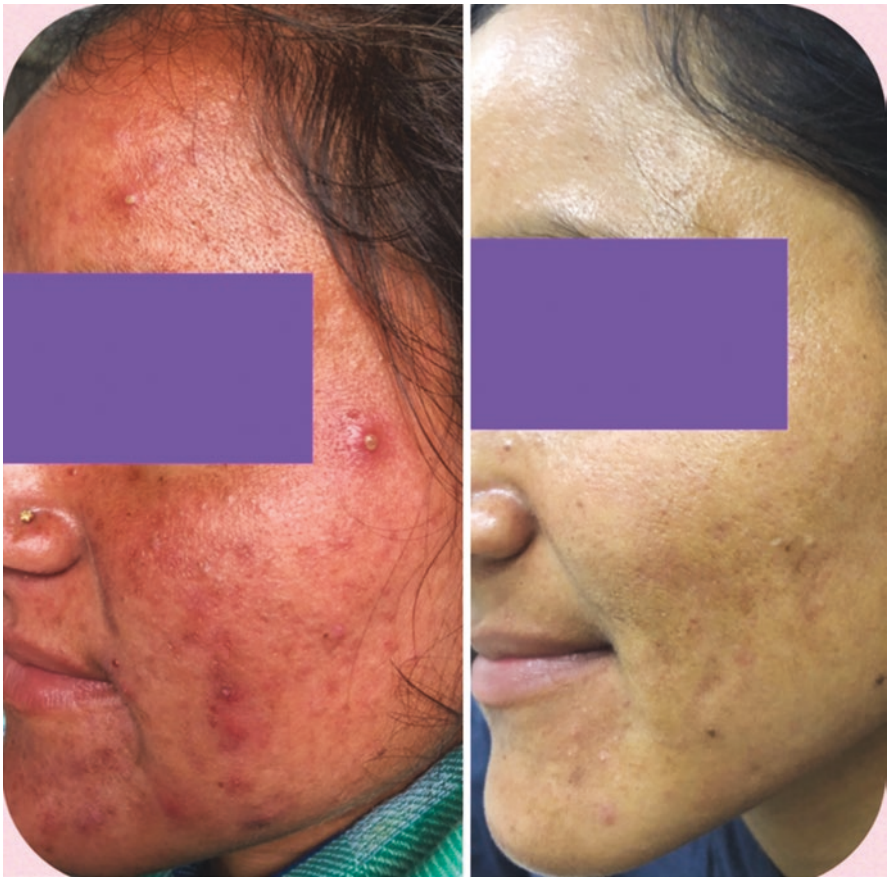


Fig. 23.4 Three sessions of Jessner's peel (two coats) done every 3 weeks in a patient with grade 3 acne

Table 23.4 Jessner's peel

Contents	Classical Jessner's[31]	Modified Jessner's [30]	Important actions	Disadvantages
Lactic acid	14%	17%	Lightening properties, as it inhibits tyrosinase enzyme	
Salicylic acid	14%	17%	Lipophilic in nature	Risk of salicylism, hence limited application advised [31]
Resorcinol	14%	–	Similar to hydroquinone	May cause contact allergy [32]
Citric acid	–	8%	Additional skin thickening effect with repeated use	
Ethanol	qs	Qs		

Table 23.5 Depth of penetration of TCA according to concentration

Concentration of TCA peel (in %)	Histological depth of penetration
10–15	Epidermis
15–30	Epidermis
35	Upper papillary dermis
50–100	Upper reticular dermis, with increasing r/o side effected, hence advised for focal use only

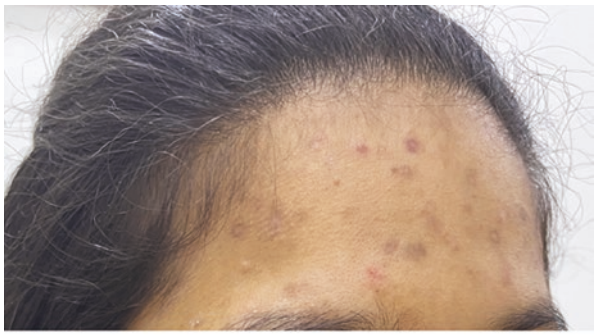
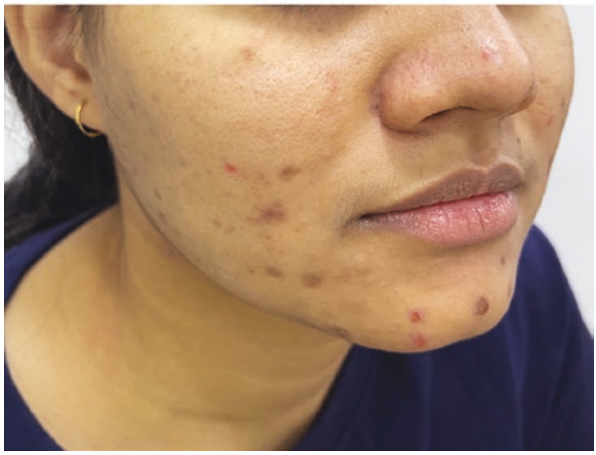


Fig. 23.5 A common side effect of crusting due to deep necrosis seen after 2 days of TCA 20% peel



TCA displays three levels of frosting:

1. a light reticular frost with background erythema,
2. a confluent light white frost with background erythema and
3. a solid white frosting without erythema [31].

At higher concentrations TCA has a narrow therapeutic index. There is a relatively high risk of complications, including dyschromia, scarring and occasionally bacterial superinfection and cutaneous herpes simplex virus (HSV) reactivation [35] (Fig. 23.5). Hence, TCA (>50%) in higher concentrations is not being favoured as a single-agent chemical peel [36].

Monheit peel: The most commonly researched and used combination peel is Jessner's solution plus TCA. G D Monheit had popularised the combination of Jessner's and TCA (thus known as Monheit peel) in 1995. According to him the combination is a safe and effective medium depth chemical peel to achieve a more uniform penetration. The combination achieved a uniform penetration when used for indications like photoaging, actinic keratoses and superficial acne scars. This procedure first requires degreasing with acetone/alcohol solvent and then using Jessner's peel and TCA 35% sequentially [37].

Coleman peel: GA 70% plus TCA 35%.

In this peel, degreasing with acetone is not necessary. Patients may simply wash their faces before procedure. First, GA 70% is applied for approximately 2 min till erythema is visible and then washed with water. It is followed by TCA 35% until the endpoint frosting is reached [38].

23.2.3.1 The Baker–Gordon Peel

Constituents: 88% phenol (USP; 3 mL), croton oil (3 guttae), hexachlorophene (Septisol)

Soap (Vestal Laboratories, St Louis, MO, USA; 8 guttae) and distilled water (2 mL) [39].

23.2.3.2 Side Effects: [40]

It is an extremely painful peel.

Associated with a risk of cardiac arrhythmias.

Risk of kidney and liver toxicity.

It must therefore be performed in the operating room under sedation and with continuous monitoring of vital signs.

Mechanism of action of Baker-Gordon peel constituents [42] is enlisted in Table 23.6.

Table 23.6 Baker-Gordon peel constituents and their effects

Peeling agent	Effect
Phenol 88% (3 ml)	Penetrates up to reticular dermis and leading to neo collagenosis
Croton oil (3 guttae)	A vesicant in nature, promotes deeper penetration and absorption of phenol
Hexachlorophene (8 guttae)	A liquid soap, it increases surface tension, acts as an emulsifier and retards phenol absorption It decreases maceration and irritation caused due to phenol and croton oil

Table 23.7 Peels and its safety in pregnancy [42]

Peeling agent	Effect	Safety
Glycolic acid	Induce epidermolysis and desquamation in concentration of 30–70%	Insufficient data Generally considered safe
Lactic acid	Induce keratolysis Used in concentration of 2% for treatment of gestational acne	No foetal risk reported
Salicylic acid	It is lipophilic and has comedolytic and keratolytic effect Can have up to 25% systemic absorption due to dermal penetration	Pregnancy category C Lack of clinical trials in pregnancy and lactation. Avoid in pregnancy If use necessary, area of coverage should be limited
TCA peel	It causes local irritation without systemic absorption Conventionally used as topical solution for genital warts in pregnancy	Relatively safe in pregnancy Avoid its use over mucosal surfaces, reports suggest f absorption through oral and ocular surfaces systemically
Jessner's peel	Contains salicylic acid (lactic acid, salicylic acid and resorcinol)	Pregnancy category C Avoid in pregnancy

23.2.4 Peels in Pregnancy: Table 23.7

Non-essential surgical procedures should be deferred at least till the second trimester of the pregnancy. Counsel the patient regarding possible risks of the procedures and absence of proper data of safety of such peels. Safest peel as a general consensus is lactic acid 2% and glycolic acid concentration of 30% to 70% due to negligible dermal penetration [41].

The left lateral decubitus position is the recommended positioning during surgery because it ensures optimum dynamics of the blood circulation.

23.3 Fundamentals of Peeling

23.3.1 Chemical Peel Consultation

23.3.1.1 History

1. Medical: History of smoking, diabetes, HIV or immunosuppression, cardiac, hepatic or renal disease, or nutritional deficiency (increased risk of toxicity, delayed wound healing and infection) [43].
2. Drug history: Patients on oral isotretinoin (avoid medium depth and deep peels if taken in last 6 months) [44].

   Topical retinoids (discontinue before 1 week)

Photosensitisers, e.g. minocycline, amiodarone, thiazides, tricyclic antidepressants.

Systemic therapies: Oral contraceptives and hormonal treatments (may cause hyperpigmentation)

3. Viral infection: History of recurrent HSV infection—consider prophylactic valacyclovir (1 g every 6 h)—2 days before treatment until 10–14 days after the treatment. Molluscum contagiosum may show pseudo-koebnerisation [45].
4. Keloidal tendency: Enquire about previous personal or family history of scarring—use superficial very light peels [17].
5. Inflammatory disorders: Concomitant inflammatory skin disease may worsen with chemical peeling. (These include eczema, psoriasis, vitiligo, rosacea and seborrhoeic dermatitis) [17].
6. Reconstructive surgery/radiotherapy: Recent reconstructive surgery or radiotherapy to the skin may interfere with collagen remodelling—hence a relative contra-indication [17].

23.3.1.2 Examination: [15, 17]

Reaction to trauma in past should be examined to seek skin reaction type.

Examine covered skin of person to know the degree of tanning and photoaging and correctly assess Fitzpatrick s skin type.

Staining of teeth—for smoking, as it can delay healing in deep peels.

Photographic documentation for pre- and post-pictures.

Look out for any hypertrophic scar or keloid to avoid using medium depth or deep peels.

23.3.1.3 Documentation

A detailed informed consent in patient's own language with counselling about achievable results, complications, downtime, need of multiple sessions, compliance and cost of therapy should be taken by the treating clinician and with meticulous record keeping.

23.3.1.4 Pre-peel Priming of Skin

Priming of skin encompasses all pre-treatment and preparation method which may be performed on the skin prior to chemical peeling [42]. These activities go a long way in ensuring patient compliance, detect intolerances and reduce the risk of complications such as post-inflammatory hyperpigmentation and scarring [46]. The basic purpose of these activities is to avoid complications, thin the stratum corneum, enhance the penetration of the active agent and expedite healing [47]. Priming is

commenced at least 2–4 weeks before the chemical peel and stopped 1–3 days prior with the exception of sunscreens [48].

Priming primarily encompasses the following:

1. Sunscreens: Broad-spectrum sunscreens should be used with a sun protection factor of ideally 50+ with equal UV A spectrum coverage each day half an hour before going into sun. [42] Photoprotection helps in preventing phototoxicity, reduces immediate and delayed pigment darkening and reduces melanocyte activity [49].
2. Tretinoin: It can be applied in 0.025–0.05% cream at night for a minimum of 2 weeks before commencing chemical peel [42]. It reduces epidermal cohesion resulting in thinning of the stratum corneum. This ensures deep, even and rapid penetration of the active ingredient [50].
3. Hydroquinone: Hydroquinone (2–4%) is an effective priming agent and also reduces the risk of post-inflammatory hyperpigmentation [17]. Hydroquinone (2%) has been shown to be a superior priming agent to tretinoin (0.25%) with respect to post-peeling reactive hyperpigmentation [51].
4. Anti-viral therapy: Before medium and deep depth peels to prevent herpes simplex virus reactivation. There is no common consensus but according to author Acyclovir 400 mg twice daily starting 2 days before till 5 days after procedure helps in preventing recurrence of herpes simplex infection.

Priming especially with tretinoin should be stopped at least 2 days -1 week before to prevent overpenetration and post-inflammatory pigmentary changes.

23.3.1.5 Test Spot Testing

The usefulness of test spot in chemical peeling is not defined and thus is infrequently performed [52]. Although if time permits, the author recommends doing test spot in any inconspicuous area of the treatment field. Any exaggerated reaction in the test spot warrants discontinuation or postponement of peel. Further treatments should also be preceded by test spot testing.

23.3.1.6 Steps of Peeling

1. Choose the correct peeling agent according to the indication, ethnic skin type and depth of peeling required. For example, salicylic acid peel for acne in skin type 4/5 is safe.
2. Clean the face first to remove any makeup or products and then with a degreasing agent like acetone to remove excess oil.
3. Keep hair tied in a bun or with the help of a band.
4. Look for any signs of recent injury/burn/tanning/redness, to avoid such cases or if localised avoid peeling, thereby occluding that spot with petroleum jelly.

5. Apply occlusive agent like petroleum jelly to lips, both canthi of eyes and sides of nose.
6. After test peel to pre-auricular area, apply peel to the face starting from forehead and moving downward until neck. Create a uniform coat and maintain a uniform pressure and amount of peel used.
7. A second or third coat may be required depending upon the desired depth of peel.
8. Neutralisation of peel is done once the end point is achieved. Neutralisers used are water, sodium bicarbonate solution, etc.
9. Do icing to soothe out any irritation post pee.
10. Apply moisturiser and sunscreen immediately post-peel.

23.3.1.7 General Considerations

Pre-Peel: Patients should avoid depilation, bleaching, scrubbing, waxing, electrolysis and manual or micro-dermabrasion for a minimum of 3–4 weeks prior to chemical peeling [53]. They should also not plan any important event atleast 1 week before procedure [17].

23.3.1.8 Post-Peel

Avoid washing the area after peel for 24 h.

Patients are advised to avoid sun exposure for 1 week post-peel.

Apply moisturiser and sunscreen after the procedure.

Avoid any bleaching/swimming for 2 weeks.

In case of oedema or mild discomfort use ice packs.

For ensuring re-epithelialisation, gentle soaking and bland emollients should be advised for 3 to 5 days.

In case of crusting or intolerable burning, apply mid-potent steroids for 2–3 days.

As already discussed, men have thicker, more oleaginous skin due to increased sebum production and pore size, along with hairy skin, making the penetration less predictable. While women have thinner skin, less sebaceous glands and less hair. Thus, the **depth of penetration in women is slightly more predictable**.

According to Reserva et al. men tolerate more aggressive degreasing, greater volume of peeling agents and more aggressive clinical pressure when applying the peeling solution, which correlates with a deeper and more effective chemical peel [54]. But there is paucity of convincing evidence suggesting special considerations in any gender.

In general, deep depth peels should be avoided in women, especially of reproductive age group.

Medium depth peels should be employed with equal precautions in both men and women.

Table 23.8 Common complications and disadvantages of common chemical agents [55]

Chemical agent	Complications
Salicylic acid peel	1. Risk of salicylism if used over large areas 2. Peeling effect is limited to upper layers 3. No benefits in photodamaged skin 4. To be avoided in patients allergic to aspirin
Glycolic acid peel	1. Endpoint is difficult to judge 2. Uneven peeling 3. Risk of dermal wounds and scarring 4. Expensive 5. Achromia
TCA peel	1. More chances of scarring at higher concentration 2. Can cause hypo- or hyperpigmentation 3. Shelf life is limited 4. Melanocyte toxicity in higher concentration and skin type 4 and above
Jessner's peel	Resorcinol: 1. Risk of methemoglobinemia, cyanosis, convulsions or even death when applied by chance to mucous membranes or ingested (more than 1 g) 2. Risk of hypothyroidism 3. Sensitisation leading to allergic contact dermatitis 4. Prolonged erythema Salicylism when applied to large body surface areas
Phenol peel	1. Delayed wound healing 2. Melanocyte toxicity—Leading to depigmentation 3. Hyperpigmentation 4. Secondary infections 5. Avoided in patients of MI, heart diseases as stress associated can trigger angina 6. Avoided in liver/kidney diseases due to risk of toxicity

Salicylic acid, Jessner's and Phenol based peels should be avoided in pregnancy. Safety of chemical peels in pregnancy has been outlined in Table 23.7.

End point of chemical peels is as enlisted in Table 23.8.

23.4 Conclusion

Chemical peels remain an effective and safe procedure among women. Even though there is paucity of data regarding special considerations among women with respect to chemical peels, superficial peels in general are safer in women of all age groups. Equal precautions should be taken in both men and women with regard to deeper peels. Salicylic acid, Jessner's peel and phenol based peels should be avoided in pregnancy. Female patients should avoid any parlour procedures atleast 3–4 weeks before undergoing chemical peels. Chemical peel is satisfying for both patients' and clinicians when done with thorough knowledge, proper technique and realistic counselling.

Contraindications to chemical peeling: [15]

1. Active infections (viral, bacterial or fungal)
2. History of recurrent herpes
3. Barrier loss due to wounds or allergies
4. History of intake of photosensitising drugs
5. Pre-existing inflammatory dermatoses
6. Uncooperative or non-compliance on part of the patient
7. Patient with unrealistic expectations.
8. Medium depth and deep peels—history of abnormal scarring and keloidal tendency
9. History of isotretinoin in the last 6 months
10. Recent reconstructive surgery or radiotherapy

Peeling agent	End point
Glycolic acid	1–5 min (erythema) 5–10 mins (gray membrane)
Salicylic acid	3–5 mins (pseudo-frosting)
Lactic acid	Mild erythema
TCA peel	Pin point, uniform frosting
Jessner's peel	1–3 coats, even frosting or erythema
Phenol	Single coat, uniform frosting

References

1. Brody HJ, Monheit GD, Resnik SS, Alt TH. A history of chemical peeling. Dermatol Surg. 2000;26(5):405–9. https://doi.org/10.1046/j.1524-4725.2000.00505.x.
2. Dewandre L, Tenenbaum A. The chemistry of peels: a hypothesis of action mechanisms and a proposal of a new classification of chemical peelings. In: Tung RC, Rubin MG, editors. Procedures in cosmetic dermatology series: chemical peels. 2nd ed. Philadelphia, PA: Saunders; 2011. p. 1–16.
3. Chen W, Mempel M, Traidl-Hofmann C, Al Khusaei S, Ring J. Gender aspects in skin diseases. J Eur Acad Dermatol Venereol. 2010;24(12):1378–85. https://doi.org/10.1111/j.1468-3083.2010.03668.x.
4. Jacobi U, Gautier J, Sterry W, Lademann J. Gender-related differences in the physiology of the stratum corneum. Dermatology. 2005;211(4):312–7. https://doi.org/10.1159/000088499.
5. Giacomoni PU, Mammone T, Teri M. Gender-linked differences in human skin. J Dermatol Sci. 2009;55(3):144–9. https://doi.org/10.1016/j.jdermsci.2009.06.001.
6. Shuster S, Black MM, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. Br J Dermatol. 1975;93(6):639–43. https://doi.org/10.1111/j.1365-2133.1975.tb05113.x.
7. Leveque JL, Corcuff P, de Rigal J, Agache P. In vivo studies of the evolution of physical properties of the human skin with age. Int J Dermatol. 1984;23:322–9.
8. Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. J Invest Dermatol. 1974;62(3):191–201. https://doi.org/10.1111/1523-1747.ep12676783.
9. Roh M, Han M, Kim D, Chung K. Sebum output as a factor contributing to the size of facial pores. Br J Dermatol. 2006;155(5):890–4. https://doi.org/10.1111/j.1365-2133.2006.07465.x.

10. Kalla AK. Ageing and sex differences in human skin pigmentation. Z Morphol Anthropol. 1973;65(1):29–33.
11. Kalla AK, Tiwari SC. Sex differences in skin colour in man. Acta Genet Med Gemellol. 1970;19(3):472–6. https://doi.org/10.1017/s1120962300014876.
12. Frost P. Human skin color: a possible relationship between its sexual dimorphism and its social perception. Perspect Biol Med. 1988;32(1):38–58. https://doi.org/10.1353/pbm.1988.0010.
13. Green A, Martin NG. Measurement and perception of skin colour in a skin cancer survey. Br J Dermatol. 1990;123(1):77–84. https://doi.org/10.1111/j.1365-2133.1990.tb01826.x.
14. Tse Y. Choosing the correct peel for the appropriate patient. In: Tung RC, Rubin MG, editors. Procedures in cosmetic dermatology series: chemical peels. 2nd ed. Philadelphia, PA: Saunders; 2011. p. 17–22.
15. Khunger N, IADVL Task Force. Standard guidelines of care for chemical peels. Indian J Dermatol Venereol Leprol. 2008;74(Suppl):S5–12.
16. Grimes PE. Salicylic acid peels. In: Rubin MG, editor. Chemical peels. Procedures in cosmetic dermatology. Elsevier Inc.; 2006. p. 47–55.
17. Salam A, Dadzie OE, Galadari H. Chemical peeling in ethnic skin: an update. Br J Dermatol. 2013;169(Suppl 3):82–90. https://doi.org/10.1111/bjd.12535.
18. Grimes PE. The safety and efficacy of salicylic acid chemical peels in darker racial-ethnic groups. Dermatol Surg. 1999;25:18–22.
19. Bari AU, Iqbal Z, Rahman SB. Tolerance and safety of superficial chemical peeling with salicylic acid in various facial dermatoses. Indian J Dermatol Venereol Leprol. 2005;71:87–90.
20. Lee HS, Kim IH. Salicylic acid peels for the treatment of acne vulgaris in Asian patients. Dermatol Surg. 2003;29:1196–9.
21. Ahn HH, Kim IH. Whitening effect of salicylic acid peels in Asian patients. Dermatol Surg. 2006;32:372–5.
22. Haynes WM. CRC handbook of chemistry and physics. 92nd ed. Boca Raton, FL: CRC Press; 2011. ISBN 1439855110
23. Rendon M, Berneburg M, Arellano I, et al. Treatment of melasma. J Am Acad Dermatol. 2006;54:S272–81.
24. Becker FF, Langford FP, Rubin MG, et al. A histological comparison of 50% and 70% glycolic acid peels using solutions with various pHs. Dermatol Surg. 1996;22:463–5.
25. Sarkar R, Arsiwala S, Dubey N, Sonthalia S, Das A, Arya L, et al. Chemical peels in melasma: a review with consensus recommendations by Indian pigmentary expert group. Indian J Dermatol. 2017;62:578–84.
26. Usuki A, Ohashi A, Sato H, et al. The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells. Exp Dermatol. 2003;12(Suppl. 2):43–50.
27. Sachdeva S. Lactic acid peeling in superficial acne scarring in Indian skin. J Cosmet Dermatol. 2010;9:246–8.
28. Sharquie KE, Al-Tikreety MM, Al-Mashhadani SA. Lactic acid chemical peels as a new therapeutic modality in melasma in comparison to Jessner's solution chemical peels. Dermatol Surg. 2006;32:1429–36.
29. Monheit GD. The Jessner's–trichloroacetic acid peel. An enhanced medium-depth chemical peel. Dermatol Clin. 1995;13:277–83.
30. Safoury OS, Zaki NM, El Nabarawy EA, Farag EA. A study comparing chemical peeling using modified Jessner's solution and 15% trichloroacetic acid versus 15% trichloroacetic acid in the treatment of melasma. Indian J Dermatol. 2009;54:41–5.
31. Lee KC, Wambier CG, Soon SL, Sterling JB, Landau M, Rullan P, Brody HJ, International Peeling Society. Basic chemical peeling: superficial and medium-depth peels. J Am Acad Dermatol. 2019;81(2):313–24. https://doi.org/10.1016/j.jaad.2018.10.079.
32. Ekmekŋy P, Bostanci S, Gurgey E. The efficacy of chemical peeling performed with Jessner's solution and 35% TCA in the treatment of melasma. Klin J Dermatol. 2001;11:211–6.
33. Otley CC, Roenigk RK. Medium-depth chemical peeling. Semin Cutan Med Surg. 1996;15:145–54.

34. Glogau RG, Matarasso SL. Chemical peels. Trichloroacetic acid and phenol. Dermatol Clin. 1995;13(2):263–76.
35. Brody HJ. Trichloroacetic acid application in chemical peeling, operative techniques. Plast Reconstr Surg. 1995;2(2):127–8.
36. Soleymani T, Lanoue J, Rahman Z. A practical approach to chemical peels: a review of fundamentals and step-by-step algorithmic protocol for treatment. J Clin Aesthet Dermatol. 2018;11(8):21–8.
37. Monheit GD. The Jessner's 1 TCA peel: a medium-depth chemical peel. J Dermatol Surg Oncol. 1989;15:945–50.
38. Coleman WP 3rd, Futrell JM. The glycolic acid trichloroacetic acid peel. J Dermatol Surg Oncol. 1994;20:76–80.
39. Matarasso SL, Glogau RG. Chemical face peels. Dermatol Clin. 1991;9:131–50.
40. Truchuelo M, Cerdá P, Fernández LF. Chemical peeling: a useful tool in the office. Actas Dermosifiliogr. 2017;108:315–22.
41. Bozzo P, Chua-Gocheco A, Einarson A. Safety of skin care products during pregnancy. Can Fam Physician. 2011;57:665–7.
42. Trivedi MK, Kroumpouzos G, Murase JE. A review of the safety of cosmetic procedures during pregnancy and lactation. Int J Women's Dermatol. 2017;3(1):6–10. https://doi.org/10.1016/j.ijwd.2017.01.005.
43. O'Connor AA, Lowe PM, Shumack S, Lim AC. Chemical peels: a review of current practice. Australas J Dermatol. 2018;59(3):171–81. https://doi.org/10.1111/ajd.12715.
44. Waldman A, Bolotin D, Arndt KA, Dover JS, Geronemus RG, Chapas A, Iyengar S, Kilmer SL, Krakowski AC, Lawrence N, Prather HB, Rohrer TE, Schlosser BJ, Kim JYS, Shumaker PR, Spring LK, Alam M. ASDS guidelines task force: consensus recommendations regarding the safety of lasers, dermabrasion, chemical peels, energy devices, and skin surgery during and after isotretinoin use. Dermatol Surg. 2017;43(10):1249–62. https://doi.org/10.1097/DSS.0000000000001166.
45. Resnik SS, Resnik BI. Complications of chemical peeling. Dermatol Clin. 1995;13:309–12.
46. Khunger N. Step by step chemical peels. New Delhi: Jaypee; 2014.
47. Zakopoulou N, Kontochristopoulos G. Superficial chemical peels. J Cosmet Dermatol. 2006;5:246–53.
48. Rendon MI, Berson DS, Cohen JL, et al. Evidence and considerations in the application of chemical peels in skin disorders and aesthetic resurfacing. J Clin Aesthet Dermatol. 2010;3:32–43.
49. Mangat DS, Tansavatdi K, Garlich P. Current chemical peels and other resurfacing techniques. Facial Plast Surg. 2011;27:35–49.
50. Demas PN, Bridenstine JB, Braun TW. Pharmacology of agents used in the management of patients having skin resurfacing. J Oral Maxillofac Surg. 1997;55:1255–8.
51. Nanda S, Grover C, Reddy BS. Efficacy of hydroquinone (2%) versus tretinoin (0.025%) as adjunct topical agents for chemical peeling in patients of melasma. Dermatol Surg. 2004;30(3):385–8; . Discussion 389. https://doi.org/10.1111/j.1524-4725.2004.30106.x.
52. Cortez EA, Fedok FG, Mangat DS. Chemical peels: panel discussion. Facial Plast Surg Clin North Am. 2014;22:1–23.
53. Anitha B. Prevention of complications in chemical peeling. J Cutan Aesthet Surg. 2010;3:186–8.
54. Reserva J, Champlain A, Soon SL, Tung R. Chemical peels: indications and special considerations for the male patient. Dermatol Surg. 2017;43(Suppl 2):S163–73. https://doi.org/10.1097/DSS.0000000000001281.
55. Deprez P. Textbook of chemical peels. In: Deprez P, editor. Superficial, medium, and deep peels in cosmetic practice. 2nd ed. CRC Press, Taylor & Francis Group, LLC.; 2017. p. 325–72. ISBN 9781482223934.

Chapter 24
Lasers: Special Considerations in Women

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LASER is an acronym for "light amplification by stimulated emission of radiation." Stimulated emission occurs when an excited atom is unsettled by a photon with a frequency corresponding to the energy gap between the excited and ground states. The excited atom goes back to the resting state after the impact, releasing energy as a second photon. Because the incident photon is not absorbed, two coherent photons of same wavelength are emitted. When the above process happens in an optical cavity with an active medium and two opposing mirrors, it allows amplification of light and the production of a laser beam [1].

Over the last four decades, various laser sources have been used in skin diseases, and their role has been steadily increasing in dermatology. Presently, laser technology is helpful in the management of various inflammatory, neoplastic, and pigmentary skin diseases and also for better esthetics.

In this chapter, we shall discuss the use of laser in skin diseases in females. Female skin has some physiological differences when compared to male skin. So a better understanding of the physiological, chemical, and biophysical characteristics of female skin will aid a dermatologist in planning the appropriate laser and the dose of radiation required for treatment. The mechanisms responsible for sex-related differences in dermatoses are mostly undetermined. Hormonal and behavioral factors, race, and environmental differences may contribute to these differences [2, 3].

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A review of available literature has revealed no significant difference between male and female skin in terms of the hydration, adhesion of stratum corneum, and trans-epidermal water loss [2]. However, overall thickness of skin is significantly more in men as compared to women, as noted in various studies, with skin thickness showing linear decrease in males and a constant skin thickness in females till the age of 50 [4]. In recent studies from various parts of the world, women have been found to exhibit less sebum secretion as compared to men [5–7]. Skin pH is lower in females as compared to males as found in various studies [8, 9]. Firooz et al. reported significantly lower skin melanin index and erythema index in female subjects as compared to male subjects [10]. Spectrophotometric studies from diverse populations in Europe, Asia, Africa, and North and South America have shown higher skin reflectance in female skin than that of males, meaning a paler skin in females [2]. Skin elasticity is more in women as compared to men and it is maintained in females till old age [11]. Subcutaneous fat remains identical in thickness in both sexes till puberty but thereafter, it increases significantly more in women due to elevated activity of lipoprotein lipase [3].

We will review the use of lasers in various dermatological conditions occurring predominantly in women which are as follows: Rosacea, melasma, hirsutism, connective tissue diseases, lichen sclerosus, notalgia paresthetica, syringomas, and acne scars.

24.1 Rosacea

Rosacea is a chronic inflammatory disease which mainly affects the centrofacial region and eyes, predominantly in women and individuals with lighter skin types. Rosacea has four types: erythematotelangiectatic (ETTR), papulopustular, phymatous, and ocular [12]. Erythema and persistent telangiectasia are the main complaints in the ETTR type. Lasers particularly have a role in ETTR and various studies (Table 24.1) have shown the role of pulsed dye laser (PDL) and

Table 24.1 Recent studies on use of different lasers in rosacea

Researcher	Lasers used	No. of patients	Results
Campos et al. [15]	Comparison of efficacy of 595 nm PDL v/s multiplexed 595 nm PDL and 1064 nm Nd:YAG laser	27	Equal efficacy of both. Multiplexed PDL/Nd:YAG had better safety profile
Baskan and Belli [16]	PDL	14	Significant improvement in erythema and telangiectasia with long term efficacy
Ustuner et al. [17]	Q-switched potassium titanyl phosphate (KTP) laser and LPNY	37	LPNY laser better for erythema and Q-switched KTP laser better for thin and superficial telangiectasias

Table 24.1 (continued)

Researcher	Lasers used	No. of patients	Results
Bernstein et al. [18]	PDL with 15 mm diameter treatment beam	20	Improves the appearance and favorable safety profile
Kwon and Park et al. [19]	Comparison between PDL and LPNY	20	Both lasers have equal efficacy with PDL being safer
Goo et al. [20]	Q-switched, 595-nm Nd:YAG laser	2	Significant improvement in ETTR lesions
Bernstein and Kligman [21]	High energy, long pulse-duration, 595 nm, PDL	20	Significant decrease in average rosacea score
Lonne-Rahm et al. [22]	Flashlamp PDL, 585 nm	32	Effective in sensitive skin in rosacea

long-pulsed Nd:YAG (LPNY) lasers. Pulsed dye laser (585 nm; 595 nm) is currently the laser of choice for ETTR [13]. However, a significant side effect of PDL is immediate post-procedure purpura and to reduce its occurrence, pulse stacking with a lower fluence can be done while maintaining the high efficacy [14]. CO_2 laser resurfacing has also shown a positive effect in phymatous rosacea, however that subtype is more common in males and so is not discussed in detail here.

24.2 Melasma

Melasma is an acquired hyperpigmentation disorder affecting the photoexposed areas especially the face. It most commonly affects adult females and can worsen during pregnancy. In vitro, estradiol has induced melanogenesis and increased the expression of human melanocortin-1 receptor, which could be contributing to the increased prevalence of pigmentary dermatoses in females. Melasma is usually refractory to treatment and various modalities are tried for its treatment. Most important component of treatment is photoprotection by using sunscreens [23].

Lasers are generally used as second or third line of treatment in refractory melasma. The lasers mentioned below have been used in melasma with variable success: intense pulsed laser (IPL), fractional lasers—both non-ablative and ablative (1540 nm/1550 nm Er: Glass, 2940 nm Er: YAG, 10,600 nm CO_2), fractional lasers with transdermal drug delivery, Q-Switched (QS) Lasers-QS 1064 nm, QS 585/595 nm laser, fractional QSNY laser and fractional QS Ruby 694 nm lasers, and Picosecond lasers [24].

Out of the above list, non-ablative fractional 1550/1540 nm laser (2005) and Lutronic's 1064 nm, Q-switched Nd:YAG laser (2012) have got US FDA approval for the treatment of melasma [25].

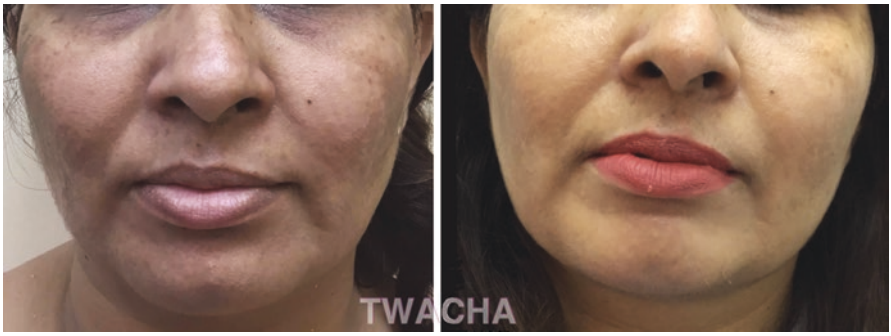

Fig. 24.1 Pre- and post-treatment images of a patient with melasma treated with Q switched ND:YAG laser (1064 nm) (image courtesy Dr. Richa Sharma)

The Q-switched (QS) Nd:YAG laser has got the best evidence for use in the treatment of melasma, especially in skin of color (Fig. 24.1). However, till now, no randomized controlled trials (RCTs) have been conducted to compare the effectiveness of the QS Nd:YAG laser (532 nm) to the standard topical treatments [26]. The traditional QSL treatment was based on the principle of selective photothermolysis in which a high fluence was used to destroy the pigment-containing cell. Subsequent release of prostaglandins and cytokines as a result of cell death results in inflammatory state and damage to basement membrane, resulting in relapse, exacerbation of melasma, or pigmentary changes [27].

Nowadays, low fluence or subthermolytic Q-switched treatment (variant of Q-switched laser) is becoming increasingly popular. Here, the fluence is lower and spot size is larger as compared to traditional QS Nd:YAG laser. It destroys the melanosomes and melanin granules within melanocytes and keratinocytes without causing any damage to the cell membrane and nucleus, thus avoiding cell death. It also causes functional downregulation of melanocytes resulting in reduced number of melanosomes [28].

A study from Korea has shown a 50–74% improvement in melasma in Asian patients with the use of low-fluence 1064 nm QS Nd:YAG laser therapy [29]. QS Nd:YAG laser usually shows best results when used in combination with other therapy like oral tranexamic acid or peels [30]. Kauvar [31] has demonstrated good results by using a combination of microdermabrasion and low-fluence QS Nd:YAG laser along with the use of topical depigmenting agents.

Fractional resurfacing lasers create selective columns of microthermal damage in which treated and untreated areas are intermixed. However, short term side effects such as erythema, swelling, and pain are usual with non-ablative fractional lasers at 1440, 1540, and 1550 nm [32]. Tourlaki et al. [33] assessed the efficacy of non-ablative laser along with triple therapy topical cream in treatment of recalcitrant melasma. Melasma Activity Severity Index (MASI) scores were used to assess the response. After 1 month, 67.1% of patients had >75% clearing and 21% had 51–75%

clearing of pigmentation. However, at 6 months, only 21.1% of patients persisted with marked improvement despite continuously using the triple combination cream.

24.3 Hirsutism

Hirsutism is the condition of excessive growth of terminal hairs in a female in the male pattern distribution—beard, moustache, and chest. In women, hirsutism is often seen in endocrine disorders characterized by features of hyperandrogenism; however, "idiopathic" hirsutism (normal values of androgens for age and ethnicity) is also very frequent. The Ferriman and Gallwey scale is used for assessing and quantifying the severity of hirsutism. The treatment of hirsutism is focused on removing the unwanted hairs as well as reducing the androgen drive for vellus-terminal conversion [34].

Excess and/or unwanted hairs are of important medical, social, and cultural concern for females in all races. Removal of hairs can be done by shaving, waxing, depilation, electrolysis, and laser. Laser hair removal is a multifactorial process which causes hair follicle damage while sparing the epidermis due to a complex photothermal reaction via the epidermis–dermis matrix [35]. Thus, laser hair removal is dependent on various laser and tissue parameters such as power, spot size, irradiation time, repetition rate, absorption, scattering coefficients, density, and thermal conductivity [36]. Hair reduction lasers are avoided during pregnancy due to possible risk to the fetus and the medico-legal issues involved; more so, the hyperprolactinemia during pregnancy upregulates melanocyte-stimulating hormone in hair stem cells and may render the laser treatment ineffectual.

The laser hair removal is based on the principle of selective photothermolysis as introduced by Anderson and Parrish. The required energy density (i.e. fluence) for coagulating a hair follicle is directly proportional to the hair shaft diameter [37]. The duration of laser pulse should lie between the thermal relaxation time (TRT) for epidermis (3–10 ms) and the TRT for the hair follicles (40–100 ms) to minimize thermal damage to the hair follicle. The pulse width has a key role in determining selective photothermolysis because if the pulse width is too long, there will be very less time for the heat to dissipate, and the unwanted temperature rise will cause thermal injury to surrounding non-follicular structures, resulting in scarring or dyspigmentation [38]. The spot size should be as large as possible because light penetration gets very efficient with large spot size, due to an almost planar geometry of the "source" of photons [39].

Fitzpatrick skin type I–IV and dark hairs show best results with hair removal lasers because of reduced risk of light absorption by epidermal melanin. Laser hair removal is challenging in patients with Fitz skin type V–VI because the high density of competing chromophore (melanin) in the epidermis can lead to residual pigmentation and scarring. If a wavelength which is slightly absorbed by melanin is used, then clinical efficacy is compromised as the target chromophore for hair removal

Table 24.2 Recent studies on the use of different lasers in hirsutism

Researcher	Lasers used	No. of patients	Results
Shrimal et al. [40]	LPNY and IPL-755 nm for idiopathic facial hirsutism	33	LPNY (1064 nm) is more safe and effective than IPL (755 nm)
Puri [41] Randomized controlled trial (RCT)	Diode laser, Nd:YAG laser and IPL	30	Maximum hair reduction after eight sessions with diode laser (92%), 90% reduction with Nd:YAG and 70% reduction with IPL
Dhalimi and Kadhum [42]	Long-pulsed (ALX) Alexandrite laser and IPL for hair removal	30	Better reduction of facial hairs, longer hair-free intervals, and more patient satisfaction with IPL than ALX
Giambrone et al. [43]	Novel 650 μs pulsed Nd:YAG laser	298	Effective for laser hair removal
Barolet [44] RCT	Low level fluence 810 nm (15 J/cm^2) diode laser	17	Well-tolerated, safe and effective
Rao and Sankar [45]	LPNY laser hair removal in Fitzpatrick skin types IV–VI	150	Safe and effective in dark skinned individuals

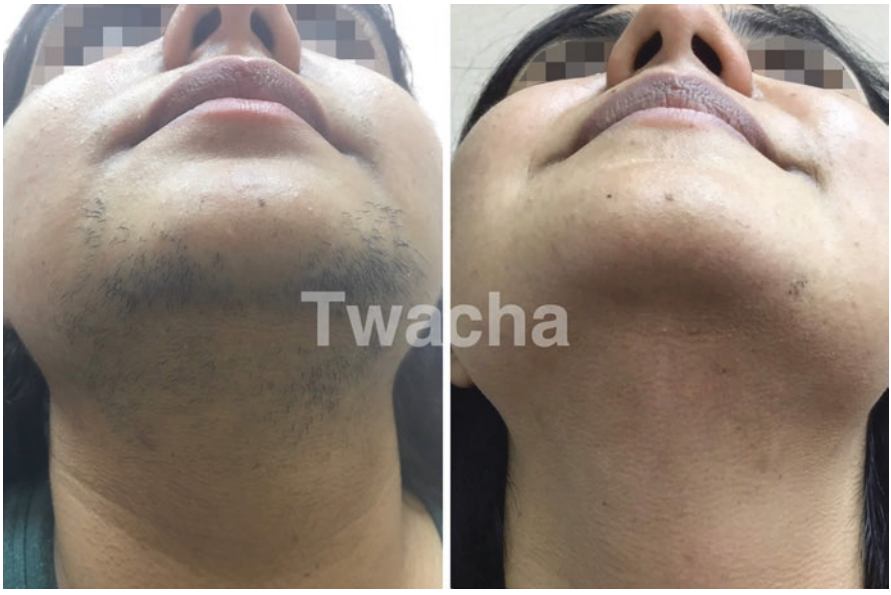

Fig. 24.2 Pre- and post-treatment images of a patient with hirsutism treated with Diode laser (image courtesy Dr. Richa Sharma)

laser is melanin in the hair bulb and bulge [35]. Latest studies on the use of hair removal lasers are tabulated in Table 24.2 and a clinical image is shown in Fig. 24.2.

24.4 Lichen Sclerosus

Lichen sclerosus is a chronic inflammatory dermatosis that predominantly affects the anogenital skin and is 6–10 times more frequent in females than males [3]. The disease typically has an inflammatory phase followed by chronic scarring and skin atrophy. The presenting symptom usually is severe and distressing pruritus. Its management consists of topical steroids, immunomodulators, and supportive therapy like stool softeners and topical anesthetics for analgesia [46]. The laser can help in lichen sclerosus by inducing a controlled thermal injury to the superficial skin, which removes the epithelium and papillary dermis and stimulates tissue repair and remodeling [47].

Table 24.3 Recent studies on use of different lasers in lichen Sclerosus

Researcher	Lasers used	No. of patients	Results
Pagano et al. [49]	Fractional microablative CO_2 laser	40	Significant improvement in vulvar itching, dryness, and dyspareunia after two cycles
Hobson et al. [50]	Fractional ablative Er: YAG laser	2	Successful treatment in LS refractory to topical steroids
Gómez and Laynez [51]	Non-ablative, thermal only Er:YAG laser	28	Significant improvement in pruritus, pain, ecchymosis, and hypopigmentation
Ogrinc et al. [52]	Non-ablative Er: YAG laser	40	Better efficacy than topical steroids
Lee et al. [53]	Fractional CO_2 laser resurfacing	4	Successful in achieving remission

A study by Gardner and Ashckenazi showed fractional CO_2 laser to be safe and effective in vaginal lichen sclerosus with improvement in female sexual function index and vaginal dryness [48]. The level of evidence for using CO_2 laser in vaginal lichen sclerosus is 4 and grade of recommendation is C [47]. Recent studies are summarized in Table 24.3.

24.5 Connective Tissue Diseases

Connective tissue diseases can have various dermatologic manifestations which are usually resistant to conventional line of treatments. Lasers offer an advanced treatment modality for these dermatological manifestations like erythema, telangiectasia, and fibrosis.

Pulsed dye laser (585–595 nm) has best evidence for the management of telangiectasias in lupus erythematosus (LE) [54]. Majority of the studies with PDL for the treatment of cutaneous lupus have reported successful results with no recurrence over 10 months follow-up. Ablative lasers like CO_2 laser and Er:YAG laser have been found to be useful in managing the scarring of cutaneous lupus. Non-ablative Nd:YAG laser has demonstrated significant cosmetic improvement as it can target the dermal melanosomes without causing much adverse effects [55]. Response to

Table 24.4 Recent studies on use of different lasers in lupus erythematosus

Researcher	Lasers used	No. of patients	Results
Rerknimitr et al. [56] RCT	PDL, 595 nm	9	Significant improvement in erythema index, texture index, and mCLASI
Bras et al. [57]	PDL, 595 nm	3	Significant improvement of erythema, edema, scaling, and telangiectasia
Ekback and Troilius [58]	PDL, 585 nm, 595 nm	12	Improvement in lesions. Recurrence of lesions—2 cases
Diez et al. [59]	PDL, 595 nm	9	Improvement of erythema and scaling, in all except 1 patient No improvement in pigmentation, scarring and atrophy
Erceg et al. [60]	PDL, 585 nm	12	Decrease in active CLASI No effect on damage CLASI

Table 24.5 Levels of evidence for use of laser in cutaneous lupus erythematosus [61]

PDL	1B—III
IPL (intense pulsed light)	III
Nd:YAG	III
Er:YAG	III
CO_2	III
1450 nm-diode laser	III

the lasers can be assessed by the use of Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). Table 24.4 lists recent studies on lasers in LE and Table 24.5 lists the levels of evidence.

Dermatomyositis is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and specific dermatological findings like confluent violaceous macular erythema, periungual telangiectasias, heliotrope rash, and Gottron's papules. Most of these skin manifestations are resistant to conventional medical therapies [62]. PDL laser has been found to be highly effective for the treatment of telangiectasia and Gottron's papules [63]. For the treatment of telangiectasias in patients with juvenile DM, argon laser has also been found to be effective without any adverse effects [64].

Calcinosis cutis is infrequent and difficult to treat complication of DM. Abrouk et al. [65] in a recent case report showed that the use of picosecond laser immediately followed by fractional ablative CO_2 laser led to the melting of the calcium into a liquid, which was easily removed from the skin leading to significant clinical improvement.

IPL and pulsed CO_2 laser have been reported to improve microstomia associated with systemic sclerosis [66]. Benani et al. [67] have reported in their study on four patients that pulsed CO_2 laser treatment has led to softening of the perioral skin. After 12 months, a gain of 8.5 mm was seen in inter-incisal distance. The side effects observed in their study were transient erythema and dyschromia.

24.6 Syringomas

Syringomas are benign skin appendageal tumors that present as small dome-shaped papules with characteristic angulated borders and often present in a periorbital distribution [68]. However, they have high recurrence rates with any treatment including lasers. A prospective study by Lee et al. [69] showed that use of a pinhole method with an ablative 10,600 nm CO_2 laser on the periorbital skin showed marked to moderate improvement in 86.2% patients. In a study by Wang and Roenigk, treatment of patients with periorbital syringomas with CO_2 laser at high energy resulted in the successful removal of syringomas in all patients and patients remained lesion free for 1–24 months [70]. Further, the use of low energy radiofrequency ablation and CO_2 laser in combination has been found to have maximal tumor destruction and minimal adverse effects, thus producing good cosmetic results [71].

24.7 Acne and Post-acne Scars

Acne vulgaris is an inflammatory disease of the pilosebaceous unit characterized by the presence of non-inflammatory as well as inflammatory lesions [72]. Scarring usually occurs as sequelae of intradermal inflammatory lesions, but may also occur

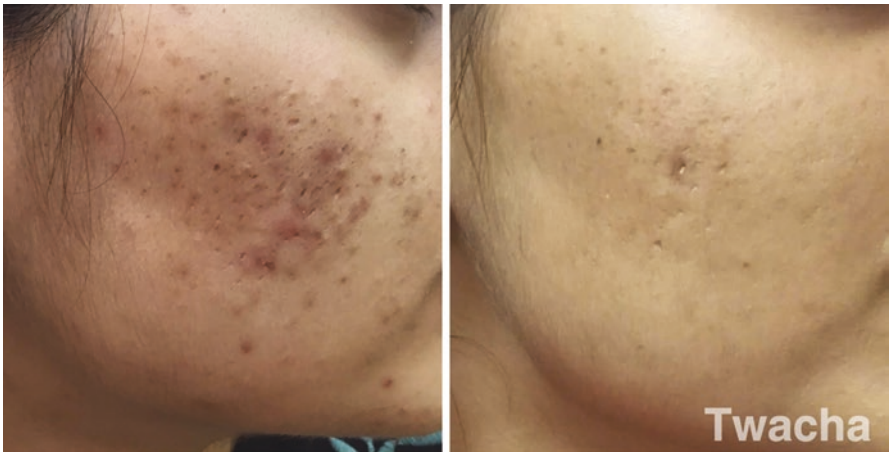

Fig. 24.3 Pre- and post-treatment images of a patient with post-acne scarring treated with CO_2 fractional laser (image courtesy Dr. Richa Sharma)

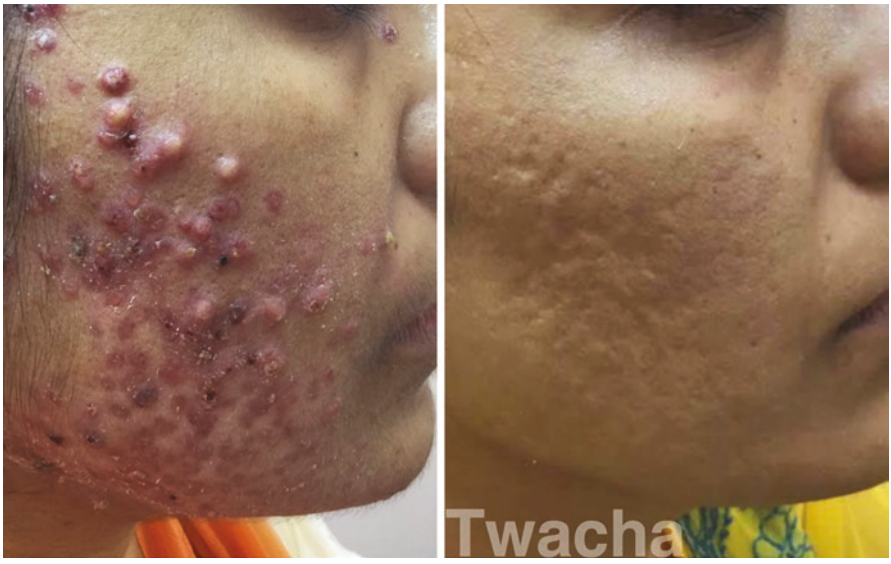

Fig. 24.4 Pre- and post-treatment images of a patient with active acne treated with Intense Pulsed Light (IPL) (image courtesy Dr. Richa Sharma)

after more superficial inflamed lesions. Acne scarring can be atrophic or hypertrophic and is formed as a result of insufficient matrix remodeling with decreased deposition of collagen factors and excessive healing response, respectively [73]. Lasers are mainly used in the management of atrophic acne scars and sometimes in active acne as well (Figs. 24.3 and 24.4).

Table 24.6 Recent studies on use of different lasers in post-acne scars

Researcher	Lasers used	No. of patients	Results
Faghihi et al. [77]	CO_2 laser 30 mJ/500 μm	16	Fair or good response in 2/3 of patients
Zhou et al. [78]	CO_2 laser (Han's Laser)	13	MQGS was 2.08/4 for patients MQGS was 2.00/4 for physicians
Reinholz et al. [76] RCT	Fractional Er:YAG and fractional CO_2 laser (5–25 J/S/500 μm)	14	Fractional CO_2 laser more efficacious than Er:YAG laser
Yuan et al. [79] RCT	Lumenis UltraPulse Encore fractional CO_2 laser 20 mJ/10% v/s 20 mJ/20%	10	Improvement in both the groups
Bjørn et al. [80]	Lumenis UltraPulse Encore fractional CO_2 laser	13	No advantage of different treating interval on results or on the postoperative adverse effects
Kim et al. [81]	Lutronic Mosaic CO_2 laser 30–50 mJ/100–200 MTZ/cm	20	Moderate-to-much improved scores in scars

Petrov and Pljakovska [74] in their study on 40 patients showed that fractional CO_2 laser is effective and safe in the treatment of acne scars with best results in dotted and ice pick scars. Approximately six sessions were required and the time interval between two sessions was 1 month. Fractional Er:YAG laser treatment has also shown good efficacy and safety in treatment of acne scars when compared with microneedling [75]. A comparison of fractional Er:YAG and CO_2 lasers in acne scars has shown that fractional CO_2 laser results in better skin smoothening [76].

Table 24.6 summarizes recent work on use of lasers in post-acne scars.

24.8 Notalgia Paresthetica

Notalgia paresthetica (NP) is a chronic, neuropathic often undiagnosed disorder presenting with itching, burning, or pain mostly at the interscapular region (T2–T6 dermatomes). It is more prevalent in female and females usually have severe symptoms and longer course of the disease [82]. The disease has a chronic and relapsing course with poor response to various available treatment options [83]. A prospective study on the use of 308 nm excimer lamp in 11 patients of notalgia paresthetica showed a significantly decreased pruritus among the patients providing benefit in a lingering condition with frequent relapses [84].

24.9 Lasers During Pregnancy and Lactation

Elective laser treatments are generally not advised during pregnancy and can be deferred to be performed postpartum. The indications for laser therapy in pregnancy are cervical carcinoma, urolithiasis, condyloma acuminata, Buschke–Löwenstein tumor, verrucous carcinoma, and acne vulgaris. Wilkerson et al. have not found any definitive proof for spontaneous abortion, fetal malformations, or preterm labor occurring secondary to laser therapy during pregnancy after reviewing the use of PDL, Nd:YAG, 2100-nm holmium:YAG, and 10,600-nm CO_2 lasers [85].

A case of premature rupture of the membranes (PROM) after CO_2 laser therapy for condyloma acuminata at 35 weeks of pregnancy has been reported by Schwartz [86]. Further, there is increased risk of delayed healing, hyperpigmentation, and scarring during pregnancy and proper counselling should be done prior to laser session in a pregnant patient [87]. Based on the review of existing literature, it can be assumed that there is no contraindication of laser therapy during any of the trimesters of pregnancy and fresh guidelines should be formulated regarding use of laser in pregnancy.

Lasers can be used safely during lactation as they do not affect the lactiferous ducts and CO_2 laser has been used for the treatment of acute lactation mastitis without any adverse effects [88]. Hence, lasers can be considered safe during lactation as there is no risk of systemic absorption of any agents in laser therapy.

References

1. Madan V, Barlow RJ. Principles of cutaneous laser therapy. In: Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology. 9th ed. West Sussex: Wiley Blackwell; 2016. p. 23.1.
2. Rahrovan S, Fanian F, Mehryan P, Humbert P, Firooz A. Male versus female skin: what dermatologists and cosmeticians should know. Int J Women's Dermatol. 2018;4(3):122–30.
3. Chen W, Mempel M, Traidl-Hofmann C, Al Khusaei S, Ring J. Gender aspects in skin diseases. J Eur Acad Dermatol Venereol. 2010;24:1378–85.
4. Shuster S, Black MM, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. Br J Dermatol. 1975;93:639–43.
5. Roh M, Han M, Kim D, Chung K. Sebum output as a factor contributing to the size of facial pores. Br J Dermatol. 2006;155:890–4.
6. Mizukoshi K, Akamatsu H. The investigation of the skin characteristics of males focusing on gender differences, skin perception, and skin care habits. Skin Res Technol. 2013;19:91–9.
7. Li X, Galzote C, Yan X, Li L, Wang X. Characterization of Chinese body skin through in vivo instrument assessments, visual evaluations, and questionnaire: influences of body area, intergeneration, season, sex, and skin care habits. Skin Res Technol. 2014;20:14–22.
8. Fox C, Nelson D, Wareham J. The timing of skin acidification in very low birth weight infants. J Perinatol. 1998;18:272–5.
9. Ehlers C, Ivens UI, Moller ML, Senderovitz T, Serup J. Females have lower skin surface pH than men. A study on the surface of gender, forearm site variation, right/left difference and time of the day on the skin surface pH. Skin Res Technol. 2001;7:90–4.

10. Firooz A, Sadr B, Babakoohi S, Sarraf-Yazdy M, Fanian F, Kazerouni-Timsar A, et al. Variation of biophysical parameters of the skin with age, gender, and body region. Sci World J. 2012;2012:386936.
11. Luebberding S, Krueger N, Kerscher M. Mechanical properties of human skin in vivo: a comparative evaluation in 300 men and women. Skin Res Technol. 2014;20:127–35.
12. Powell FC. Rosacea. In: Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology. 9th ed. West Sussex: Wiley Blackwell; 2016. p. 91.1.
13. Iyer S, Fitzpatrick RE. Long-pulsed dye laser treatment for facial telangiectasias and erythema: evaluation of a single purpuric pass versus multiple subpurpuric passes. Dermatol Surg. 2005 Aug;31(8):898–903.
14. Rohrer TE, Chatrath V, Iyengar V. Does pulse stacking improve the results of treatment with variable-pulse pulsed-dye lasers? Dermatol Surg. 2004;30:163–7.
15. Campos MA, Sousa AC, Varela P, Baptista A, Menezes N. Comparative effectiveness of purpuragenic 595 nm pulsed dye laser versus sequential emission of 595 nm pulsed dye laser and 1,064 nm Nd:YAG laser: a double-blind randomized controlled study. Acta Dermatovenerol Alp Pannonica Adriat. 2019;28(1):1–5.
16. Bulbul Baskan E, Akin Belli A. Evaluation of long-term efficacy, safety, and effect on life quality of pulsed dye laser in rosacea patients. J Cosmet Laser Ther. 2019;21(4):185–9.
17. Üstüner P, Balevi A, Özdemir M. The comparison of the efficacy and safety of Q-switched potassium titanyl phosphate laser and long-pulsed neodymium-doped yttrium aluminum garnet laser in the treatment of erythematotelangiectatic and papulopustular rosacea. Turk J Dermatol. 2018;12:90–5.
18. Bernstein EF, Schomacker K, Paranjape A, Jones CJ. Pulsed dye laser treatment of rosacea using a novel 15 mm diameter treatment beam. Lasers Surg Med. 2018;50(8):808–12.
19. Kwon WJ, Park BW, Cho EB, Park EJ, Kim KH, Kim KJ. Comparison of efficacy between long-pulsed Nd:YAG laser and pulsed dye laser to treat rosacea-associated nasal telangiectasia. J Cosmet Laser Ther. 2018;20(5):260–4.
20. Goo BL, Kang JS, Cho SB. Treatment of early-stage erythematotelangiectatic rosacea with a Q-switched 595-nm Nd:YAG laser. J Cosmet Laser Ther. 2015 Jun;17(3):139–42.
21. Bernstein EF, Kligman A. Rosacea treatment using the new-generation, high-energy, 595 nm, long pulse-duration pulsed-dye laser. Lasers Surg Med. 2008;40(4):233–9.
22. Lonne-Rahm S, Nordlind K, Edström DW, Ros AM, Berg M. Laser treatment of rosacea: a pathoetiological study. Arch Dermatol. 2004;140(11):1345–9.
23. Geel N, Speeckaert R. Acquired pigmentary disorders. In: Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology. 9th ed. West Sussex: Wiley Blackwell; 2016. p. 88.10–1.
24. Sarkar R, Aurangabadkar S, Salim T, Das A, Shah S, Majid I, et al. Lasers in melasma: a review with consensus recommendations by Indian pigmentary expert group. Indian J Dermatol. 2017;62(6):585–90.
25. https://www.accessdata.fda.gov/cdrh_docs/pdf11/K113588.pdf
26. Spierings NMK. Melasma: a critical analysis of clinical trials investigating treatment modalities published in the past 10 years. J Cosmet Dermatol. 2020;19(6):1284–9.
27. Torres-Álvarez B, Mesa-Garza IG, Castanedo-Cázares JP, Fuentes-Ahumada C, Oros-Ovalle C, Navarrete-Solis J, et al. Histochemical and immunohistochemical study in melasma: evidence of damage in the basal membrane. Am J Dermatopathol. 2011;33:291–5.
28. Kim JE, Chang SE, Yeo UC, Haw S, Kim IH. Histopathological study of the treatment of melasma lesions using a low-fluence Q-switched 1064-nm neodymium: yttrium-aluminium-garnet laser. Clin Exp Dermatol. 2013;38:167–71.
29. Sim JH, Park YL, Lee JS, Lee SY, Choi WB, Kim HJ, et al. Treatment of melasma by low-fluence 1064 nm Q-switched Nd:YAG laser. J Dermatolog Treat. 2014;25(3):212–7.
30. Shin JU, Park J, Oh SH, Lee JH. Oral tranexamic acid enhances the efficacy of low-fluence 1064-nm quality-switched neodymium-doped yttrium aluminum garnet laser treatment for melasma in Koreans: a randomized, prospective trial. Dermatol Surg. 2013;39(3 Pt 1):435–42.

31. Kauvar AN. Successful treatment of melasma using a combination of microdermabrasion and Q-switched Nd:YAG lasers. Lasers Surg Med. 2012;44(2):117–24.
32. Trivedi MK, Yang FC, Cho BK. A review of laser and light therapy in melasma. Int J Women's Dermatol. 2017;3(1):11–20.
33. Tourlaki A, Galimberti MG, Pellacani G, Bencini PL. Combination of fractional erbium-glass laser and topical therapy in melasma resistant to triple-combination cream. J Dermatolog Treat. 2014;25:218–22.
34. Messenger AG, Sinclair RD, Farrant P, Berker DA. Acquired disorders of hair. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology. 9th ed. West Sussex: Wiley-Blackwell; 2016. p. 89.64–8.
35. Bhat YJ, Bashir S, Nabi N, Hassan I. Laser treatment in hirsutism: an update. Dermatol Pract Concept. 2020;10(2):e2020048.
36. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science. 1983;220:524–7.
37. Nestor MS. Laser hair removal: clinical results and practical applications of selective photothermolysis. Skin Aging. 1998;10:34–9.
38. Lask G, Elman M, Slatkine M. Laser-assisted hair removal by selective photothermolysis. Preliminary results. Dermatol Surg. 1997;23:737–9.
39. Lask G, Eckhouse S, Slatkin M, et al. The role of laser and intense light source in photoepilation: a comparative evaluation. J Cutan Laser Ther. 1999;1:3–13.
40. Shrimal A, Sardar S, Roychoudhury S, Sarkar S. Long-pulsed Nd: YAG laser and intense pulse light-755 nm for idiopathic facial hirsutism: a comparative study. J Cutan Aesthet Surg. 2017;10(1):40–4.
41. Puri N. Comparative study of diode laser versus neodymium-yttrium aluminum: garnet laser versus intense pulsed light for the treatment of hirsutism. J Cutan Aesthet Surg. 2015;8(2):97–101.
42. Al-Dhalimi MA, Kadhum MJ. A split-face comparison of facial hair removal with the long-pulsed alexandrite laser and intense pulsed light system. J Cosmet Laser Ther. 2015;17(5):267–72.
43. Giambrone D, Ahn CS, Rao B. Laser hair removal using a650 microsecond pulsed ND:YAG laser: a study of 298 patients. Glob Dermatol. 2014;1(1):9–12.
44. Barolet D. Low fluence-high repetition rate diode laser hair removal 12-month evaluation: reducing pain and risks while keeping clinical efficacy. Lasers Surg Med. 2012;44(4):277–81.
45. Rao K, Sankar TK. Long-pulsed Nd:YAG laser-assisted hair removal in Fitzpatrick skin types IV-VI. Lasers Med Sci. 2011;26(5):623–6.
46. Marfatia Y, Surani A, Baxi R. Genital lichen sclerosus et atrophicus in females: an update. Indian J Sex Transm Dis AIDS. 2019;40(1):6–12.
47. Preti M, Vieira-Baptista P, Digesu GA, et al. The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: an ICS/ISSVD best practice consensus document. Neurourol Urodyn. 2019:1–15.
48. Gardner AN, Aschkenazi SO. The short-term efficacy and safety of fractional CO_2 laser therapy for vulvovaginal symptoms in menopause, breast cancer, and lichen sclerosus. Menopause. 2021;28(5):511–6. https://doi.org/10.1097/GME.0000000000001727.
49. Pagano T, Conforti A, Buonfantino C, Schettini F, Vallone R, Gallo A, et al. Effect of rescue fractional microablative CO_2 laser on symptoms and sexual dysfunction in women affected by vulvar lichen sclerosus resistant to long-term use of topic corticosteroid: a prospective longitudinal study. Menopause. 2020;27(4):418–22.
50. Hobson GJ, Ibrahim FS, Gail Mercurio M. Recalcitrant vulvar lichen sclerosus treated with Erbium YAG laser. JAMA Dermatol. 2019;155(2):254–6.
51. Gómez-Frieiro M, Laynez-Herrero E. Use of Er:YAG laser in the treatment of vulvar lichen sclerosus. Int J Women's Dermatol. 2019;5(5):340–4.
52. Bizjak Ogrinc U, Senčar S, Luzar B, Lukanović A. Efficacy of non-ablative laser therapy for lichen sclerosus: a randomized controlled trial. J Obstet Gynaecol Can. 2019;41(12):1717–25.

53. Lee A, Lim A, Fischer G. Fractional carbon dioxide laser in recalcitrant vulval lichen sclerosus. Australas J Dermatol. 2016;57(1):39–43.
54. LaRosa C, Chiaravalloti A, Jinna S, Berger W, Finch J. Laser treatment of medical skin disease in women. Int J Women's Dermatol. 2017;3(3):131–9.
55. Park KY, Lee JW, Li K, Seo SJ, Hong CK. Treatment of refractory discoid lupus erythematosus using 1,064-nm long-pulse neodymium-doped yttrium aluminum garnet laser. Dermatol Surg. 2011;37(7):1055–6.
56. Rerknimitr P, Tekacharin N, Panchaprateep R, Wititsuwannakul J, Tangtanatakul P, Hirankarn N, et al. Pulsed-dye laser as an adjuvant treatment for discoid lupus erythematosus: a randomized, controlled trial. J Dermatolog Treat. 2019;30(1):81–6.
57. Brás S, Gonzalez B, Segurado-Miravalles G, Boixeda P. Treatment of lupus erythematosus of the eyelids with pulsed dye laser. Lasers Med Sci. 2018;33(1):215–9.
58. Bras S, Gonzalez B, Segurado-Miravalles G, Boixeda P. Treatment of lupus erythematosus of the eyelids with pulsed dye laser. Lasers Med Sci. 2018;33:215–9.
59. Diez MT, Boixeda P, Moreno C, et al. Histopathology and immunochemistry of cutaneous lupus erythematosus after pulsed dye laser treatment. Dermatol Surg. 2011;37(7):971–81.
60. Erceg A, Bovenschen HJ, van de Kerkhof PC, et al. Efficacy and safety of pulsed dye laser treatment for cutaneous discoid laser erythematosus. J Am Acad Dermatol. 2009;60(4):626–32.
61. Creadore A, Watchmaker J, Maymone MBC, Pappas L, Vashi NA, Lam C. Cosmetic treatment in patients with autoimmune connective tissue diseases: best practices for patients with lupus erythematosus. J Am Acad Dermatol. 2020;83(2):343–63.
62. Callen JP. Dermatomyositis. Lancet. 2000;355:53–7.
63. Yanagi T, Sawamura D, Shibaki A, Shimizu H. Treatment for poikilodermatous erythema of dermatomyositis with the pulsed dye laser. Br J Dermatol. 2005;153(4):862–4.
64. Zachariae H, Bjerring P, Cramers M. Argon laser treatment of cutaneous vascular lesions in connective tissue disease. Acta Derm Venereol (Stockh). 1988;68:179–82.
65. Abrouk M, Nousari Y, Waibel JS. Novel treatment of calcifications from dermatomyositis with picosecond and carbon dioxide laser. JAAD Case Rep. 2020;6(9):852–3.
66. Comstedt LR, Svensson A, Troilius A. Improvement of microstomia in scleroderma after intense pulsed light: a case series of four patients. J Cosmet Laser Ther. 2012;14:102–6.
67. Bennani I, Lopez R, Bonnet D, Prevot G, Constantin A, Chauveau D, Paul C, Bulai Livideanu C. Improvement of microstomia in scleroderma after carbon dioxide laser treatment. Case Rep Dermatol. 2016;8(2):142–50.
68. Yates B, Que SK, D'Souza L, Suchecki J, Finch JJ. Laser treatment of periocular skin conditions. Clin Dermatol. 2015;33(2):197–206.
69. Lee SJ, Goo B, Choi MJ, Oh SH, Chung WS, Cho SB. Treatment of periorbital syringoma by the pinhole method using a carbon dioxide laser in 29 Asian patients. J Cosmet Laser Ther. 2015;17(5):273–6.
70. Wang JI, Roenigk HH Jr. Treatment of multiple facial syringomas with the carbon dioxide (CO_2) laser. Dermatol Surg. 1999;25(2):136–9.
71. Hasson A, Farias MM, Nicklas C, Navarrete C. Periorbital syringoma treated with radiofrequency and carbon dioxide (CO_2) laser in 5 patients. J Drugs Dermatol. 2012;11:879–80.
72. Layton AM, Eady EA, Zouboulis CC. Acne. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology. 9th ed. West Sussex: Wiley-Blackwell; 2016. p. 90.1.
73. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. Clin Exp Dermatol. 1994;19(4):303–8.
74. Petrov A, Pljakovska V. Fractional carbon dioxide laser in treatment of acne scars. Open Access Maced J Med Sci. 2016;4(1):38–42.
75. Osman MA, Shokeir HA, Fawzy MM. Fractional erbium-doped yttrium aluminum garnet laser versus microneedling in treatment of atrophic acne scars: a randomized split-face clinical study. Dermatol Surg. 2017;43(Suppl 1):S47–56.

76. Reinholz M, Schwaiger H, Heppt MV, et al. Comparison of two kinds of lasers in the treatment of acne scars. Facial Plast Surg. 2015;31(05):523–31.
77. Faghihi G, Keyvan S, Asilian A, Nouraei S, Behfar S, Nilforoushzadeh MA. Efficacy of autologous platelet-rich plasma combined with fractional ablative carbon dioxide resurfacing laser in treatment of facial atrophic acne scars: a split-face randomized clinical trial. Indian J Dermatol Venereol Leprol. 2016;82(02):162–8.
78. Zhou BR, Zhang T, Bin Jameel AA, et al. The efficacy of conditioned media of adipose-derived stem cells combined with ablative carbon dioxide fractional resurfacing for atrophic acne scars and skin rejuvenation. J Cosmet Laser Ther. 2016;18(03):138–48.
79. Yuan XH, Zhong SX, Li SS. Comparison study of fractional carbon dioxide laser resurfacing using different fluences and densities for acne scars in Asians: a randomized split-face trial. Dermatol Surg. 2014;40(05):545–52.
80. Bjørn M, Stausbøl-Grøn B, Braae Olesen A, Hedelund L. Treatment of acne scars with fractional CO_2 laser at 1-month versus 3-month intervals: an intra-individual randomized controlled trial. Lasers Surg Med. 2014;46(02):89–93.
81. Kim HW, Chang SE, Kim JE, Ko JY, Ro YS. The safe delivery of fractional ablative carbon dioxide laser treatment for acne scars in Asian patients receiving oral isotretinoin. Dermatol Surg. 2014;40(12):1361–6.
82. Situm M, Kolic M, Franceschi N, Pecina M. Notalgia paresthetica. Acta Clin Croat. 2018;57:721.
83. Ansari A, Weinstein D, Sami N. Notalgia paresthetica: treatment review and algorithmic approach. J Dermatolog Treat. 2019;31:424–32.
84. Fonda-Pascual P, Collantes-Rodriguez C, Sanchez-Los Arcos L, Fernandez-Gonzalez P, Canseco-Martin M, Alcantara-Nicolas F, Rueda-Correa F, Vidal-Asensi S. Effectiveness of 308-nm excimer lamp in the treatment of notalgia paresthetica. J Eur Acad Dermatol Venereol. 2021;35(2):e111–3.
85. Wilkerson EC, Van Acker MM, Bloom BS, Goldberg DJ. Utilization of laser therapy during pregnancy: a systematic review of the maternal and fetal effects reported from 1960 to 2017. Dermatol Surg. 2019;45(6):818–28.
86. Schwartz DB, Greenberg MD, Daoud Y, Reid R. Genital condylomas in pregnancy: use of trichloroacetic acid and laser therapy. Am J Obstet Gynecol. 1988;158:1407–16.
87. Goldberg D, Maloney M. Dermatologic surgery and cosmetic procedures during pregnancy and the post-partum period. Dermatol Ther. 2013;26:321–30.
88. Mokmeli S, Khazemikho N, Niromanesh S, Vatankhah Z. The application of low-level laser therapy after cesarean section does not compromise blood prolactin levels and lactation status. Photomed Laser Surg. 2009;27:509–12.

Chapter 25
Treatment of Cellulite

Madhuri Agarwal

25.1 Introduction

Cellulite is a common lipodystrophy or skin composition disorder mostly affecting women of different ages from maturation to menopause. Medically named as liposclerosis, edematofibrosclerosis, edematous adiposity, gynoid lipodystrophia, and dermopanniculosis deformans [1–4], cellulite is often referred to as "cottage cheese" or "orange peel" because of its characteristic appearance. The affected skin displays tuberosity, fissures, and depressions mostly on buttocks, thighs, or hips where fat is under the influence of estrogen [5, 6]. Cellulite can also be found in the breasts, in the lower abdomen, arms, and nape—areas where deposition of the adipose tissue is commonly observed [1, 5].

Even though no accurate epidemiologic data exist on its prevalence, it is thought to affect 80–90% of postpubertal women [7] and is rarely seen in men. The common advent around 20–30 years of age has led to the possibility of hormonal etiology.

Goldman described cellulite as a normal physiologic state in postpubescent females that enhances adipose retention to guarantee sufficient caloric availability for pregnancy and lactation [8].

Cellulite is mostly seen in people who are overweight or obese, but also in people having correct body mass [9–11]. However, being overweight exacerbates the presence of cellulite. Some of the contributing factors for cellulite are as follows [12–14]:

1. Genetic predisposition
2. Hormonal imbalance
3. High body mass index
4. Sedentary lifestyle
5. Smoking
6. Inadequate diet

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7. Metabolic disorders like diabetes
8. Cardiovascular diseases
9. Posture defects
10. Emotional disorders

25.2 Histopathology

The epidermis is typical. A discreet perivascular lymphocytic infiltrate is seen in papillary and high reticular dermis, as well as in the normal skin. The collagen fibers in the superior layers of the dermis are to some extent edematous. The eosinophilic coloration of the collagen fibers is lighter than in the normal skin. No sign of fibrosis, sclerosis, or hyalinization is found. The elastic fibers are reduced in the subepidermic plexus; the fragments cling together in the deeper layers of the dermis. In the arrectores musculi pilorum region, there are indistinct signs of edema and, occasionally, of vacuolar degeneration. The blood vessels do not display pathological features. The superior dermis lymphatic vessels are visibly expanded. Fat cells in the subcutaneous tissue appear enlarged. The adipose tissue's septa are normal but may present discreet edema [15].

25.3 Pathophysiology

Cellulite is a complex result of genetic predisposition, and metabolic and biochemical disturbances. Based on magnetic resonance imaging (MRI) and gross ex vivo and in vivo examination, cellulite is postulated to be the result of the herniation of fat through perpendicularly oriented collagen fibrous septa. The collagenous septa course through the subcutaneous tissue, from the deep fascia and attach just under the skin. These septations have variable thickness and distribution in patients with cellulite [16].

When a patient is standing, the fat that encircles the fibrous bands projects outward, giving the "dimpling" appearance of cellulite [17].

Tissue vascularity and inflammation have also been assumed to play a role in cellulite development. It is hypothesized that adipocytes in cellulite prone areas have unique biochemical properties and are more resistant to lipolysis [18]. De Godoy and colleagues [19] hypothesized that an accumulation of fluids in the interstitial space, of both the lymphatic and venous systems, produces the changes that favor the development of cellulite. The accumulation of certain macromolecules results in local inflammation hindering the exchange of particles between both systems which leads to stasis in the lymphatic system that results in cellulite [19]. As a result of stasis, increased microedema results in further stress on the subcutaneous fat layer and surrounding connective tissue and collagen. In response, the number

and thickness of reticular fibers intensifies which leads to accentuation of skin irregularities and ultimately the appearance of cellulite [20].

25.4 Etiopathogenesis

A variety of reasons contribute to the development of cellulite including structural, circulatory, hormonal, and inflammatory factors [21–23].

The three main etiologic theories are based on anatomical and hormonal alterations, microcirculation, and chronic inflammatory processes.

25.4.1 Anatomical and Hormonal Alterations

Anatomical hypothesis is grounded on the fact that there are differences between men and women regarding the structural characteristics of subcutaneous fat lobules and of the conjunctive tissue septa that separate them. According to this philosophy, originally detailed by Nurnberger and Muller [15], the appearance of cellulite is caused by the protrusion of fat in the dermohypodermal junction. This alteration specifically occurs in women, due to the presence of vertical fascial bands. Piérard [24] believes that cellulite is caused by the genetically determined extension of those fascial bands. This, in turn, weakens and makes the base of the dermal conjunctive tissue thinner and allows the protrusion of fat into the dermo-hypodermic junction, causing the dimpled skin.

Men's subcutaneous region is composed of horizontal and diagonal fascial bands, which obstruct the herniation of fat [25]. Cellulite is extremely rare in men with normal levels of androgens, regardless of their weight, due to the genetic and hormonal nature of the architecture of the skin.

Hormonal differences are responsible for the structural variations in the anatomy of women's subcutaneous fat, meaning it is fundamentally regarded as an anatomic alteration [5].

25.4.2 Vascular Alterations

Cellulite is formed with the weakening of cutaneous vascularization, particularly in response to changes of the arteriolar precapillary sphincter in affected areas, in conjunction with deposits of hyperpolymerized glycosaminoglycans in the dermal capillary walls and between the collagen and elastic fibers [16, 22]. The increase in capillary pressure increases the permeability of the venular capillaries and causes the retention of excess liquid in the dermis, among the adipocytes and the interlobular septa, leading to variations in the cells and tissular hypoxia.

The increase in lipolytic resistance resulting from hypoxia and the increase in lipogenesis—caused by the action of estrogen, prolactin, and a diet rich in carbohydrates—enable the excessive growth of the adipocytes. The enlarged adipocytes, in combination with the growth and hyperplasia of the periadipocyte reticular fibers, form micronodules surrounded by proteins fragments that, later on, cause sclerosis of the fibrous septa, ultimately leading to the appearance of cellulite. Various therapies based on this theory encourage to improve circulation and drainage, with the objective of reducing the dimpled and irregular appearance of the skin [22].

25.4.3 Inflammatory Factors

Inflammatory factors also form the basis of physiopathology of cellulite [26–28]. Though not supported by enough evidence, some studies suggest that septa are responsible for the light inflammation that results in the lysis of the adipocytes and cutaneous atrophy.

Figure 25.1 summarizes the probable factors involved in the etiology of cellulite [29].

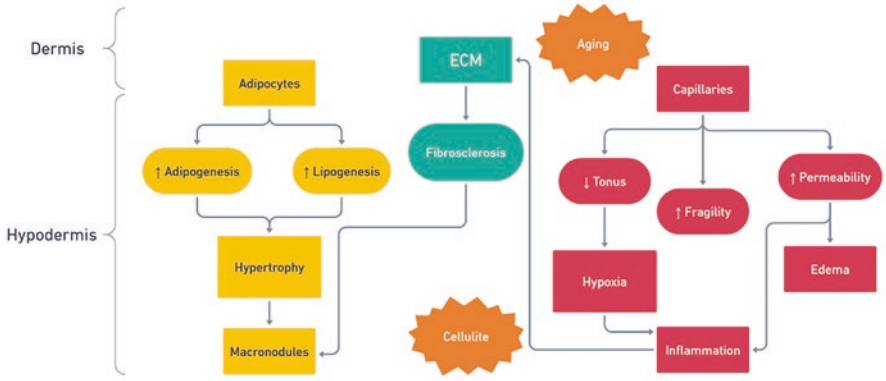

Fig. 25.1 The figure depicts the major factors contributing to cellulite. *eCM* extracellular matrix. (*Reference from Dupont E and colleagues. Clin Cosmet Investig Dermatol. 2014 7:73–88* [28])

25.5 Differential Diagnosis

Cellulite is sometimes referred to as fat or adipose but there exists a vast difference between them. Adipose tissue known as body fat refers to a type of connective tissue made up of adipocytes, collagen, blood vessels, and nerves. Fat tissue resides as two main reservoirs in the body—visceral fat and subcutaneous fat. Body contouring procedures like liposuction and cryolipolysis target subcutaneous fat. Though subcutaneous fat makes up an element of cellulite, not all subcutaneous fat is cellulite. Cellulite results from the underlying subcutaneous fat herniating between subcutaneous fibrous connective tissue which results in nodularity and dimpling of the skin. Hence treatments which aim to reduce subcutaneous fat fail to lessen cellulite. The proposed complex factors that interact in the formation of cellulite are reduced microcirculation, interstitial liquid infiltration (edema), localized hypertrophy of adipocytes, oxidative stress, and persistent low-grade inflammation, combined with extracellular matrix alterations [30–34]. The extensibility, elasticity, and resilience of the skin are also atypical [35].

Cellulite may be confused with **Lipoatrophy** which clinically appears as depressions in the skin and may be the consequence of trauma, a history of steroid injections, post-traumatic fat necrosis, or removal of excess subcutaneous tissue during liposuction.

Infragluteal bulges, folds, or protrusions, frequently referred to as a "banana roll," are the outcome of infragluteal fascial bands present at the base of the gluteal folds that may accentuate adipose tissue inferior to the buttocks [35].

Generalized edema or lymphedema and generalized obesity can also lead to alternating depressions and protrusions of the skin, prominently on the lower extremities, as a result of diminished lymphatic flow or diminished microcirculation.

It is imperative to consider these conditions during the evaluation and treatment since the modalities targeting cellulite may lead to exacerbations in the above-mentioned conditions [35].

25.6 Classification

Two classifications most commonly used in classifying cellulite are Nurnberger and Muller classification and the other proposed by Hexsel.

In 1978 Nürnberger and Müller classified cellulite into grades created on the clinical presentation of the condition [15]:

Table 25.1 Cellulite severity scale variables as proposed by Hexsel

Cellulite severity scale	
Number of evident depressions	0 = No depressions 1 = 1–4 visible depressions 2 = 5–9 visible depressions 3 = 10+ visible depressions
Depth of the visible depressions	0 = No depressions 1 = Superficial depressions 2 = Medium depth depressions 3 = Deep depressions
Morphologic appearance of the alterations of the surface of the skin	0 = No raised areas 1 = Orange peel appearance 2 = Cottage cheese appearance 3 = Mattress appearance
Degree of flaccidity or cutaneous laxity	0 = Absence of laxity 1 = Slight draped appearance 2 = Moderate draped appearance 3 = Severe draped appearance
Nürnberger and Müller classification scale	0 = Zero grade 1 = First grade 2 = Second grade 3 = Third grade

- Grade 0: absence of alterations of the cutaneous surface.
- Grade I: the surface of the affected area is flat when the patient is lying on his or her back or standing up; however the alterations can be observed when the area is pinched with the fingers or is under contraction of the local musculature.
- Grade II: an "orange peel" or "padded" appearance is evident without any pinching or muscular contraction when the patient is standing up.
- Grade III: the alterations described in Grade II are present and combined with elevations and nodulations.

Hexsel proposed a new objective classification by using photonumeric gradations [36]. He designed a more complex scale, composed of 5 variables (ranked 0–3) whose total sum classifies the patient into 1 of 3 groups based on severity: light (1–5 points), moderate (6–10 points), or severe (11–15 points).

The 5 analyzed variables are noted in Table 25.1:

The buttock- and thigh-specific Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) (Fig. 25.2) were postulated to resolve the shortcomings of the above classification scales. These new scales evaluated the cellulite severity, employing a photonumeric reference, cellulite severity and corresponding descriptors, from both physician and patient perspectives. The traditional scales of cellulite severity were assessed using the CR-PCSS and PR-PCSS ratings [37].

a Patient Reported Photonemeric Cellulite Severity Scale (PR-CSS) Buttocks

0-None No evidence of cellulite.	**1-Almost none** A few superficial dimples or ridges.	**2-Mild** Several dimples or ridges of which most are superficial.	**3-Moderate** Many dimples or ridges of which most are somewhat deep.	**4-Severe** A lot of dimples or ridges of which many are deep covering most of the skin area.

Clinician Reported Photonemeric Cellulite Severity Scale (CR-PCSS) Buttocks

0-None No dimples or evident cellulite.	**1-Almost None** Few dimples that are superficial in depth.	**2-Mild** Several dimples out of which most are shallow in depth.	**3-Moderate** Many dimples of which most are moderate in depth.	**4-Severe** A lot of dimples with some of more severe depth.

b Patient Reported Photonemeric Cellulite Severity Scale (PR-PCSS) Thigh

0-None No evident cellulite	**1-Almost None** A few superficial dimples or ridges.	**2-Mild** Several dimples or ridges of which most are superficial.	**3-Moderate** Many dimples or ridges of which most are somewhat deep.	**4-Severe** A lot of dimples or ridges of which many are deep covering most of the skin area.

Clinician Reported Photonemeric Cellulite Severity Scale (CR-PCSS) Thigh

0-None No depressions or raised areas.	**1-Almost None** A few depressions or undulations that are mostly superficial in depth.	**2-Mild** Several undulations that are shallow in depth with areas of slight protuberances.	**3-Moderate** Many undulations with alternating areas of protuberances and depressions of which most are moderate in depth.	**4-Severe** A lot of undulations with alternating areas of protuberances and depressions some of more severe depth.

Fig. 25.2 Assessment of cellulite severity using the PR-PCSS and CR-PCSS for the buttocks (**a**) and thighs (**b**). *CR-PCSS* Clinician Reported Photonumeric Cellulite Severity Scale, *PR-PCSS* Patient Reported Photonumeric Cellulite Severity Scale. (@ 2017 Auxilium Pharmaceuticals, LLC. *Reference Neil S and colleagues. Dermatol Surg. 2019;45:1047–1056* [37])

25.7 Treatment

Due to complex, multifactorial and indefinite etiopathogenesis, there is still no effective or absolute treatment. Many therapeutic proposals have been introduced which lack sufficient scientific evidence, durability, and reproducible results. There have been advances in the treatment of cellulite, and the most commonly reviewed treatment options have been discussed ahead.

25.7.1 Past Treatment Modalities for Cellulite

Microvascular Dysfunction and Tissue Edema

1. Methylxanthines (e.g., caffeine)
2. Mechanical stimulation (manually or with the use of a device)
3. Acoustic wave therapy or extracorporeal shock wave therapy

Excessive Subcutaneous Adipose Tissue

1. Weight loss
2. Cryolipolysis
3. High-intensity focused ultrasound
4. Low-level laser therapy (e.g., wavelengths varying from 532 nm, 635 nm, and 808 nm)
5. High-powered laser therapy (e.g., 1064-nm Nd:YAG)
6. Liposuction

Collagen Denaturation and Tissue Laxity

1. Radiofrequency (unipolar, bipolar, or tripolar)
2. Infrared light

Cellulite treatments mentioned in the international medical literature are classically divided into two groups:

- Noninvasive
- Invasive

Both can be further classified as:

– Treatments that do not involve the use of biologically active substances (medications)
– Treatments that involve use of active substances

25.7.2 Noninvasive Treatments Without the Use of Biologically Active Substances

Massage/Endermologie® In this category lymphatic drainage is the most widespread, due to the hypothesis that alterations in the physiological lymphatic drainage are linked to cellulite's etiopathogenesis. Massage can be performed manually or using devices designed to obtain higher speed and consistency (e.g., Endermologie® machine) [28, 38, 39].

Light-Based Devices Intense pulsed light (IPL) and laser belong in this category. IPL is used to stimulate the formation of new collagen and thickening of the dermis, thus making it less susceptible to cellulite. The isolated use of laser is uncommon and scarcely quoted. Many devices combine laser and IPL with massage, vacuum, ultrasound, or multiple techniques in a single device to address several etiopathogenic mechanisms of cellulite such as structural alterations in the collagen, microcirculation, and lymphatic drainage [40].

Dermal Fillers Recently, fillers like poly-l-lactic acid microspheres and calcium hydroxylapatite (CaHA) combined with MFU-V have been used effectively for improving the appearance of cellulite [41]. When combining these procedures on the same day, the energy device is used first, such as MRF or MFU-V, immediately followed by the injectable biostimulatory agent. If the dermal filler is done first, MRF or MFU-V is performed at least 1 week, preferably 1 month, later [42, 43].

Collagenase Clostridium Histolyticum (CCH) It is composed of 2 purified collagenases (AUX-I and AUX-II) that hydrolyze collagen under physiologic conditions, resulting in disruption of collagen structures (e.g., fibrous septa) [44]. CCH is approved by the US Food and Drug Administration for the treatment of collagen-associated disorders and has provided benefits in cellulite too [37, 45, 46].

25.7.3 Noninvasive Treatments with Biologically Active Substances

Topical preparations containing several pharmacological agents have been very commonly used. Topical treatments can be indicated as adjuvant therapies. Agents like methylxanthines, retinoids, lactic acid, and herbal extracts are used alone or in combination. These agents exert their anti-cellulite effects by several biological mechanisms. Methylxanthines such as caffeine, aminophylline, and theophylline have documented action in the treatment of cellulite. Herbal extracts include plants such as forskolin (*Coleus forskohlii*), sacred lotus (*Nelumbo nucifera*), carnitine, and escin, Ginkgo biloba, also rich in flavonoids, *Centella asiatica*, *Ruscus*

aculeatus, and *Carica papaya* [32]. Topical retinoic and related vitamin A derivates have been also used as topical cellulite treatments.

25.7.4 Invasive Treatments with Biologically Active Substances

Mesotherapy consists of the injection of multiple substances including xanthines such as caffeine, aminophylline, and theophylline, into the subcutaneous tissue which lead to lipolysis [23].

Carboxytherapy involves injecting carbon dioxide in the subcutaneous tissue with the target of affecting adipose tissue and circulation [47].

25.7.5 Invasive Treatments Without Biologically Active Substances

Subcision is the invasive surgical technique in which a needle is introduced in the subcutaneous tissue, and subsequently moved parallel to the cutaneous surface with the objective of rupturing the fibrous tissue bands that have a relevant role in cellulite's etiopathogenesis.

Other options are ultrasonic liposculpture [48–50] and autologous transplant of adipose tissue with the application of Nd-Yag laser in the subcutaneous tissue [51].

A treatment algorithm outlining the different cellulite combination treatment, the timespan of the procedures, and the sequence of treatment is given in Table 25.2.

The algorithm shares the entire spectrum of available cellulite treatments ranging from minimally invasive (Option 1) to the most invasive procedures (Option 3) [52]. The multifactorial etiologies in cellulite can be efficiently dealt by utilizing the combination treatments at times in a single session.

25.8 Conclusion

Cellulite is a condition that negatively impacts quality of life, and there has been enormous growth in available technologies to treat cellulite. Researchers are trying to seek a reliable treatment option for years which can be durable and reproducible. A better understanding of the role fibrous septa play in the pathogenesis of cellulite has led to the emergence of several treatment options that have shown objective, significant, and durable results.

Table 25.2 Algorithm for cellulite treatment

	Option 1	Option 2	Option 3
Volume loss and cellulite	MFU-V or RF	Controlled subcision	Controlled subcision
	PLLA or CaHA	MFU-V or RF	Fat transfer
		PLLA or CaHA	
Excess fat and cellulite	Detergent lipolysis or cryolipolysis	Liposuction or field radiofrequency	Controlled subcision
	1 month later: Controlled subcision	1 month later: Controlled subcision	1 month later: Liposuction or cryolipolysis
Skin laxity and cellulite	MFU-V or RF	Controlled subcision	Controlled subcision
	Controlled subcision	PLLA or CaHA	1 month later 2. MFU-V or MRF 3. PLLA or CaHA
Volume loss/skin laxity and cellulite	MFU-V or RF	Fat transfer	Fat transfer
	PLLA or CaHA	1 month later MFU-V or RF	Controlled subcision
			1 month later MFU-V or RF
Volume loss/excess fat (separate locations) and cellulite	Cryolipolysis or detergent lipolysis	Liposuction	Liposuction
	Controlled subcision	Subdermal RF	Controlled subcision
	PLLA or CaHA	1 month later PLLA or CaHA	1 month later PLLA or CaHA
Skin laxity/excess fat and cellulite	Cryolipolysis or detergent lipolysis	Liposuction	Liposuction
	Controlled subcision	Subdermal RF	Controlled subcision
	MFU-V or RF		1 month later PLLA or CaHA
	PLLA or CaHA		

Reference from Davis DS and others. Cellulite: Patient Selection and Combination Treatments for Optimal Results-A Review and Our Experience. Dermatol Surg. 2019;45 (9):1171–1184 [52]

References

1. Avram MM. Cellulite: a review of its physiology and treatment. J Cosmet Laser Ther. 2004;6(4):181–5.
2. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. Int J Cosmet Sci. 2006;28(3):157–67.
3. Lotti T, Ghersetich I, Grappone C, Dini G. Proteoglycans in so-called cellulite. Int J Dermatol. 1990;29(40):272–4.
4. Rossi ABR, Vergnanini AL. Cellulite: a review. J Eur Acad Dermatol Venereol. 2000;14(4):251–62.
5. Wanner M, Avram M. An evidence-based assessment of treatments for cellulite. J Drugs Dermatol. 2008;7(4):341–5.
6. Quatresooz P, Xhauflaire-Uhoda E, Piérard-Franchimont C, Piérard GE. Cellulite histopathology and related mechanobiology. Int J Cosmet Sci. 2006;28(3):207–10.

7. Emanuele E. Cellulite: advances in treatment: facts and controversies. Clin Dermatol. 2013;31(6):725–30.
8. Goldman MP. Cellulite: a review of current treatments. Cosmet Dermatol. 2002;15:17–20.
9. Friedmann DP, Vick GL, Mishra V. Cellulite: a review with a focus on subcision. Clin Cosmet Investig Dermatol. 2017;10:17–23.
10. Callaghan Rd DJ, Robinson DM, Kaminer MS. Cellulite: a review of pathogenesis-directed therapy. Semin Cutan Med Surg. 2017;36(4):179–84.
11. Luebberding S, Krueger N, Sadick NS. Cellulite: an evidence-based review. Am J Clin Dermatol. 2015;16(4):243–56.
12. Hexsel D, Camozzato FO, Silva AF, Siega C. Acoustic wave therapy for cellulite, body shaping and fat reduction. J Cosmet Laser Ther. 2017;19(3):165–73.
13. Woźniak M, Kaczmarek-Skamira E, Zegarski T, Zegarska B. Cellulite diagnosis: anthropometric interview and research. Dermatol Estet. 2014;1(16):19–22. (Polish).
14. Grudnik-Wroniszewska M. From diagnosis to therapy. Beauty Forum. 2013;6:20–2. (Polish).
15. Nurnberger F, Muller G. So-called cellulite: an invented disease. J Dermatol Surg Oncol. 1978;4(3):221–9.
16. Querleux B, Cornillon C, Jolivet O, Bittoun J. Anatomy and physiology of subcutaneous adipose tissue by in vivo magnetic resonance imaging and spectroscopy: relationships with sex and presence of cellulite. Skin Res Technol. 2002;8:118–24.
17. de Godoy JMP, de Godoy ACP, Godoy MFG. Considering the hypothesis of the pathophysiology of cellulite in its treatment. Dermatol Rep. 2017;9:7352.
18. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: part II. Advances and controversies. J Am Acad Dermatol. 2010;62:373–6; quiz 385–6.
19. de Godoy JM, de Godoy MF. Physiopathological hypothesis of cellulite. Open Cardiovasc Med J. 2009;3:96–7.
20. Rao J, Gold MH, Goldman MP. A two-center, double-blinded, randomized trial testing the tolerability and efficacy of a novel therapeutic agent for cellulite reduction. J Cosmet Dermatol. 2005;4:93.
21. Kligman AM. Cellulite: facts and fiction. J Geriatric Dermatol. 1997;5:136–9.
22. Alster TS, Tehrani M. Treatment of cellulite with optical devices: an overview with practical considerations. Lasers Surg Med. 2006;38(8):727–30.
23. Afonso JPJM, Tucunduva TCM, Pinheiro MVB, Bagatin E. Cellulite: a review. Surg Cosmet Dermatol. 2010;2(3):214–9.
24. Piérard GE, Nizet JL, Pierard-Franchimont C. Cellulite: from standing fat herniation to hypodermal stretch marks. Am J Dermatopathol. 2000;22(1):34–7.
25. Avram AS, Avram MM, James WD. Subcutaneous fat in normal and diseased states II (anatomy and physiology of white and brown adipose tissue). J Am Acad Dermatol. 2005;53(4):671–9.
26. Draelos Z, Marenus KD. Cellulite etiology and purported treatment. Dermatol Surg. 1997;23(12):1177–81.
27. Scherwitz C, Braun-Falco O. So-called cellulite. J Dermatol Surg Oncol. 1978;4(3):230–4.
28. Collis N, Elliot LA, Sharpe C, Sharpe DT. Cellulite treatment: a myth or reality: a prospective randomized, controlled trial of two therapies, endermologie and aminophylline cream. Plast Reconstr Surg. 1999;104(4):1110–4.
29. Dupont E, Journet M, Oula ML, Gomez J, Léveillé C, Loing E, Bilodeau D. An integral topical gel for cellulite reduction: results from a double-blind, randomized, placebo-controlled evaluation of efficacy. Clin Cosmet Investig Dermatol. 2014 Feb;20(7):73–88.
30. Kruglikov I. The pathophysiology of cellulite: can the puzzle eventually be solved? J Cosmet Dermatol Sci Appl. 2012;2(1):1–7.
31. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: part I. Pathophysiology. J Am Acad Dermatol. 2010;62(3):361–70.
32. Hexsel D, Soirefmann M. Cosmeceuticals for cellulite. Semin Cutan Med Surg. 2011;30(3):167–70.

33. de la Casa Almeida M, Suarez Serrano C, Rebollo Roldán J, Jiménez Rejano JJ. Cellulite's aetiology: a review. J Eur Acad Dermatol Venereol. 2013;27(3):273–8.
34. Draelos ZD. The disease of cellulite. J Cosmet Dermatol. 2005;4(4):221–2.
35. Green JB, Cohen JL. Cellfina observations: pearls and pitfalls. Semin Cutan Med Surg. 2015;34:144–6.
36. Hexsel DM, Dal'forno T, Hexsel CL. A validated photonumeric cellulite severity scale. J Eur Acad Dermatol Venereol. 2009;23:523–8.
37. Sadick NS, Goldman MP, Liu G, et al. Collagenase clostridium histolyticum for the treatment of edematous fibrosclerotic panniculopathy (cellulite): a randomized trial. Dermatol Surg. 2019;45(8):1047–56.
38. Marchand JP, Privat Y. A new instrumental method for the treatment of cellulite. Med Femin. 1991;39:25–34.
39. Güleç AT. Treatment of cellulite with LPG endermology. Int J Dermatol. 2009;48(3):265–70.
40. Fink JS, Mermelstein H, Thomas A, Trow R. Use of intense pulsed light and a retinyl-based cream as a potential treatment for cellulite: a pilot study. J Cosmet Dermatol. 2006;5(3):254–62.
41. Casabona G, Pereira G. Microfocused ultrasound with visualization and calcium hydroxylapatite for improving skin laxity and cellulite appearance. Plast Reconstr Surg Glob Open. 2017;5:e1388.
42. England LJ, Tan MH, Shumaker PR, Egbert BM, et al. Effects of monopolar radiofrequency treatment over soft-tissue fillers in an animal model. Lasers Surg Med. 2005;37:356–65.
43. Shumaker PR, England LJ, Dover JS, Ross EV, et al. Effect of monopolar radiofrequency treatment over soft-tissue fillers in an animal model: part 2. Lasers Surg Med. 2006;38:211–7.
44. French MF, Mookhtiar KA, VanWart HE. Limited proteolysis of type I collagen at hyperreactive sites by class I and II Clostridium histolyticum collagenases: complementary digestion patterns. Biochemistry. 1987;26:681–7.
45. Goldman M, Sadick N, Young L, Kaufman GJ, et al. Phase 2a, randomized, double-blind, placebo-controlled dose-ranging study of repeat doses of collagenase clostridium histolyticum for the treatment of edematous fibrosclerotic panniculopathy (cellulite). J Am Acad Dermatol. 2015;72:AB19.
46. Dagum B, Badalamente MA. Collagenase injection in the treatment of cellulite. Presented at: Plastic surgery; October 6–11, 2016; San Francisco, CA.
47. Brandi C, D'Aniello C, Grimaldi L, Bosi B, Dei I, Lattarulo P, et al. Carbon dioxide therapy in the treatment of localized adiposities: clinical study and histopathological correlations. Aesthet Plast Surg. 2001;25(3):170–4.
48. Gasparotti M. Superficial liposuction: a new application of the technique for aged and flaccid skin. Aesthet Plast Surg. 1992;16(1):141–53.
49. Karnes J, Salisbury M, Schaeferle M, Beckham P, Ersek RH, et al. Hip lift. Aesthet Plast Surg. 2002;26(1):126–9.
50. Adamo C, Mazzocchi M, Rossi A, Scuderi N. Ultrasonic liposculpturing: extrapolations from the analysis of in vivo sonicated adipose tissue. Plast Reconstr Surg. 1997;100(1):220–6.
51. Goldman A, Gotkin RH, Sarnoff DS, Prati C, Rossato F. Cellulite: a new treatment approach combining subdermal Nd:YAG laser lipolysis and autologous fat transplantation. Aesthet Surg J. 2008;28(6):656–62.
52. Davis DS, Boen M, Fabi SG. Cellulite: patient selection and combination treatments for optimal results—a review and our experience. Dermatol Surg. 2019;45(9):1171–84.

Chapter 26
Breast Augmentation: Cutaneous Aspects and Complications

Suruchi Garg, Anuva Bansal, and Manjot Kaur Marwah

26.1 Introduction

The female breast undergoes several changes throughout life as a result of ageing, hormonal influence, pregnancy, and lactation. Understanding the changes in breast shape, parenchymal tissue, and skin overlying the breast that accompany ageing is important to improve the outcomes of breast reshaping or rejuvenating surgical procedures. The shape of the breast changes with ageing in a manner that the nipple deviates caudally. Breast volume tends to increase with age, an effect probably related to the influence of the downward pull of gravity on the skin or connective tissue. Ageing breasts undergo sagging also known as ptosis, a consequence of parenchymal maldistribution, connective tissue, and skin dysfunction. Furthermore, the changes in the thickness and elasticity of breast skin that occur with ageing significantly influence the internal, anatomical breast support structure.

Breast augmentation (BA) is a procedure where the breast size is enhanced where as a breast lift procedure can lift the nipple and reshape the breasts to sit higher on the chest in a more youthful position. Conventionally, these procedures have been done surgically and are associated with complications inherent to surgery, are invasive, and result in incision related scars. Non-surgical breast augmentation and breast lift using fillers, radiofrequency based devices, threads, lasers, platelet rich plasma injection, and Botox offer non-invasive or minimally invasive alternatives to patients not desirous of going under the knife and provide results comparable to the surgical procedures, with the advantage of minimal downtime and a reduced risk of complications.

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26.2 Anatomy of the Breast and the Effects of Ageing

26.2.1 Anatomy of the Breast and Its Practical Implications

Knowledge of the breast morphology and structure is crucial to improving the cosmetic outcomes and reducing the complications associated with the various aesthetic procedures involving the breast. The human breast consists of 15–20 lobes arranged in a circular fashion around the nipple. Each lobe drains numerous small lobules via a system of converging ducts, and each lobule in turn consists of multiple alveoli which produce milk. The terminal duct lobular unit comprising the terminal duct and the lobule is the basic functional unit of the breast.

Histologically, the breast tissue can be divided into glandular and fatty tissue. The glandular tissue is composed of epithelial cells, which line the ductal system, as well as the stromal elements, and provide a supportive connective tissue framework to the epithelium. Fatty tissue is dispersed heterogeneously between the breast lobules (Fig. 26.1).

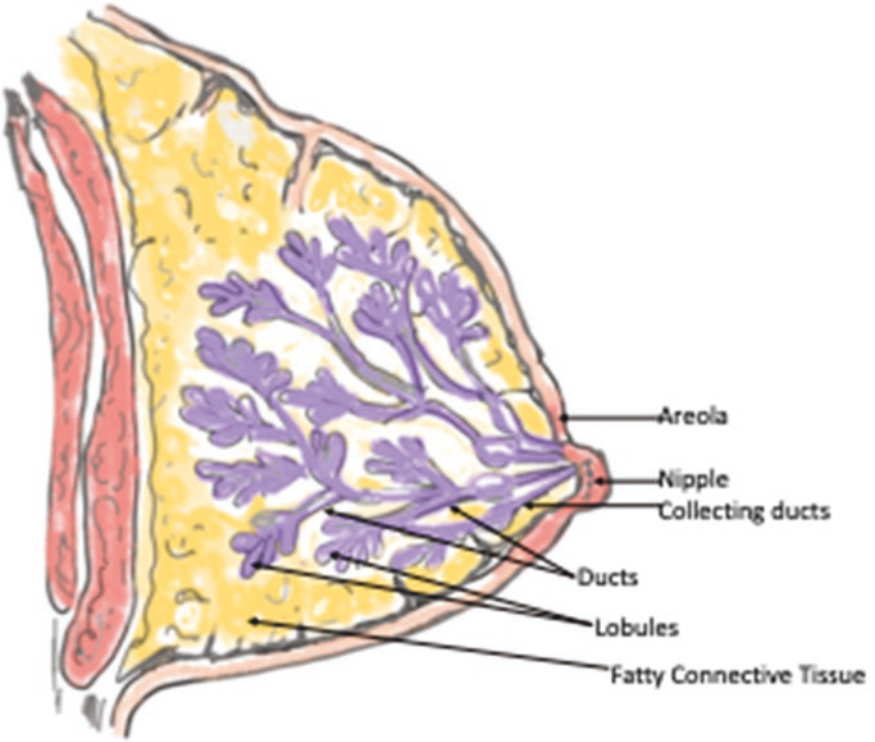

Fig. 26.1 Structure of the breast: The breast consists of 15–20 lobes which drain the numerous small lobules via a system of converging ducts, and each lobule in turn consists of multiple alveoli which produce milk. The terminal duct lobular unit comprising of the terminal duct and the lobule is the basic functional unit of the breast. Histologically, the breast tissue can be divided into glandular and fatty tissue

However, this composition tends to undergo several changes throughout life as a result of the fluctuations in the hormonal milieu which induces cellular changes in the breast tissue composition. These age-related variations in the breast tissue have been studied extensively and are detailed in the next section [1]. The adult breast rests over the pectoralis muscle, above the ribcage. The breast tissue extends horizontally from the edge of the sternum to the mid-axillary line. The breast tissue is surrounded by a thin layer of connective tissue called fascia. The deep layer of this fascia lies immediately on top of the pectoralis muscle, and the superficial layer lies just beneath the skin. The glandular tissue lies in a pocket formed by the two layers of this superficial fascia, which lies immediately beneath the dermis and allowing injections as well as insertion of threads avoiding the glandular mass and in a relatively avascular plane. Fibrous processes of the thick deeper fascia extend up to the skin and to the nipple. They are more developed over the upper part of the breast, where they form suspensory ligaments of Cooper, the contraction of which provides the lift in the breast lift procedures.

26.2.2 Age-Related Changes

Understanding the changes in breast shape, parenchymal tissue, and skin overlying the breast that accompany ageing is important to improve the outcomes of breast reshaping or rejuvenating surgical procedures. Besides clinical examination, various investigative modalities such as multidetector row computed tomography, mammography, and MRI have been utilized to investigate this relationship between ageing and changes in the breast shape and tissue [1, 2].

26.2.2.1 Caudal Nipple Deviation

The shape of the breast itself changes with ageing in a manner that the nipple deviates caudally. This change in shape probably occurs as a result of the elongation of the skin of the breast, mainly cranial to the nipple as well as elongation of the other supporting structures. Several studies report that the caudal nipple deviation shows significant correlation with age and also corresponds to the change in the ratio of the upper pole to the lower pole in clinical examinations of breast shape. In a study by Machida et al., the caudal nipple deviation correlated indirectly but positively with an elongation of the suprasternal notch to nipple (SSN) distance in clinical measurements. Therefore, shortening of the upper pole of the breast or SSN may lead to a rejuvenation of the breast's shape [1, 2].

26.2.2.2 Volume of the Breast

The breast volume tends to increase with age and a significant correlation exists between caudal nipple deviation and breast volume has also been reported. This is probably related to the effect of gravity as the skin or connective tissue of the breast may be stretched and lengthened by this continuous force pulling them downward, resulting in caudal nipple deviation, especially in larger breasts. The breast parenchyma has been reported to decrease with age or after menopause and this increase in breast volume with ageing may be attributed to an increase in adipose tissue. This increase in breast volume with ageing accelerates the influence of gravity on the breast shape as well as the caudal nipple deviation [1, 2].

26.2.2.3 Ptosis

Breast ptosis can be a consequence of parenchymal maldistribution as well as connective tissue and skin dysfunction. Regression of the glandular tissue due to hormonal changes after menopause or pregnancy, weight loss, skin pathologies, and previous surgery has been mentioned as potential causes. The weight of the breast tissue and the laxity of the breast-supporting ligaments as well as the Cooper's ligaments are other factors responsible for breast ptosis. Age, history of weight loss greater than 50 lb, higher BMI, larger breast size, pregnancy, and smoking have been identified as significant risk factors for the development of breast ptosis [3, 4]. The degree of breast ptosis can be graded according to the Regnault modified scale (Fig. 26.2) as (Table 26.1):

- **Pseudoptosis:** The nipple is located either at or above the inframammary fold, while the lower half of the breast sags below the fold.
- **Parenchymal Maldistribution:** The lower breast tissue is lacking fullness, the inframammary fold is very high, and the nipple and areola are relatively close to the fold. This is usually a developmental deformity.

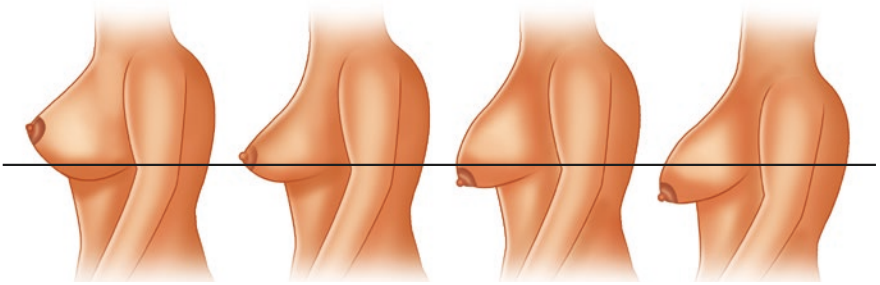

Fig. 26.2 Regnault scale for breast ptosis: Normal, mild sagging, moderate sagging, severe sagging

Table 26.1 Regnault's classification of breast ptosis [5]

Grade	Degree	Description
Pseudoptosis	–	Nipple at the IMF but gland below the IMF
I	Mild	Nipple at or within 1 cm below the IMF
II	Moderate	Nipple below the IMF but above the lowest point of the breast
III	Severe	Nipple at the lowest point of the breast

IMF inframammary fold

26.2.2.4 Changes in the Skin Overlying the Breast

A significant decrease occurs in breast skin thickness as well as elasticity with increasing age, with the latter change taking place earlier in life. The decrease in skin elasticity has been attributed to degradation as well as a decline in the production of elastin and collagen fibres in the dermis. The initiation of these age-related changes in breast skin thickness and skin elasticity has been reported to occur as early as mid-1940s and mid-1920s, respectively. The weight of the breast is supported largely by the overlying skin, and these age-related cutaneous changes have serious implications for breast support and these structural alterations might also contribute to the clinical changes in breast shape observed with ageing.

26.2.2.4.1 Autologous Fat Grafting

Non-implant breast augmentation with injections of autologous fat grafts (adipocyte tissue) serves as an alternative augmentation mammoplasty procedure and is indicated for women requiring breast reconstruction, defect correction, or the aesthetic enhancement of the breast.

Fat-graft augmentations of the breast utilize adipocyte fat from sites other than the breast. The fat is harvested via liposuction, undergoes centrifugation refinement which removes blood products and free lipids to produce autologous breast filler. The successful outcome is enhanced by achieving a pre-expanded recipient site to create the breast tissue matrix that will receive grafts of autologous adipocyte fat tissue. The breasts are contoured by layering the fat grafts into different levels within the breast, allowing the surgeon's precise control in accurately contouring the breast to achieve a natural appearance of the breast [6].

The skin of the superior and medial breast quadrants is associated with the most marked decrease in thickness from age 45 years onwards and these regional skin changes are consistent with the reported changes in breast shape associated with increasing age, where the breasts tend to spread downward and outward with progressing age, under the influence of gravitational force.

Thus, the changes to the thickness and elasticity of breast skin that occur with ageing significantly influence the internal, anatomical breast support structure and since the decrease in elasticity is most evident at the superior and medial breast quadrants, the corresponding shift in breast mass takes place downwards and outwards [4, 7].

26.3 Surgical Breast Augmentation

Breast augmentation (BA) is a surgical procedure where the breast size is enhanced. Surgical BA (Table 26.2) can be done via the placement of an implant, or less commonly, through fat transfer [7]. A breast augmentation is often performed to replace volume lost from weight loss, breast feeding, or age or to increase the size of the breast for aesthetic reasons. It is most appropriate for patients with breasts that do not show ptosis.

26.3.1 Indications for Breast Augmentation

- *Breast reconstruction*: Post-mastectomy re-creation of the breast(s), trauma-damaged tissues (blunt, penetrating), disease (breast cancer), and explantation deformity (empty breast-implant socket).
- *Congenital defect correction*: Micromastia, tuberous breast deformity, Poland's syndrome, etc.
- *Primary augmentation*: The aesthetic enhancement (contouring) of the size, form, and feel of the breasts [8, 9].

26.3.1.1 Surgical Implantation

There are two main types of breast implants: saline-filled or silicone-filled, but both have an outer silicone shell. Saline-filled implants are filled with sterile saline. The implants can be placed above or beneath the pectoralis muscle. This is also referred to as sub-glandular and submuscular, respectively. Common access incisions include the inframammary crease, transaxillary, and the peri-areolar locations (Fig. 26.3). The choice of incision is based on multiple factors including surgeon preference, patient preference, patient anatomy, and/or type of implant. Breast implants are composed of an outer silicone shell that is either filled with silicone gel at the time of manufacture or filled with saline by the surgeon at the time of implant placement. General anaesthesia is most commonly used for this procedure, but it can also be done under sedation or even local anaesthesia in select cases. Breast augmentation is considered an outpatient procedure and the usual operating time is 45–90 min. Recovery is rapid with a return to work and light activity within a week. Return to full activity may take up to 6 weeks [8, 9].

26.3.1.2 Autologous Fat Grafting

Non-implant breast augmentation with injections of autologous fat grafts (adipocyte tissue) serves as an alternative augmentation mammoplasty procedure and is indicated for women requiring breast reconstruction, defect correction, or the aesthetic enhancement of the breast.

Table 26.2 Surgical breast augmentation [6, 8, 9]

Name of Procedure	Indications	Technique	Principle	Advantages	Disadvantages	Safety
Surgical implantation	**1. Breast reconstruction:**	The first stage	Silicone-filled implants	Reduced occurrences of	Concern over safety issues[a]	FDA approved to increase or enhance breast size in any patient over the age of 22
	• Post-mastectomy	Placement of the tissue expander—a silicone shell that is filled with saline through a port	• Outer shell of solid silicone	• Filler leakage ("silicone gel bleed")	Larger incision site	
	• Trauma-damaged tissues	Appropriate breast shape reached; expander is removed; replaced with an implant.	• Filled inside with a viscous silicone gel	• Migration of the silicone filler from the implant pocket to other areas		
	2. Congenital defect correction:	***Types of Implants***	• May have a smooth surface or a textured surface on the outer shell	• Better aesthetic results		
	• Micromastia	**(a) Silicone Filled**		• Less rippling of the implant edges when compared to saline implants		
	• Tuberous breast deformity	*filled with viscous silicone gel*		• Preferred in case of		
	3. **Primary augmentation:**			• Small amounts of soft tissue coverage in their breasts		
	• Aesthetic enhancement			• Thin patients		

(continued)

Table 26.2 (continued)

Name of Procedure	Indications	Technique	Principle	Advantages	Disadvantages	Safety
		(b) Saline Filled	• Usually inserted empty and then a small port is used, add the desired amount of sterile saline	• Smaller incision scars	Rippling and the wrinkling of the breast-envelope skin	Approved by the FDA for
		filled with sterile saline solution	• The port is removed	• Less invasive	Implant's presence noticeable to the eye and to the touch	• Patients 18 years and older for breast augmentation and
		Preferred for person with	• Implant has a self-sealing tab for the port insertion site	• Smoother hemisphere-contour		• Any age patient for breast reconstruction
		• Much breast tissue		• Realistic consistency		
		• Submuscular placement is the recommended surgical approach				
		Placement of implant	Implant is placed above the pectoralis muscle	Preferred in	• Can reduce glandular volume	
		(a) Sub-glandular		• Patients with small amounts of soft tissue coverage in their breasts and thin patients	• Ripples and wrinkles may be seen	
					• Capsular contracture incidence rate is slightly greater	
					• Larger looking augmentation	
					• Sharper transition at edges of the implant	

		(b) Submuscular	Implant is placed below the pectoralis muscle	• Provides maximal coverage of the breast implants • Lower risk of capsular contracture • Lower chance of rippling • Better coverage in thin women • More natural upper pole contour	Can reduce the volume of the pectoralis major muscle	–
		(c) Subfascial	The breast implant is emplaced beneath the fascia of the pectoralis major muscle	Layer of fascial tissue provides greater implant coverage and better sustains its position	Can reduce the volume of the pectoralis major muscle	–
Fat grafting	• Breast reconstruction • Defect correction • Aesthetic enhancement • Correct implant related complications	Utilize adipocyte fat from sites other than the breast Up to 300 mL of fat in three equal injections, is placed into: • Subpectoral space • Intra-pectoral space • Sub-mammary space	The careful harvesting and centrifugal refinement of the mature adipocyte tissue (injected in small aliquots) allows the transplanted fat tissue to remain viable in the breast	Provides the anatomical structure and the hemispheric contour that cannot be achieved solely with breast implants or with corrective plastic surgery	Adipocyte tissue can undergo • Necrosis • Metastatic calcification • Develop cysts • Agglomerate into palpable lumps • Scarring of the incisions	Safe procedure when performed by experienced surgeons

[a] There is no increase in primary or recurrent breast cancer in implanted women. Some women with or without breast implants would be expected to develop connective tissue diseases, cancer, neurologic diseases, or other systemic complaints or conditions. Evidence suggests that such diseases or conditions are no more common in women with breast implants than in women without implants. There is no evidence of elevated silicone in breast milk or any other substance that would be deleterious to infants; therefore, all mothers with implants should attempt breast feeding

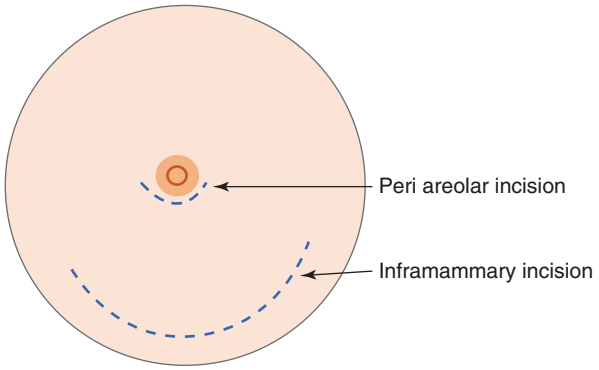

Fig. 26.3 Implants are most often inserted through one of two different small incisions. (1) Incision around the lower half of the nipple areola (peri-areolar); (2) Incision in the breast crease between the breast and the chest wall (inframammary incision)

Fat-graft augmentations of the breast utilize adipocyte fat from sites other than the breast. The fat is harvested via liposuction, undergoes centrifugation refinement which removes blood products and free lipids to produce autologous breast filler. The successful outcome is enhanced by achieving a pre-expanded recipient site to create the breast tissue matrix that will receive grafts of autologous adipocyte fat tissue. The breasts are contoured by layering the fat grafts into different levels within the breast, allowing the surgeon's precise control in accurately contouring the breast to achieve a natural appearance of the breast [6].

26.3.2 Complications

Complications associated with implant-based breast augmentation can be classified as:

Early postoperative complications

- Infection, scarring, asymmetry, hematoma, seroma, breast pain, poor cosmetic outcome, nipple/breast sensation changes

Later complications

- Implant malposition or displacement
- Implant deflation or leak
- Capsular contracture which is tightening of the tissue capsule around the implant

These complications can also be classified as:

1. General complications due to surgery,
2. Implant based complications, and
3. Related to aesthetic and cosmetic outcome [10] (Table 26.3).

Table 26.3 Complications of implant based breast augmentation surgery [10]

Complication	Cause	Prevention	Clinical features	Management
General complications due to surgery				
1. Seroma	Most seromas occur following removal of a drain.	If seroma develops with drains still in place, the patient should be cautioned to reduce activity	Significant fluid accumulation within the breast implant pocket may cause	Early seromas can be drained percutaneously with or without placement of a short-term drainage catheter:
	Increased movement of the expander or implant, possibly the result of		• Asymmetry	• Avoids damage to implant
	• A large pocket		• Breast enlargement	• Infection suspected: send drained fluid for culture
	• Too much activity by the patient		• Implant rotation	• If a drain is placed, it is left in place for 1–2 weeks until drainage is ≤30 mL/24 h
	Late fluid collections		• Implant malposition	Evaluation of a late fluid collection
	• Friction between the rough surface of the textured prosthesis and the fibrous capsule		• Infection	• Cell counts, microbiology
				• Ultrasound or magnetic resonance imaging
				• Oncologic evaluation may be indicated[a]
				If infection and malignancy have been ruled out:
				• Surgical exploration with complete capsulectomy
				• Implant removal (placement of new implant)
				• Drain placement: if the fluid collection persists after percutaneous drainage

(continued)

Table 26.3 (continued)

Complication	Cause	Prevention	Clinical features	Management
2. Hematoma	Develops within the first 12–24 h after surgery.	• Careful dissection	The affected breast is usually enlarged, tender, and may have ecchymosis or bruising	• Exploration of the breast, drainage of the hematoma, and establishing haemostasis
	Late hematomas	• Attention to haemostasis		• Any underlying coagulation abnormalities must be addressed and corrected
	• Trauma	• Platelet inhibitors, anticoagulants		• Unfortunately, associated with subsequent capsular contracture
	• Clotting disorders	• Should be discouraged		
	• Overactivity	• Drains may be placed		
	• Intraoperative corticosteroids			
3. Infection	Independent risk factors for infection include:	Prevention of seroma and hematoma formation	Abnormal redness and swelling, peri-implant gas, cellulitis	Initial management
	• Body mass index			• Empirical oral antibiotic therapy
	• Preoperative radiation			• Drained cultured peri-implant fluid collection after ultrasound
	• Necrosis			In case of progressive cellulitis
	• Seroma			• Start intravenous antibiotics.
	• Hematoma			• Wound drainage and send for culture
				Skin breakdown/incisional dehiscence/lack of resolution within 24–48 h
				• Operative exploration
				Infected implant
				• Remove, irrigate pocket, drain

4. Persistent breast Pain	• Infection	–	Persistent and significant breast pain beyond the typical postoperative course	Spasm of the pectoralis major muscle in the setting of subpectoral breast implants
	• Chest wall injury			Pre-pectoral conversion
	• Capsular contracture			• Placing the pectoral muscle back to its normal position
	• Radiation injury			• Placing a new implant above the pectoralis
	• Nerve injury			
Implant based complications				
5. Capsular contracture	Capsular contracture is an inherent risk of implant usage.	• Textured implants	• Breast pain, tenderness, and distortion	Non-surgical methods[b]
	When a breast implant is placed, a capsule of fibrous tissue forms around it	• Partial or complete submuscular or subfascial implant	• The Baker scale[b] is commonly used to rate the significance and severity	• Breast massage
	The capsule is typically thin and does not cause any symptoms, but in some cases it may progress to a more firm and calcified capsule		• Baker grades III and IV contracture to be significant enough to be classified as a complication	• External ultrasound
				• Zafirlukast, Montelukast, Vitamin E, Papaverine, Diclofenac
				Only breasts with Baker III and IV capsules require surgical treatment:
				1. **Open capsulotomy** internal circumferential and longitudinal incisions through the capsule.
				2. **Open capsulectomy** is similar to open capsulotomy, but the offending scar tissue and capsule are removed
				3. **Implant pocket repositioning from subcutaneous to a dual-plane position** may reduce the recurrence
				4. Capsulectomy with implant removal and no further implant replacement—when there is recurrence

(continued)

Table 26.3 (continued)

Complication	Cause	Prevention	Clinical features	Management
6. Deflation of saline implants	Deflation within the first few days	–	Implant failure leads to a decrease in breast volume with the patient noticing that the breast becomes smaller over a few days	• Implant can be replaced when convenient for the patient
	• Iatrogenic damage (suture needle)			• It may be better to replace the implant soon after deflation to preserve the size of the original implant pocket
	• Improperly closed valve.			• No evidence that not removing a deflated saline implant has any negative health effects
	A saline implant may leak later:			
	• Fill valve malfunction			
	• Iatrogenic damage			
	• External physical trauma.			
	• Small pinhole defects in the shell			
7. Rupture of silicone gel implants	Rupture if silicone gel implant and leakage of gel. Two types:	–	Failure of a silicone gel implant is difficult to detect, on physical examination, as in case of **intracapsular rupture**	• Ruptured silicone gel implants should be removed due to the possibility of the gel material causing inflammation and other tissue reactions, particularly in case of extracapsular rupture
	Intracapsular rupture:		**Mammography/MRI should be used**	• If rupture is suspected or known, a capsulectomy is performed to remove the gel material from the breast pocket
	Gel typically remains confined within the breast capsule			• Total capsulectomy should be considered given the possibility of ALCL in women with a ruptured textured surface breast implants

8. Implant exposure	Multiple factors contribute to the development of implant exposure, including	• Proper dimensional planning	Implant may be visible through the skin	• If the expander is in place, removing fluid may resolve the increased pressure leading to exposure
	• Too rapid expansion	• Appropriate implant size		• Incisional dehiscence can be salvaged if the aetiology is purely mechanical. Counter-incisions are often considered
	• Thinning of the skin with areas of nonhealing	• Prevention of infection, smoking, and external irritation		• If dimensional planning and implant size are appropriate and infection, smoking, and external irritation are eliminated, attempts at closure may be fruitful
	• Infection			• If the implant exposure is large and the aetiology significant, removal of the implant may be warranted, allowing adequate time for healing
	• Seroma formation			
	• Incisional dehiscence			
	• Overactivity			
	• Excessive external pressure			
9. Malposition	Implant malposition can occur shortly after surgery or years later	The use of a breast support device (elastic band) may help facilitate the proper positioning of the implant	Abnormal positioning of the implants	If there is continued malposition
	Common for implants to be in a higher than expected position for a few weeks after placement and then to settle more inferiorly as the skin and soft tissue swelling resolve			Surgical revision may be considered once the final implant position has occurred and swelling has resolved
				This may be 3–6 months after the implants are placed

(continued)

Table 26.3 (continued)

Complication	Cause	Prevention	Clinical features	Management
(a) Lateral implant malposition	Frequently due to over-dissection of the lateral breast pocket or from prolonged pectoralis major muscle forces on the medial implant	Identification of chest wall deformities, proper implant width selection, careful lateral pocket dissection, and medial pectoralis muscle release	Appearance of the implants being positioned too laterally	Depends on the underlying cause and may require
	Occasionally, due to			• Medial pocket release
	• Oversized implants			• Lateral capsulorrhaphy
	• Unrecognized chest wall deformity			• New implant pocket creation
				• Use of ADM
				• And placement of a narrower implant
(b) Medial implant malposition	It may be due to excessive medial pocket dissection or from the use of implants that are too wide for the patient's chest	Avoid over-dissection of the medial implant pocket and proper choice of implant width	Severe forms can result in symmastia where the definition of the medial edge of each breast is lost and cleavage is absent	• Medial capsulorrhaphy
				• New implant pocket creation
				• Use of a narrower implant
				• If the above techniques are not suitable, placing a sheet of ADM medially in the pocket may be useful
(c) Superior implant displacement	• Placement of a large implant without releasing the inframammary crease to compensate for the implant size	• Proper inferior pocket creation and muscle release	Appearance of the implants being positioned too superiorly	If superior displacement is unimproved 3–6 months after implant placement, the inferior pocket can be extended and the muscle released. If inframammary fold release is needed, it should be done carefully to prevent future inferior implant displacement
	• Capsular contracture also displaces the implant superiorly	• Care should be taken to preserve the inframammary fold		
	• Implants in a subpectoral pocket can move superiorly with pectoralis major muscle contraction			

(d) Inferior implant displacement	Stretching of the inferior breast skin (bottoming out) or migration of the implant across the inframammary fold may lead to inferior implant displacement	Proper breast assessment with an appropriately matched implant	Appearance of the implants being positioned too inferiorly	• Inferior skin excess due to stretching may require a mastopexy, possibly with a smaller implant
		Care should be taken if the inframammary fold is released—may allow further implant migration		• In some cases, the inframammary fold needs to be repositioned superiorly
				• Sheets of ADM have been used to reinforce corrections of inferior implant displacements
(e) Implant rotation malposition	If an asymmetric (also known as a "shaped" or "anatomic") implant is used, the breast shape may change if the implant rotates inside the breast pocket.	In case of round symmetric implants, a rotation of the implant inside the pocket will not result in a change in the shape of the breast since the implant is symmetric around the axis of rotation	Affected breast has more fullness in the area where the projecting pole of the implant is positioned	Dynamic rotation: External manipulation
	Various factors may contribute			Static rotation: Surgical options include:
	• Extent of pocket dissection			• Suture anchoring the posterior tabs of the tissue expander onto the chest wall fascia
	• Not using drains			• Tightening the implant pocket using capsulorrhaphy
	• Physical properties of the implant			• Implant exchange to round implant
				• Implant removal with implant replacement in the future if desired
10. Anaplastic large cell lymphoma	Rare type of cancer arising in the scar capsule adjacent to a breast implant		Peri-implant mass or fluid collection	For localized disease
	The overall risk is extremely low			• Implant and surrounding capsule and any associated masses are removed
				• Associated axillary lymphadenopathy is excised for pathologic evaluation
				Disseminated disease: Systemic treatment

(continued)

Table 26.3 (continued)

Complication	Cause	Prevention	Clinical features	Management
Aesthetic concerns				
1. Rippling and palpability	More common in	If body mass index less than 18.5	Can be seen through the breast tissue causing skin irregularities, typically in the lateral border of the breast	• A change to a silicone implant may improve the palpability.
	• Thin patients	• Submuscular placement		• Placing a sheet of acellular dermal matrix (ADM) in the appropriate area of the breast pocket
	• Sub-glandular placement	• Silicone implant if a sub-glandular position is chosen		
	• Textured implants			
	• Saline implants			
2. Breast asymmetry	Asymmetry has as much to do with patient expectation as the skill and experience of the surgeon	Most women have some level of pre-existing asymmetry in volume, shape, or NAC. Should be noted and pointed out to the patient at the time of examination	Asymmetry: Nipple areolar, inframammary fold, or shape and projection	Surgical correction of asymmetry

NAC nipple-areolar complex, *ADM* acellular dermal matrix

[a]All seromas occurring more than 1 year after surgery should be sent for cytology to rule out breast-implant-associated anaplastic large cell lymphoma (ALCL)

[b]Baker I: The breast is soft with no palpable capsule and looks natural; Baker II: The breast is a little firm with a palpable capsule but looks normal; Baker III: The breast is firm with an easily palpated capsule and is visually abnormal; Baker IV: The breast is hard, cold, painful, and markedly distorted

26.3.2.1 Surgical Breast Lift/Mastopexy

A breast lift or mastopexy is procedure that can lift the nipple, remove excess skin, and reshape the breasts to sit higher on the chest in a more youthful position. A breast lift is most appropriate for patients with adequate breast tissue volume with ptosis (*Grade 1 and greater*). However it may also be performed in combination with an implant placement to add volume (breast lift—augmentation), to correct asymmetry, or to improve the appearance of in case of a deformity. The drawback is the presence of an incisional scar which may be lollipop shaped or inverted T-shaped. The types of mastopexy are classified by the amount of scars produced, which often are related directly to the amount of lift achieved. The choice of technique (Table 26.4) is determined by the degree of ptosis and the desired size of the breast [11, 12].

General complications due to surgery include bleeding, infection, and problems secondary to anaesthesia. In a study by Stevens et al. among 150 patients who underwent mastopexy, most common complications were poor scarring (6%) and seroma formation (2.7%). The revision rate was 8.6% and 75% of these revisions were for poor scarring [14]. Specific complications include skin necrosis, abnormal sensation/paraesthesia, and asymmetry. Seromas and hematomas are uncommon, but may cause significant problems when they occur. Nipple necrosis which is also uncommon can be a consequence of tension, torsion, pedicle compression, or over-aggressive undermining. The inverted T incision increases the risk of wound dehiscence at the junction of the three limbs. Some degree of asymmetry is almost always

Table 26.4 Different mastopexy types: indications, advantages, and complications [11–13]

Mastopexy type	Indications	Advantages	Disadvantages
Peri-areolar	Grade I or II ptosis, nipple asymmetry	Scar hidden at areolar border, can be combined with augmentation	Flattening, under projection of breast, widened scar, stretching of the areola; highest revision rate
Vertical—SPAIR	All grades of ptosis	Ptosis correction and removal of glandular tissue, little settling	Bottoming out, peri-areolar widening, pleating, suture spitting (suture is pushed out of the skin)
Vertical—Hall-Findlay	All grades of ptosis	Ptosis correction and removal of glandular tissue, structural support of elevated nipple with pillar unification	Final appearance may take months, persistent asymmetry
Wise pattern (inverted T)	Grade II or III ptosis	Greatest control of skin excision relative to parenchyma, easily adapted from reduction techniques, can be combined with augmentation	Largest scar burden, bottoming out-stretching out and lengthening of the lower half of the breast skin

SPAIR short-scar peri-areolar inferior-pedicle reduction

present preoperatively, and discussing this with the patient before surgery is imperative. Other complications include recurrent ptosis, malposition, and scarring. Studies report a higher complication rate with mastopexy-augmentation (1.86%) as compared to mastopexy alone (1.15%) [11–13].

26.4 Non-surgical Breast Augmentation and Breast Lift

Non-surgical breast augmentation procedures have recently gained popularity as non-invasive techniques for aesthetic enhancement of the breast. These modalities provide a cosmetic outcome nearly comparable to surgical augmentation but with a relatively lower rate of complications and an overall good safety profile. However, as with the other techniques, the learning curve is steep and a successful outcome depends on appropriate patient selection, technique, and an experienced cosmetic surgeon. We have classified these modalities (Box 26.1) based on the desired effect on the breast tissue and appearance.

Box 26.1 Non-surgical Options for Breast Lift and Breast Augmentation

Effect on breast	Non-surgical technique
Procedures for firmness/lift	• **Radiofrequency type devices**
	• **Threads**
	PDO (barbed/cogged/multi-cogged)
	• **Laser**
	Dual-laser—Nd-YAG and erbium YAG
	• **PRP**
	• **Botox**
Procedures for augmentation/ enhancement	**Fillers**

26.4.1 Non-surgical Procedures for Breast Firmness and Lift

26.4.1.1 Radiofrequency Type Devices

Radiofrequency (RF) devices thermally induce considerable soft tissue matrix contraction, skin tightening, collagen synthesis, and liquify fat. These effects can be utilized to provide a lift of around 2–5 cm and enhance firmness of the breast, in a non-surgical manner.

26.4.1.1.1 Indications

The ideal candidate for a RF breast lift is someone with a breast size of C-cup or less, and a body mass index of less than 30, presenting with mild to moderate breast ptosis (Grade 1 or 2).

26.4.1.1.2 Contraindications

Pacemaker or internal defibrillator or other internal electronic devices, any metal implants, pregnancy, or breast feeding. Metal implants (such as teeth braces) cannot be located near or in the path between the treatment site and grounding plate.

26.4.1.1.3 Principle

In order for neocollagenesis to occur, the dermal and soft tissue components need to be heated to an optimal temperature range of 60–80 °C and 40–42 °C for the tissue and skin surface, respectively, allowing reorganization of the collagen fibres instead of their destruction.

RF energy causes contraction of the collagen fibres in the superior pole of the breast, thus vertically raising the nipple-areola complex (NAC), and this effect has been successfully used for moderate to mild ptosis (Grade I, Grade II) and early results are encouraging.

Similarly for the inferior pole of the breast, the midline soft tissue can be contracted with RF energy to shorten the transverse length, resulting in reduction of excess tissue in that direction.

Devices available can be monopolar or bipolar, depending on the number of probes utilized [15, 16].

26.4.1.1.4 Types

Bipolar Radiofrequency Device

This minimally invasive procedure is carried out under local anaesthesia or IV sedation and takes less than 3 h to complete. RF energy is transmitted from a generator device platform to a directional handpiece. An internal probe is located in the subcutaneous adipose tissue and the external probe lies in contact with the skin. The thin internal cannula (an ultrathin rod or probe) is inserted into several points on the breast such as the fold, peri-areolar region, via standard access incisions. As the cannula advances through the breast, the external electrode follows its path on the skin's surface, allowing the RF energy to be concentrated between the two parts of the device, allowing all the soft tissue in between the electrodes to treated with the RF, delivering a uniform energy to a large area (Fig. 26.4).

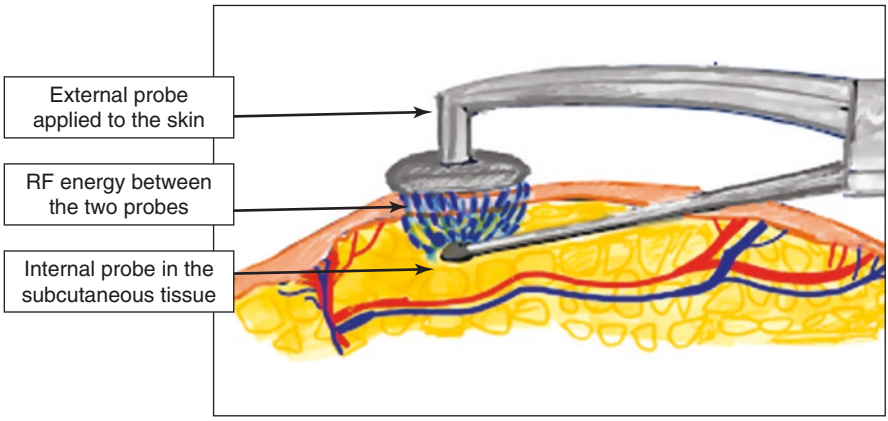

Fig. 26.4 Bipolar radiofrequency device: An internal probe is located in the subcutaneous adipose tissue and the external probe lies in contact with the skin. As the cannula advances through the breast, the external electrode follows its path on the skin's surface, allowing the RF energy to be concentrated between the two parts of the device

The device also has safety features such as real-time impedance and temperature monitoring to minimize the risk of thermal injury. Once the target temperature is reached, the device automatically stops delivering energy. An additional safety feature known as the temperature surge protection ensures that the device continuously monitors the rate of temperature rise so that if a significant temperature increase occurs, energy delivery stops [15, 16].

Monopolar Radiofrequency Device

A monopolar radiofrequency device in combination with ultrasound (Exilis Ultra 360) is a non-invasive modality which enhances breast firmness, provides a lift, and improves the overall shape and contour. It uses a combination of radiofrequency energy [3.4 MHz up to 120 Watts (W)], ultrasound and skin cooling to deliver controlled heating to target deep tissues, as well as the superficial skin. The device comes with a handpiece which is kept in almost constant motion during the procedure. The tip of the applicator at the end of the handpiece uses focused thermal energy to disrupt the triple helix structure of collagen fibres within the skin. The aim of treatment is to raise the temperature at the skin surface to 40–42 °C, perceived as a warming sensation by the patient, for around 4–5 min, to achieve collagen tightening (Fig. 26.5). The healing process promotes neocollagenesis through fibroblast activation, improving the skin texture, reducing the appearance of striae, and wrinkles while providing a skin tightening effect, giving the breasts an overall more youthful appearance [17, 18]. By delivering a continuous emission of radiofrequency and ultrasound waves concurrently, the mechanical effect is more effective than RF alone. The continuous ultrasound produces an increase in temperature which enhances the cell permeability and facilitates the release of growth factors

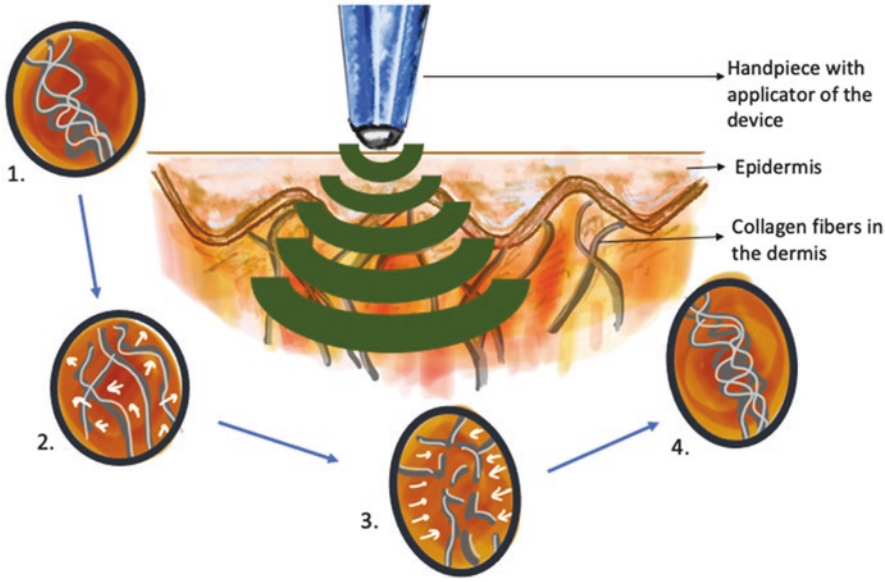

Fig. 26.5 The monopolar radiofrequency device delivers focused radiofrequency energy to the skin and deeper tissues. The thermal energy causes disruption of the normal triple helical structure of collagen (1) and (2); followed by stimulation of fibroblast and neocollagenesis (3); resulting in formation of new collagen fibres in the dermis leading to a skin tightening effect (4)

and platelets across the cell membrane that stimulate fibroblast production [19]. A temperature higher than 42 °C induces lipolysis and is recommended only for specific indication, when a reduction in the breast size is required to enhance the effect of the lift by decreasing the gravitational influence. This can be achieved by maintaining the temperature well beyond 42 °C for a period of 8 min.

The applicator tip has an in-built thermometer which prevents overheating. Another safety mechanism known as "layered advanced cooling" allows the practitioner to precisely regulate the amount and level at which the energy is delivered, ensuring a real-time control of heating and cooling. This prevents pain and burns over the skin, ensures that the treatment is comfortable for the patient, although during the treatment the skin may feel slightly warm [17, 18].

26.4.1.1.5 Procedure

The procedure is carried out without any local anaesthesia or sedation. At the start of the procedure, a grounding plate is placed on the back to enable the RF energy to return to the device after entering the body. A lubricating gel is the applied to the area to be treated to facilitate the movement of the handpiece. The time taken for the session depends upon the size of the area being treated and generally the treatment duration for each breast is 30 min. Changing the power and cooling during

treatment allows the practitioner to treat the deep tissue all the way up to the superficial layer. The treatment starts with the device output at 90 W, surface cooling at 10 °C and deep heating for 5 min followed by 80 W and 15 °C cooling for 5 min, 70 W and 20 °C for 5 min; 60 W and 25 °C for 5 min; 60 W output and 30 °C cooling for next 5 min. The cooling mode is then switched off to allow for surface heating at 60 W output, for the last 5 min of the session to rejuvenate the skin [17, 18].

Results

Two to six sessions once every 2 weeks are recommended and maintenance sessions may be required. The procedure provides real, predictable, and noticeable results (Fig. 26.6). Most patients begin to notice the lift a few weeks after, and it becomes quite evident within 3 months. The firmness and lift may continue to increase for up to 12–24 months, as a result of new collagen formation [17, 18].

The authors have also noted that middle aged women with large, pendulous breasts and a slouching posture with subsequent early signs of cervical spondylitis, who underwent radiofrequency breast lift, noticed subjective improvement in spondylitis as well.

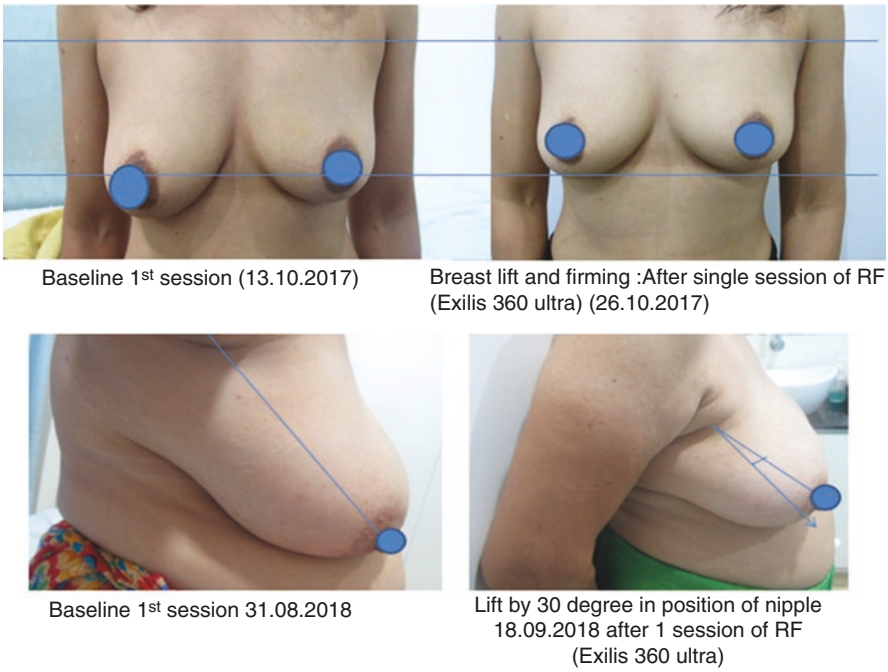

Fig. 26.6 Results 2 weeks after a single session of monopolar radiofrequency breast lift using the Exilis 360 Ultra Device. Visible breast lift seen as lifting of the nipple-areolar complex above the inframammary line. Breast firmness, enhancement in shape and contour was also noted

26.4.1.1.6 Complications

Radiofrequency breast lift is a day care procedure; however, a few days of rest post procedure are recommended to reduce risk of complications and enhance speed of recovery. Complications include bruising, swelling, temporary erythema and tenderness which may last for 1–2 weeks. Seroma, hematoma, infections, and burns are other known complications with the bipolar RF device and these can be managed conservatively. Monopolar radiofrequency, however, is practically devoid of any such side effects. Mild local tenderness can be encountered over treated area by some patients. Inherent risk of burns is minimal due to the in-built device safety mechanisms described above [17, 18].

26.4.1.2 Threads

Thread lift is a new minimally invasive technique that can generate collagen and elastin, offering a subtle and natural looking lift with the effects lasting typically 1–2 years. Thread lift offers a non-surgical alternative to breast lift or mastopexy and may also be used as an adjunct for finer correction after surgery. It may be prudent to avoid surgical breast lift and therefore its associated complications and risks in thin, younger females, those with mild ptosis or minimal breast asymmetry [5, 20].

26.4.1.2.1 Principle

The most commonly used threads are made of PDO (polydioxanone) material, which is considered safe and hypoallergenic. They act as a "scaffold" for the skin, provide support allowing it to hold up against gravity. Various types of threads (Table 26.5; Fig. 26.7) are available; however, cogged threads are commonly used.

Table 26.5 Types of threads

Types of threads	
Barbed threads	
1. Bi-directional thread (long suture)	Inserted into a hollow needle and then placed in the treated area
	Bi-directional thread cannot move in either direction because of the two-way fixation provided by the barbs
2. Uni-directional barbed threads (long suture)	Designed to be anchored to a fixed structure, such as the deep temporal fascia
3. Cogged threads (short sutures)	The cog threads are barbed with different types of barbs and they are used for lifting the tissue and inducing collagenThey come in sharp needle and blunt cannula types
	PDO uni-directional cogged thread
	• PDO bi-directional cogged thread
	• PDO multi-directional cogged thread
Non-barbed threads (smooth thread)	
1. Monofilament plain	The plain thread or Mono is used for collagen induction
2. Bi-filament plain	Applied in a grid pattern or mesh pattern
3. Monofilament (Braided) Screw or Spiral	

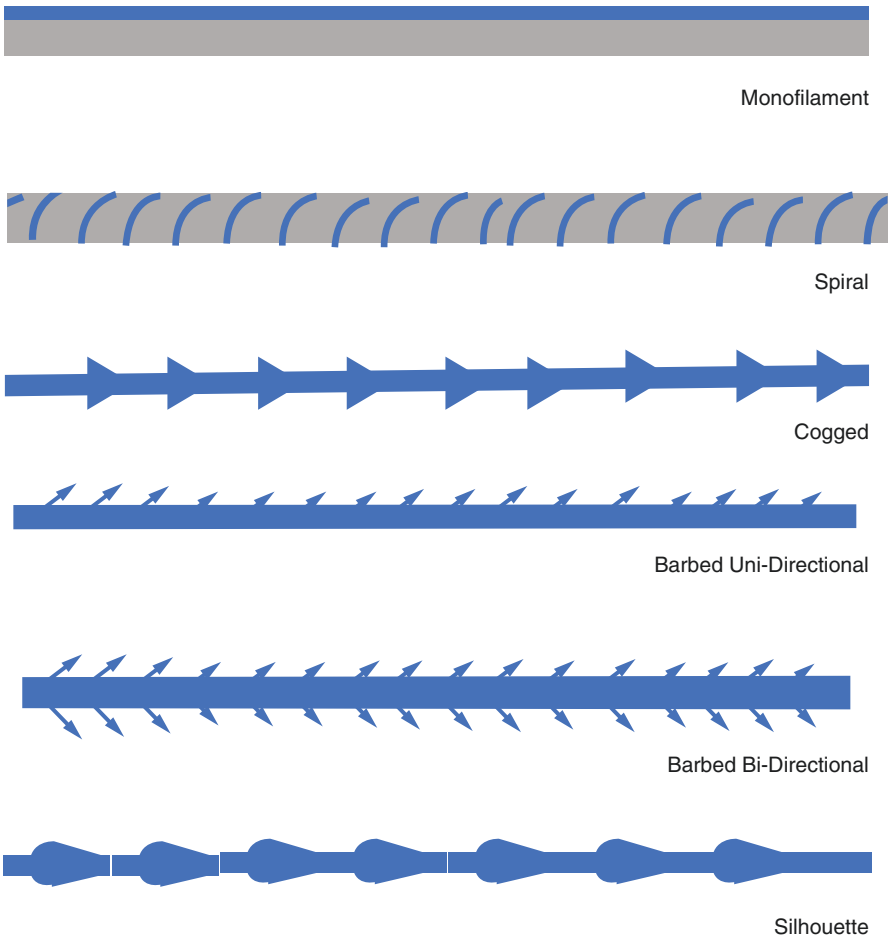

Fig. 26.7 Various types of threads

The threads can be barbed in one direction only (called uni-directional barbed threads), barbed in two directions (bi-directional barbed threads), or non-barbed. Bi-directional threads are preferred as the barbs allow the thread to get locked into the tissue in both directions, anchoring it and providing stability. These barbs also cause micro-abrasions in the tissues, stimulating wound repair and neocollagenesis. Rather than being smooth or barbed, the silhouette threads contain a number of sutures interspersed with small "cones" that are adept at grasping tissue.

PDO also stimulates neocollagenesis, improves elasticity and vascularity of the skin, which goes on continuously, and therefore the results are expected to improve with time (Fig. 26.8). The threads are absorbable and will be reabsorbed in around 4–6 months. The skin structure or scaffold formed remains and continues to support the breast for another 1–2 years. When absorption of the threads is completed, the stimulation effect also stops, and at 18 months we witness a full recovery with a slight increase of fibrous type I collagen [20].

Fig. 26.8 Effects of thread lift

26.4.1.2.2 Indications

Female patients with breast ptosis of grade 1 and 2, breast cup size less than 3, looking for correction of breast ptosis [5].

26.4.1.2.3 Contraindications and Precautions

Pre-existing breast disease or any abnormality detected during a pre-procedure breast examination is considered contraindications for the procedure. Women with severe obesity (BMI > 40 kg/m^2), ptosis of grade 3, breast cup size >3, pregnant, and lactating women and those with a history of keloids are generally not deemed suitable for the procedure.

Precautions prior to the procedure include discontinuing aspirin and other antiplatelet/anticoagulant drugs 3 days before the procedure as they may increase bruising. Antibiotic prophylaxis is advisable and since smoking has a detrimental effect on healing, it may advisable to limit the amount for a few weeks [5, 20, 21].

26.4.1.2.4 Procedure

The patient is treated in a sitting down position and the breasts are taped, using dynaplast to completely encircle the chest, in order to ensure that the chest volume is shifted upwards. The area is thoroughly disinfected using chlorhexidine, especially the peri-areolar region where bacteria are concentrated in and around the tubercles of Montgomery. Each insertion point is anaesthetized with local anaesthetic and adrenaline. The PDO bi-directional cogged threads are inserted using an 18 G blunt needle in the subcutaneous plane in the following manner (Fig. 26.9):

1. U-shaped insertion of three threads in the upper pole of the breast, around 2 cm above the NAC, with an upward pointing vector to circumvent the gravitational pull.
2. Lateral insertion of one thread upwards and laterally traversing from the nipple to the upper outer breast quadrant, in the direction of the axilla.

This provides a three-dimensional lifting effect with the mechanical pull provided by the bi-directionally and helically positioned barbs which strongly anchor into the soft tissue, including the connective tissue septa between the fat lobules, induce traction and hold it into position. This itself provides a 1–2 cm lift to the

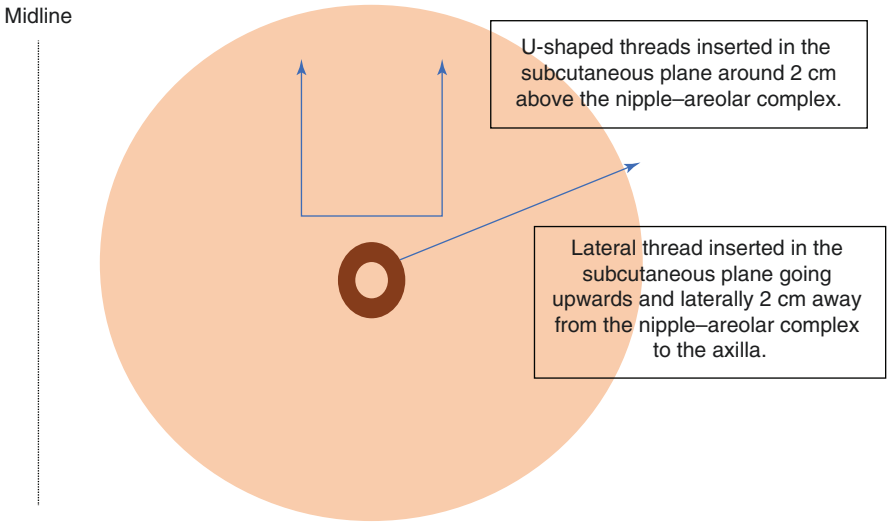

Fig. 26.9 Direction of thread insertion for breast lift

NAC, while rest of the lifting occurs as a result of the new collagen fibre synthesis, due to the fibroblast activation at the entry and exit points in the skin. Advantages of the subcutaneous insertion of threads as advocated by the authors include an instant lift due to the strong mechanical traction induced by the barbs pulling the fat, reduced risk of thread extrusion and foreign body reaction.

Various other techniques have been utilized, particularly with intradermal insertion of threads.

- A *crosshatch technique* for thread insertion is used to create a basket-weave or grid pattern in the upper pole as well below the nipple-areolar complex [5].
- *Overlapping linear threading* to provide a lift along vectors directed upwards against gravity in the upper pole to provide a scaffold has also been suggested.
- Non-barbed monofilament *screw threads* can be used intradermally to induce new collagen synthesis.
- A *weaving pattern* using non-barbed monofilament screw threads with simultaneous and alternate intradermal and subcutaneous thread insertion in a zig zag fashion provides an elastic effect induced by the smaller thread traversing over a large area.

The PDO thread insertion may also be combined with other modalities such as RF assisted breast lift to provide a synergistic effect and enhance the cosmetic outcomes (Fig. 26.10).

The patient can return to her daily activity within days after the procedure. Erythema at the thread insertion sites disappears 3–5 h post-treatment. The breasts remain taped for 48–72 h post-procedure and wearing of a supportive brassiere for 2 weeks is recommended. The procedure involves mild discomfort, some bleeding, and post-procedural bruising for up to 10 days after [5, 20, 21].

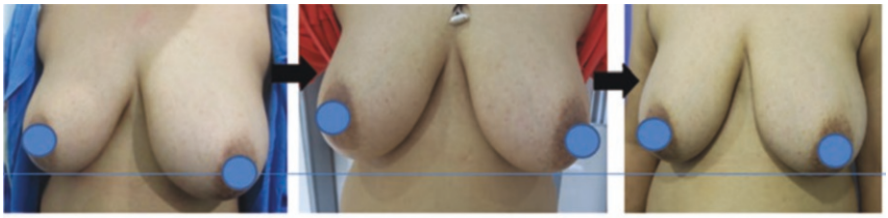

Fig. 26.10 Results after two sessions of monopolar radiofrequency breast lift using the Exilis 360 Ultra Device and Barbed PDO thread insertion. (**a**) Baseline; (**b**) thread insertion; (**c**) after second session of monopolar RF. Visible breast lift seen as lifting of the nipple-areolar complex above the inframammary line. The combined effect of the two treatment modalities provides a better cosmetic outcome as compared to either of these used alone

26.4.1.2.5 Results

The first effects are visible instantly, but considerable improvement appears after 2–3 months, when induction of new collagen begins.

26.4.1.2.6 Advantages

Minimal invasiveness, absence of incisional scar, extremely small incisions at the entry points, minimal risk of bleeding or hematoma formation with instant as well as long-lasting results.

26.4.1.2.7 Complications

- Mild asymmetry, erythema, bleeding, bruising, swelling, and discomfort.
- Pricking from within is the most common complication and is temporary.
- Migration of the thread is possible along with extrusion of the threads.
- Skin dimpling and/or palpation of the thread is possible when the barb of the thread is present close to the skin. Gentle massage of the area will correct the deformity.
- Transient paraesthesia
- Rarely injury to vessels, nerve branches are possible [20, 21].

26.4.1.3 Other Modalities for Breast Lift and Firmness

Recently, various other non-surgical treatment modalities (Table 26.6) are being used to provide a breast lift, firmness as well improve the skin texture, shape, and contour. These include

Table 26.6 Other modalities for breast lift and firmness

Technique	Principle	Indications	Method	Advantages	Disadvantages
Botox breast lift [22]	Botox is injected into strategic points within the pectoralis minor chest muscle	• Ideal for a woman aged 30–50	Botox is injected into the pectoralis minor chest muscle at strategic points	• Non-surgical modality	• Non-FDA approved indication
Breast lift and firmness	It functions by temporarily paralysing chest tissue in those muscles that pull down the breast. This, in turn, forces opposing muscles to strengthen, giving the breast an added lift	• A or B cup breast size		• No incisions	• Safety not established: large amount of Botox needs to be injected to get desirable effect, theoretical risk of respiratory paralysis
		• Temporary, modest or mild improvement in ptotic breasts		• No scars	• Temporary fix-effect lasts only 3–4 months
				• Minimal pain	• Expensive
				• Zero downtime	• No effect on NAC
					• Not suitable for patients with very large breasts
Platelet rich plasma [23, 24] (PRP)	• Activation of growth factors	Women who are not looking to dramatically change the size of their breasts and would desire to have	20 mL of patient's blood is collected, centrifuged, and injected subcutaneously into the necessary areas	Results generally last for 9–18 months	Not recommended for women with:
Breast lift, firmness, and skin rejuvenation	• Activation of multipotent stem cells	• Softer, rounder breasts		• Firmer breasts	• Extreme loss of volume
	• Activation of angiogenic factors	• Improved contour		• Changes in skin texture	• Excessive sagging
	• Stimulates neocollagenesis	• More youthful appearance		• Change in shape of the breast	• Previous breast implants
	• Stimulates neoangiogenesis			• Reduces appearance of striae	
	Results in rejuvenation of breast tissue and skin and increased blood flow				

Dual laser breast lift [25, 26]	Two-step process that induces the superficial tightening and deep tightening of the breast tissue	• Loss of breast volume due to weight fluctuations, ageing, pregnancy, or lactation	• Er:YAG laser is used in the first step to gently tighten the skin	• Non-invasive	Not recommended for women with:
(combination of erbium and Nd:YAG)	• Use of non-ablative Nd:YAG and ablative erbium YAG to non-invasively lift and tighten the skin around the breast tissue	• Breast ptosis	• In the second step the Nd:YAG laser thermally induces the heating of deep tissue	• No downtime,	• Extreme loss of volume
Breast lift and firmness	• The use of dual-laser technology increases the production of collagen and elastin fibres, which helps restore and rejuvenate the dermal structures of the treatment areas	• In women who have had breast augmentation laser breast lifting can help lift and tighten the areas above the implant[a]	• Minimum of three treatments is required, with intervals of every 3 weeks	• Results in no-post-procedure scarring on the breast	• Excessive sagging
			• Maintenance treatments every 6 months to sustain the effects	• Laser breast lifting does not cause any burning or adverse side effects to the breasts	Provides a temporary effect
				• Low risk of skin damage, scarring, infections, and other complications	

[a] All laser breast-lifting patients who have had surgery must wait a total of 12 months before proceeding with laser breast-lifting treatments

- *Botox breast lift* where Botox is injected into strategic points within the pectoralis minor chest muscle, causing its temporary paralysis, and in turn, forces opposing muscles to strengthen, giving the breast an added lift.
- *Platelet rich plasma* or PRP injection which improves not just the breast shape and contour, but also enhances the overlying skin texture, imparting a more youthful appearance.
- *Laser breast lift*: A two-step process that induces the superficial tightening and deep tightening of the breast tissue.

However, with the currently available evidence, the efficacy and safety of these techniques cannot be fully established. These modalities may be used at the practitioner's discretion as an adjunct to the above mentioned procedures or to provide a temporary effect or a quick fix when women are not looking to dramatically change the size of their breasts but desire to have an improved contour and a more youthful appearance.

26.4.2 Non-surgical Procedures for Breast Augmentation

26.4.2.1 Breast Fillers

Injectable hyaluronic acid represents an attractive minimally invasive treatment option for volume restoration or augmentation by providing predictable long-lasting results.

26.4.2.1.1 Principle

Hyaluronic acid, a naturally occurring polysaccharide, is a universal component of all mammalian connective tissues, with a chemical structure that is identical across species, and therefore the possibility for immunologic reactions is minimal when used as a skin filler.

Hyaluronic acid undergoes a natural, slow degradation, circumventing the potential complications associated with permanent fillers. Furthermore, it can be removed easily with the help of hyaluronidase. Hyaluronic acid in fillers works by combining to water in the tissues, imparting a smooth, gel-like consistency after injection. It supplements the intercellular matrix and intradermal tissue in order to restore the lost anatomical structures. It ends to spread uniformly throughout the skin, creating a smooth transition between treated and untreated regions. The biodegradable and biocompatible nature of the gel makes it an ideal, minimally invasive alternative to permanent breast implants [27, 28].

26.4.2.1.2 Indications

Nonpregnant, non-lactating women aged 25–40 years with small breasts (Cup size A-B) and seeking enhancement of breast shape and fullness 1–1.5 cup size increase, with a skin thickness of greater than 2 cm {measured using vernier callipers} are considered ideal candidates [27–30].

26.4.2.1.3 Contraindications and Precautions

Pregnancy and lactation, large sized breasts, ptotic breasts (>Grade 2), unrealistic expectations (anticipating greater than 1 cup size increase in breast size), and pathological findings following pre-treatment mammography/ultrasonography assessment. A known allergy to hyaluronic acid, keloidal tendency, undergoing anticoagulant therapy are other contraindications [27–30].

26.4.2.1.4 Procedure

Current recommendations suggest that all patients undergo a thorough clinical examination and a baseline mammography, and/or ultrasound scans to diagnose any underlying condition, prior to the procedure as concerns have been raised regarding difficulty in diagnosing benign and malignant lesions of the breast after filler injection. Patients aged below 40 years with no identified risk factors for breast cancer were not required to have mammography; however, women aged 40 years and above or with risk factors for breast cancer are required to undergo a mammogram within 1 year of treatment [29].

After explaining the procedure to the patient, an informed consent is taken. The procedure is done with the patient in an inclined position, for better assessment of breast shape. A local anaesthetic agent (0.5% lignocaine) is injected at the entry points to prevent pain during filler instillation. The filler (20–100 mL/breast; with consideration to the cost and individual patient needs) is injected into the subcutaneous plane, above the glandular tissue, using an 18 G blunt canula. Before introducing the filler, the canula must be withdrawn and checked to prevent the inadvertent injection of the filler into a blood vessel. The filler is injected using a fanning technique (3–4 injections parallel to each other), into the upper outer quadrant of the breast. The breast must then be massaged in a downward-medial direction, with the patient in sitting down position in order to flatten out the filler and prevent nodule formation. Each breast can be injected with a maximum of 150 mL filler (although this limit varies, from patient to patient) over multiple sessions spanning across a period of 2–3 months. The patient should be prescribed an analgesic to reduce injection-site pain and a 3-day course of antibiotics. All patients are advised to wear a supportive bra immediately following treatment and avoid strenuous exercise for up to 2 weeks.

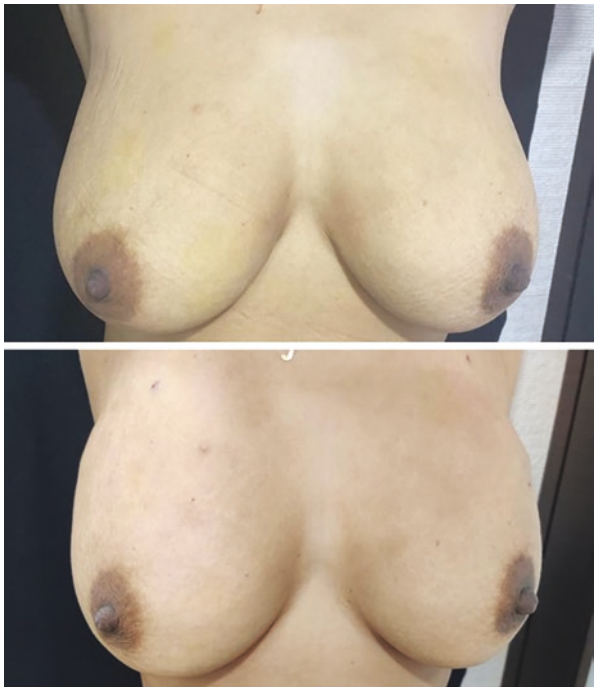

Fig. 26.11 The patients experience an enhanced breast volume (by 1 cup size) along with and overall improved shape and contour, after injection of 20 mL/breast of hyaluronic acid filler (GeneFill)

26.4.2.1.5 Results

The patients experience an enhanced breast volume (by 1 cup size) along with and overall improved shape and contour (Fig. 26.11). This improvement in volume, texture, and firmness is more appreciable upon palpation than on photographic evaluation. Satisfactory cosmetic results last for around 18–24 months, as the gel material is absorbed and degraded gradually. Retreatment can be done as described previously.

In a multicentre study from France, where stabilized HA filler (maximum 100 mL/breast) was injected in 71 women seeking breast enhancement (49—single session, 22—retreatment group) based on subject Global Aesthetic Improvement Scale (GESI) ratings, 36% of breasts in the single-treatment group and 50% of breasts in the retreatment group were improved 24 months after last treatment, but subject satisfaction had returned to baseline levels, even though complete gel degradation did not occur in any subject. Two years after last treatment, the mean percentage of remaining gel was 17% in the single-treatment group and 21% in the retreatment group [28].

26.4.2.1.6 Complications (Table 26.7)

The most commonly reported adverse events include mild to moderate injection-site pain, injection-site reactions described as bruising, swelling, redness, or hardness, which generally resolve in up to 2 weeks. The most frequently reported cosmetic

Table 26.7 Complications of fillers [27–30]

Complication	Clinical features	Prevention	Treatment
Injection-site pain	Mild to moderate pain during procedure and post-procedure	Lignocaine is injected at the entrance site as well as the breast tissue before injection of the filler	Analgesics are prescribed post-operatively
	Generally resolves in 1–2 weeks		Product may have to be aspirated in case the pain does not resolve in 1–2 weeks. Aspirate should be sent for culture
Infection	Fever	Antibiotics (oral/IV)	Filler should be injected under aseptic conditions and devote special attention to the prevention of hematoma formations
	Redness	If there is no improvement with antibiotics:	
	Swelling	Wound irrigation	
	Pain/tenderness	Incision and drainage	
	Difficulty in lifting the arm		
Capsular contracture	A thin capsule forms around the gel leading to breast firmness	Women should be informed before treatment that their breasts could become slightly firmer as a result of capsule formation after the injection procedure	Grade II—Closed capsulotomy
Most commonly reported complication	Grading is done according to the Baker scale as described before		Grade III/IV—Closed capsulotomy, feathering, or aspiration
Dislocation of injected filler	Identification of a subcutaneous nodule/mass outside of the range of injection	–	Aspiration of the dislocated filler with an 18-gauge needle and injection of hyaluronidase should be performed to dissolve any remaining gel
Early degradation of gel	Reduction in the breast volume within 6 months or earlier	Reinjection of fillers	Because a thin capsule forms around the gel after injection, degradation is slower if the gel is injected into a single location rather than dispersed through the breast
			For women who desire larger breasts, filler is injected as a single implant under the mammary gland positioned below the nipple
Firm breasts and nodules	Firmness of the breast and nodules	It should be explained that breast firmness and nodules are transient symptoms and should disappear within 3–4 months of injection	If there is no improvement within 6 months of treatment hyaluronidase may be injected
Visible subcutaneous nodules	Visible/palpable subcutaneous nodules	Massaging the breast after filler injection	• Manual compression for subcutaneous nodules in the superficial subcutaneous layer
			• If nodules are located in the deep subcutaneous tissue and cannot be broken manually aspiration of the gel using an 18-gauge needle under local anaesthesia can be done
			• If there is no improvement after aspiration, hyaluronidase injection should be used to degrade the nodule

adverse events include implant palpability and subcutaneous nodules. Most of the reported adverse events are of mild to moderate intensity, with the majority not requiring any intervention, and undergo resolution within 3–10 months [27–30].

Overall, HA fillers is an outpatient procedure carried out under local anaesthesia, associated with minimal downtime, which serves as a minimally invasive alternative for women seeking enhancement of breast size or shape without having to undergo a major surgical procedure.

26.5 Conclusion

The female breast undergoes several changes throughout life as a result of ageing, hormonal influence, pregnancy, and lactation. The shape of the breast changes with ageing in a manner that the nipple deviates caudally. Breast volume tends to increase with age, an effect probably related to the influence of the downward pull of gravity on the skin or connective tissue. Ageing breasts undergo sagging also known as ptosis, a consequence of parenchymal maldistribution, connective tissue, and skin dysfunction. Breast augmentation (BA) is a surgical procedure where the breast size is enhanced. Surgical BA can be done via the placement of an implant, or less commonly, through fat transfer. A breast augmentation is often performed to replace volume lost from weight loss, breast feeding, or age or to increase the size of the breast for aesthetic reasons. A breast lift or mastopexy is procedure that can lift the nipple, remove excess skin, and reshape the breasts to sit higher on the chest in a more youthful position. A breast lift is most appropriate for patients with adequate breast tissue volume with ptosis. Non-surgical breast augmentation and lift procedures including fillers, radiofrequency based devices, threads, lasers, platelet rich plasma, injection have recently gained popularity as non-invasive techniques for aesthetic enhancement of the breast. These modalities provide a cosmetic outcome nearly comparable to surgical augmentation but with a relatively lower rate of complications and an overall good safety profile. However, as with the other techniques, the learning curve is steep and a successful outcome depends on appropriate patient selection, technique, and an experienced cosmetic surgeon.

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References

1. Abramson RG, Mavi A, Cermik T, Basu S, Wehrli NE, Houseni M, et al. Age-related structural and functional changes in the breast: multimodality correlation with digital mammography, computed tomography, magnetic resonance imaging, and positron emission tomography. Semin Nucl Med. 2007;37(3):146–53.
2. Machida Y, Nakadate M. Breast shape change associated with aging: a study using prone breast magnetic resonance imaging. Plast Reconstr Surg Glob Open. 2015;3(6):e413.
3. Arefanian S, Azizaddini S, Neishaboury M, Zand S, Saadat S, Kaviani A. A study on predisposing factors to breast ptosis. Arch Breast Cancer. 2018;5:63–7. https://archbreastcancer.com/index.php/abc/article/view/196. Accessed 4 Jan 2021.
4. Rinker B, Veneracion M, Walsh CP. Breast ptosis: causes and cure. Ann Plast Surg. 2010;64(5):579–84.
5. Arora G, Arora S. Thread lift in breast ptosis. J Cutan Aesthet Surg. 2017;10(4):228–30.
6. Coleman SR, Saboeiro AP. Primary breast augmentation with fat grafting. Clin Plast Surg. 2015;42(3):301–6, vii.
7. Coltman CE, Steele JR, McGhee DE. Effect of aging on breast skin thickness and elasticity: implications for breast support. Skin Res Technol. 2017;23(3):303–11.
8. Fardo D, Sequeira Campos M, Pensler JM. Breast augmentation. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/books/NBK482206/. Accessed 4 Jan 2021.
9. UpToDate. Implant-based breast reconstruction and augmentation. n.d.. https://www.uptodate.com/contents/implant-based-breast-reconstruction-and-augmentation?source=autocomplete&index=0~1&search=breast%20au#H2003074947. Accessed 4 Jan 2021.
10. UpToDate. Complications of reconstructive and aesthetic breast surgery. n.d.. https://www.uptodate.com/contents/complications-of-reconstructive-and-aesthetic-breast-surgery?search=breast%20augmentation&source=search_result&selectedTitle=4~58&usage_type=default&display_rank=4. Accessed 4 Jan 2021.
11. DeLuca Plastic Surgery. Do I really need a breast lift? n.d.. https://www.delucaplasticsurgery.com/doineedalift. Accessed 17 Jan 2021.
12. Qureshi AA, Myckatyn TM, Tenenbaum MM. Mastopexy and mastopexy-augmentation. Aesthet Surg J. 2018;38(4):374–84.
13. Rohrich RJ, Gosman AA, Brown SA, Reisch J. Mastopexy preferences: a survey of board-certified plastic surgeons. Plast Reconstr Surg. 2006;118(7):1631–8.
14. Emedicine. Breast mastopexy treatment & management: surgical therapy, preoperative details, intraoperative details. 2020. https://emedicine.medscape.com/article/1273551-treatment#d14. Accessed 18 Jan 2021.
15. Theodorou SJ, Del Vecchio D, Chia CT. Soft tissue contraction in body contouring with radiofrequency-assisted liposuction: a treatment gap solution. Aesthet Surg J. 2018;38(suppl_2):S74–83.
16. Edgar J. Everything you need to know about the non-surgical breast lift. Harpers BAZAAR. 2018. https://www.harpersbazaar.com/beauty/health/a22738797/boob-lift/. Accessed 18 Jan 2021.
17. Shaw J. EXILIS 360 skin tightening Wichita KS. shawplasticsurgery.com. n.d.. https://www.shawplasticsurgery.com/plastic-surgery-procedures-wichita/non-surgical-cosmetic-enhancement/exilis-skin-tightening/. Accessed 18 Jan 2021.
18. ConsultingRoom. Exilis elite information. n.d.. https://www.consultingroom.com/treatment/exilis-elite. Accessed 18 Jan 2021.
19. Rock Bottom Lasers. BTL aesthetics exilis ultra body contouring and skin tightening. 2021. https://rockbottomlasers.com/products/2017-btl-aesthetics-exilis-ultra-body-contouring-and-skin-tightening/. Accessed 18 Jan 2021.
20. Serenity MedSpa. MINT™ PDO thread lift: minimally invasive non-surgical thread lift using PDO threads. n.d.. https://serenitymedspa.com/mint-pdo/. Accessed 23 Jan 2021.

21. Cosmetic Plastic Surgeon in Mumbai, India. Facial thread lift surgery. n.d.. https://www.csisite.com/face-threads.html. Accessed 23 Jan 2021.
22. Preminger Plastic Surgery. Botox breast lift FAQ. 2016. https://premingermd.com/2016/04/botox-breast-lift-faq/. Accessed 23 Jan 2021.
23. Art of Beauty. PRP. Plasma therapy method of non-surgical breast lift, REGENLAB® (Switzerland). 2021. http://www.artbeauty.lv/ru/service/prp-method-non-surgical-breast-lift-regenlab-therapy-switzerland/. Accessed 16 Jan 2021.
24. Global Stem Cells Group. Platelet-rich plasma for breast augmentation: how it works. 2018. https://www.stemcellsgroup.com/platelet-rich-plasma-breast-augmentation-works/. Accessed 16 Jan 2021.
25. Dr. Torgerson. Laser breast lifting – FAQ – Part 1. 2021. https://drtorgerson.com/non-surgical-procedures/fotona-laser-treatments-toronto/laser-breast-lifting-faq-part-1/. Accessed 16 Jan 2021.
26. Toronto Facial Plastic Surgery and Laser Centre | Dr. Torgerson. How does laser breast lifting work? n.d.. https://drtorgerson.com/non-surgical-procedures/fotona-laser-treatments-toronto/how-does-laser-breast-lifting-work/. Accessed 23 Jan 2021.
27. Hedén P, Sellman G, von Wachenfeldt M, Olenius M, Fagrell D. Body shaping and volume restoration: the role of hyaluronic acid. Aesthet Plast Surg. 2009;33(3):274–82.
28. Hedén P, Sarfati I, Clough K, Olenius M, Sellman G, Trevidic P. Safety and efficacy of stabilized hyaluronic acid gel for breast enhancement. Plast Reconstr Surg Glob Open. 2016;3(12):e575. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727684/. Accessed 24 Jan 2021.
29. Inglefield C. Early clinical experience of hyaluronic acid gel for breast enhancement. J Plast Reconstr Aesthet Surg. 2011;64(6):722–9.
30. Hedén P, Olenius M, Tengvar M. Macrolane for breast enhancement: 12-month follow-up. Plast Reconstr Surg. 2011;127(2):850–60.

Chapter 27
Vaginal Rejuvenation

Suruchi Garg, Anuva Bansal, and Manjot Kaur Marwah

27.1 Introduction

Vaginal rejuvenation (VR) is a treatment modality for women which includes procedures aimed at enhancing vaginal aesthetics and functionality. The term may encompass several procedures that target the overall vulvovaginal appearance, and the term vulvovaginal rejuvenation (VVR) better describes the aim of these techniques. These can be surgical (e.g. vaginoplasty, labia minoraplasty, labia majoraplasty, clitoral hood reduction, clitoral unhooding, lipofilling, and hymen reconstruction) or nonsurgical (e.g. energy-based treatments, platelet-rich plasma and fillers) interventions. Ageing, menopause, pregnancy, obesity, and many other factors contribute to vulvovaginal laxity (VVL), changes which considerably affect a woman's quality of life. VR therefore not only provides cosmetic enhancement but also improves functionality and has been known to positively impact self-esteem. Traditionally, women with VVL have been offered options ranging from Kegel exercises, which are often less effective, to traditional invasive surgery. Surgical procedures require a significant amount of recovery time and may result in complications such as dyspareunia in a significant number of patients.

With the growing need for VR, minimally invasive alternatives have emerged in recent years. Novel technology is permitting us to use minimally invasive methods

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of treating VVL and atrophy without the need for traditional surgery, and numerous studies have reported the gaining interest and popularity of these procedures amongst women.

27.2 Anatomy of the Female Genitalia and Age-Related Changes

The vagina is a part of the internal female genitalia while the vulva, or external genitalia, consists of the mons pubis, labia majora, labia minora, clitoris, vaginal introitus, and the urethral orifice (Fig. 27.1). The external genitalia receive sensory innervation via the branches of the pudendal nerve—the superficial and deep perineal nerves. The region receives blood supply from the branches of the internal pudendal artery with the majority of the supply to the labia minora entering posteriorly. The vaginal wall is composed of a superficial layer of nonkeratinized, squamous epithelium with a significant moisture content. Lubrication of the vagina occurs primarily through secretions from Bartholin glands and the cervix. The surface of the vaginal canal is covered in folds known as rugae that permit distention during intercourse and childbearing. Deeper layers of the vaginal wall consist of dense connective tissue, smooth muscle, collagen, and elastin, which are responsible for vaginal wall strength and elasticity. Underneath the epithelium is the

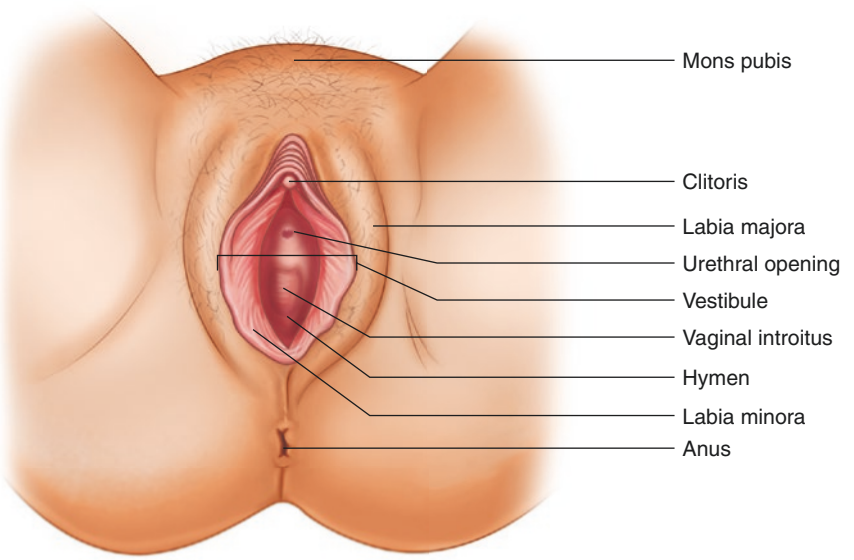

Fig. 27.1 Structure of the female external genitalia: The vagina is a part of the internal female genitalia while the vulva, or external genitalia, consists of the mons pubis, labia majora, labia minora, clitoris, vaginal introitus, and the urethral orifice

Table 27.1 Age-related changes of the external genitalia

Age-related changes of the external genitalia	Causes
Decrease in thickness of vulvar epithelium	Oestrogen influences vulvar thickness; oestrogen levels decrease with age
Pale appearance of external genitalia	Reduced vascularity due to decreased oestrogen
Decrease in tone and volume of labia majora	Decreased oestrogen leads to loss of subcutaneous fat, decreased elasticity
Labia minora appear larger	

muscularis, which consists of an inner circular and outer longitudinal layer of smooth muscle. The external most fascial layer is the adventitia that is adherent to the muscularis [1].

Vaginal mucosa undergoes cyclical changes associated with the menstrual cycle. As oestrogen production reduces with age, significant changes occur in the female genital tract including the loss of vaginal elasticity, decreased rugosity as well as vaginal wall atrophy leading to laxity and thinning. These changes can be attributed to a decreased collagen and elastin content. Blood flow and secretions in the vagina also reduce as a result of diminished oestrogen levels. Post-menopausal vaginal mucosa has a lower moisture content, which may have an impact on the efficacy and safety of treatment modalities such as lasers that utilize water as a chromophore [1, 2]. Similar changes are observed in the external genitalia which also express oestrogen receptors. The vulva becomes atrophic and thus prone to a myriad of issues experienced by post-menopausal woman (Table 27.1). The skin of the mons and labia majora consists of keratinized squamous epithelium, dermis, and subcutaneous tissue, a composition similar to the skin of rest of the body such as the face, hands, or chest. The labia minora on the other hand are lined by moist, nonkeratinized epithelium with sebaceous and mucous producing glands.

A knowledge of the anatomy of the external female genitalia is essential to effectively providing rejuvenation treatments in this area. Before initiating treatment, it is imperative to exclude pelvic organ prolapse by differentiating between vaginal laxity and the protrusion of genitopelvic structures into the vaginal canal, since there is uncertainty regarding the efficacy of nonsurgical vaginal rejuvenation in efficiently correcting severe prolapse, as suggested by current studies [2, 3].

27.3 Vaginal Rejuvenation

Vaginal rejuvenation (VR) is a treatment modality for women desiring restoration of youthful appearance and function of their genitalia. The term vaginal rejuvenation encompasses procedures that enhance vulvovaginal aesthetics and functionality. Procedures include *surgical* (e.g. vaginal tightening, labia minoraplasty, labia majoraplasty, clitoral hood reduction, clitoral unhooding, lipofilling, and hymen

Table 27.2 Procedures for vaginal rejuvenation

Procedures for vaginal rejuvenation	
Surgical vulvovaginal rejuvenation	Vaginal tightening
	Labia minoraplasty
	Labia majoraplasty
	Clitoral hood reduction
	Clitoral unhooding
	Lipofilling or fat grafting
	Hymen reconstruction
Nonsurgical vulvovaginal rejuvenation	**Radiofrequency devices**
	Lasers
	• Fractional CO_2 laser (10,600 nm)
	• Er:YAG laser (2940 nm)
	• Intense pulsed light (500–1400 nm)
	Fillers
	PRP
	Physical devices
	• Micromesh
	• Silicone threads

reconstruction) or *nonsurgical* (e.g. energy-based treatments, platelet-rich plasma [PRP], and fillers) interventions (Table 27.2).

Ageing, menopause, pregnancy, obesity, and several other factors contribute to vulvovaginal laxity (VVL) and vaginal atrophy (VA), changes which have a considerable bearing on a woman's quality of life. VR therefore not only provides cosmetic enhancement but also improves functionality and has been known to positively impact self-esteem [4–6].

27.3.1 Surgical Vaginal Rejuvenation and Female Genital Cosmetic Surgery

Surgical vaginoplasty refers to surgical vaginal tightening via the reduction of the vaginal diameter and the correction of vaginal damage or deformity. The procedure may be performed under local or regional anaesthesia. Complication rates of surgical vaginoplasty vary from 2% to 3.77% and include dyspareunia, low lubrication, constipation, wound infection, haemorrhage, suture dehiscence, prolonged pain, and wound rupture [6]. Vaginoplasty and perineoplasty constitute only a small aspect of female genital cosmetic surgery (FGCS), a term encompassing several techniques aimed at improving the vulvovaginal aesthetics and functionality [7]. The details of these procedures have been outlined in Table 27.3.

Table 27.3 Surgical vulvovaginal rejuvenation [7, 8]

Surgical technique and indications	Procedure	Result	Complications
Hymenoplasty (Fig. 27.2)	• The mucosa of PVW is tightened by creating rugae	Restoration of hymen	Pain
In young females for revirginization			Discharge (blood stained)
Vaginoplasty	Posterior vaginoplasty involves dissection of the posterior vaginal epithelium and trimming of tissue to the desired diameter. Rectovaginal muscularis is plicated creating a narrower diameter similar to traditional colporrhaphy	• Improves vaginal sensation	• Dyspareunia
Tightening of the vaginal opening and canal		• Improves sexual function	• Postop bleeding
		• Improves aesthetic appearance	• Pain
			• Over-tightening of the introitus
			• Bowel or bladder injury
Perineoplasty	Perineoplasty tightens the perineal muscles and the vagina in an effort to decrease the size of the vaginal opening	• In women with vulvar vestibulitis, relief of preoperative vulvar discomfort	• Poor wound healing
Surgical reconstruction of the vaginal introitus and is often part of a complete vaginoplasty repair	• Removal of a diamond-shaped wedge of tissue on the perineum above the anus	• Relief in dyspareunia	• Dyspareunia
Perineoplasty is often performed with a posterior colporrhaphy	• Lateral borders of the resected tissue extend to the hymeneal ring or a few centimetres past it		• Postop bleeding
	• Bulbocavernosus and superficial transverse perineal muscles are reapproximated to produce an elevated perineum, tightened vaginal orifice, and reconstructed perineal body		• Pain
			• Over-tightening of the introitus
			• Bowel or bladder injury with resultant fistula formation
Labiaplasty	• *Labia minora linear resection* with reapproximation of the epithelial edges	Preserves the contour of the lips and maintains the labial edge colour	• Infection

(continued)

Table 27.3 (continued)

Surgical technique and indications	Procedure	Result	Complications
Procedure to reduce the size and shape of either the labia majora or the labia minora	• *Wedge resection*—V-shaped centre portion of the labia minora is resected, edges reapproximated	Improved self-esteem and sexual function	• Hematoma
The mean width of the labia minora is 2.5 cm with a range of 7 mm to 5 cm	• *Inferior wedge resection*—V-shaped wedge excision of the inferior portion of the labia minora		• Asymmetry
	• *Elliptical or curved linear resection (amputation technique)*		• Poor wound healing
	• Removes protuberant tissue followed by over-sewing of the edge (Fig. 27.3)		• Wound separation
	• Goal—maintain a minimum labial length of 1 cm and permit protrusion past the introitus		• Over-zealous resection
			• Urinary retention
			• Delayed local pain
			• Dyspareunia
Clitoral hood reduction	• Clitoral hood reduction involves excision of excess skin in the fold surrounding the clitoris; involves wedge resection labiaplasty (WRL) followed by bilateral fusiform excision of excess lateral clitoral hood skin	Improves sexual function/ gratification	• Clitoral hood skin can become large and oedematous, resulting in re-formation of excess skin
Procedure to separate the prepuce from the clitoral tissue	• WRL is performed to reduce the size of the clitoral hood as well as the overall size of the labia minora	Helps alleviate	• Pain
The main surgical goal: decrease the length, protuberance, and thickness of the clitoral prepuce, or to remove redundant clitoral hood folds	• The ablated or excised exterior wedge sections of labial tissue are extended to include redundant clitoral prepuce tissue	• Coitus due to a trapped clitoris	• Denervation injury
	• Clitoris must not over-exposed, which potentially could raise the risk of hypersensitivity	• Interference with exercise	• Adverse effects on orgasm
		• Hygiene concerns	• Risk of hypersensitivity on overcorrection
Labia majora augmentation	• Autologous fat is injected into the subcutaneous fat layer of the labia majora where it serves as a filler	Enhances the	• Palpable fatty cysts

Table 27.3 (continued)

Surgical technique and indications	Procedure	Result	Complications
Hypotrophic labia majora may be too small to cover the labia minora, thus making the minora look unusually large. Atrophy of the labia majora can cause exposure of the labia minora, resulting in dryness	• Purified fat is collected from body sites or via liposuction and processed	• Volume	• Increased perspiration
	• In the syringe technique, the harvested fat is put in a small diameter blunt cannula connected by tubing to a 10–20 cm^3 Luer–Lock syringe for injection	• Shape	• Appearance of a 'camel toe' (referring to the outline of the labia majora in tight clothing)
	• The harvested fat is mixed with autologous PRP in a 4:1 ratio and injected using an 18-gauge blunt cannula subcutaneously about 20 mL in a fan-like pattern through 1-mm incisions per labium majorum	• Symmetry • Firmness • Contour of atrophied labia majora to repair sagging, lax, wrinkled skin	

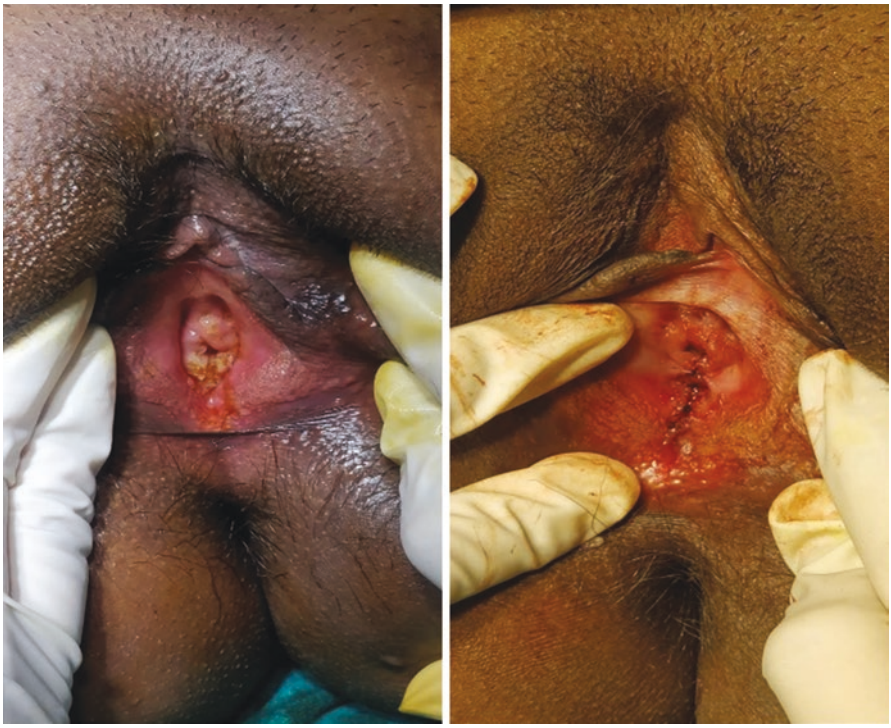

Fig. 27.2 Hymenoplasty—The mucosa of posterior vaginal wall is tightened by creating rugae

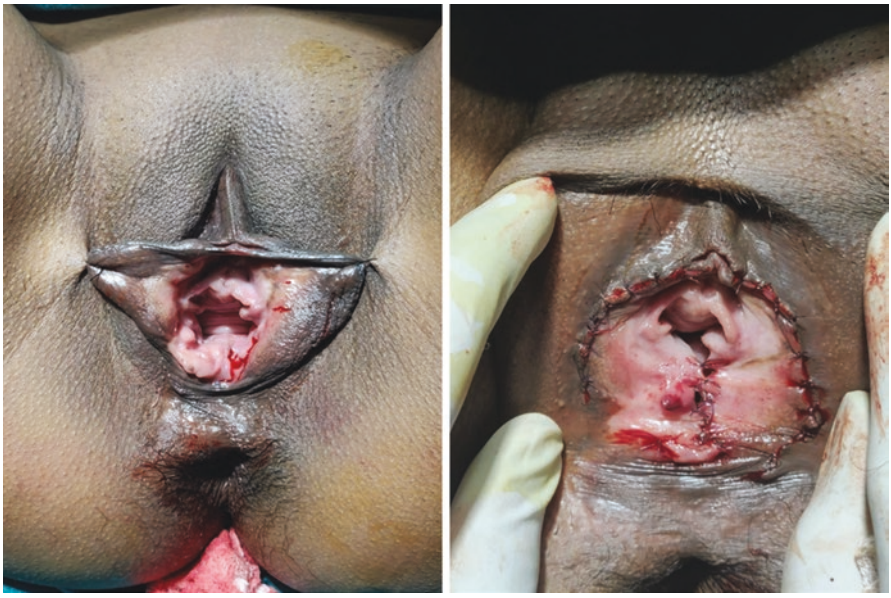

Fig. 27.3 Elliptical or curved linear resection (amputation technique) for labiaplasty. The protuberant tissue is removed followed by over-sewing of the edge. The goal is to maintain a minimum labial length of 1 cm and permit protrusion past the introitus

27.3.2 Nonsurgical Vulvovaginal Rejuvenation

Nonsurgical Vulvovaginal Rejuvenation (NVR) provides a minimally invasive alternative for women with aesthetic and/or functional problems of the external genitalia or urinary tract. Indications for NVR include VVL, VA, and genitourinary syndrome of menopause (GSM) (Table 27.4).

Vulvovaginal laxity (VVL) refers to the expansion of the vaginal introitus as a result of stretching associated with a vaginal delivery. With childbirth and ageing, vaginal atrophy ensues as a result of the decrease in the vaginal muscle tone, loss of rugosity, and thinning of the vaginal wall. These changes manifest as abnormal or decreased genital sensation, sexual dysfunction, and/or urinary incontinence. Both these entities can occur in pre-menopausal as well as post-menopausal women and differ from the genitourinary syndrome of menopause, which occurs exclusively amongst post-menopausal females and is characterized by symptoms beyond VL and includes urinary complaints-stress urinary incontinence, recurrent urinary tract infections, and/or painful micturition. It is important to distinguish these conditions from genital prolapse which is characterized by the bulging of the pelvic organs into and sometimes outside the introitus, as NVR provides limited success in such cases [4, 6, 7].

Techniques for NVR include *energy-based procedures* including radiofrequency (RF) based devices and lasers (Ablative Fractional CO_2 Laser and Nonablative Er-YAG laser). These procedures produce vaginal tightening via the heat-induced

Table 27.4 Indications for nonsurgical vulvovaginal rejuvenation [3–6]

Indications for nonsurgical vulvovaginal rejuvenation	Pathophysiology	Symptoms/signs
Vulvovaginal laxity	• Stretching and expansion of the vaginal introitus, often attributed to vaginal childbirth	• Vaginal laxity
	Can be experienced by both pre- and post-menopausal women	• Dryness and vulvovaginal atrophy
		• Itching
		• Pain during urination
		• Pain during intercourse
		• Orgasmic dysfunction
		• Changes in genital sensation
		• Urinary incontinence
Genitourinary syndrome of menopause	Myriad of symptoms associated most commonly with post-menopausal hormonal changes in oestrogen	Includes changes beyond laxity and involves urinary symptoms
		• Stress urinary incontinence (SUI)
		• Recurrent urinary tract infections
		• Pain with urination
Vulvar changes	• Ageing or rapid weight loss causes a loss of hyaluronic acid, dermal collagen, and fat in the labia majora leading to potential laxity of the labia majora, decreased volume, wrinkles, discolouration, and sometimes reduced skin elasticity	• Hypotrophic labia majora may be too small to cover the labia minora, thus making the minora look unusually large. Atrophy of the labia majora can cause exposure of the labia minora, resulting in mucosal dryness
	• Labia minora may protrude past the labia majora or may be disproportionally larger than the labia majora	• Aesthetic concerns
		• Sexual dysfunction
		• Reduced self-esteem

stimulation of neocollagenesis, neoelastogenesis, and neovascularization, restoring the vaginal epithelium and improving the symptoms associated with VVL and GSM (Fig. 27.4).

Other techniques include fillers, platelet-rich plasma therapy, and threads [6].

27.3.3 Concerns Regarding Safety

In 2018, US FDA expressed concerns over the advertising of lasers and energy-based devices for non-FDA-approved indications including vaginal rejuvenation as well as vaginal cosmetic procedures aimed at enhancing sexual function, urinary incontinence, and GSM.

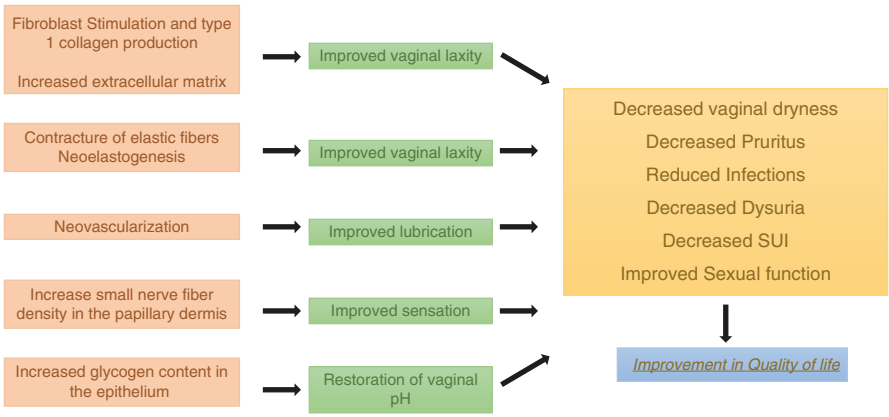

Fig. 27.4 Energy-based nonsurgical vaginal rejuvenation: mechanism of action

Furthermore, FDA issued a warning stating that procedures may cause significant adverse events including chronic pain, numbness, burning, bladder symptoms, infections, scarring, dyspareunia, worsening symptoms, exacerbation of lichen sclerosis, and deformity. A paucity of data exists about the efficacy and safety of these procedures. Potential complications of these treatments include tissue damage, adhesions, scarring, altered sensation, dyspareunia, and infection. Current recommendations encourage detailed discussion with the patient regarding the long-term implications of these complications, before undergoing these procedures. Existing studies suggest that energy-based devices are promising nonsurgical alternatives, which can help enhance vaginal function and improve the quality of life for women. However, large-scale randomized trials with long-term follow-up are essential to compare these procedures with standard therapies, and to ascertain the safety of these techniques [9].

27.3.4 Patient Evaluation

A thorough history, examination, and detailed patient evaluation is necessary before planning NVR (Table 27.3). This should focus on reviewing the patient's symptoms, assessing the associated signs, and doing certain investigations, if necessary. Since there are no objective parameters to assess VVL, VA, or GSM a careful history and examination is paramount. These findings can be augmented by utilizing self-reported patient questionnaires to assess individual experiences of VL and vulvovaginal symptoms, as the diagnosis of GSM or VL largely rests on patient-reported symptoms [1, 10, 11].

27.3.5 Techniques for Nonsurgical Vaginal Rejuvenation

27.3.5.1 Energy-Based Devices

Radiofrequency and laser devices are the main energy-based devices being used for NVR. No device is currently FDA approved for the treatment of vaginal laxity, though international bodies have varying levels of sanctions [1].

27.3.5.1.1 Radiofrequency Devices

Principle

Radiofrequency devices emit focused electromagnetic waves that heat underlying tissues, without targeting melanin. At tissue temperatures of 40–45°, fibroblasts are stimulated leading to neocollagenesis, as well as neovascularization, which assist in replenishing the elasticity and moisture of the vaginal mucosa, as well as lead to the proliferation of glycogen-enriched epithelium. RF devices can be unipolar, monopolar, bipolar, or multipolar (Box 27.1, Table 27.5) based on the variations in how the electric current travels from the device through the tissue and between the electrodes or back to a grounding pad. Monopolar devices have a greater depth of penetration as compared to bipolar and multipolar devices, with monopolar units penetrating 20–25 mm and bipolar RF reaching depths of approximately 2–8 mm. Temperatures greater than 45 °C may lead to thermal damage and pain. Devices are commonly equipped with cooling probes and reverse-heating gradients to protect the surface mucosa while deeper tissues are heated, and to decrease the pain during treatment [6, 11].

Box 27.1 Types of Radiofrequency Devices for Nonsurgical Vaginal Rejuvenation [1, 6, 11]

Radiofrequency devices for nonsurgical vaginal rejuvenation
• Monopolar RF with cooling probe
• Monopolar RF with ultrasound, no cooling probe
• Bipolar RF, no cooling probe
• Unipolar RF, no cooling device

Technique

Electronic implants, metal implants, bleeding disorders, IUDs, pregnancy and menstruation are contraindications for the procedure.

The procedure is carried out with the patient in a lithotomy position, and a grounding pad placed on them. No anaesthesia is required and the procedure is well tolerated. The patient is asked to cleanse the skin thoroughly, shave areas with excess hair, and avoid applying any lotion to the area of treatment. The monopolar RF device with ultrasound uses two attachments to address the two target areas, the

Table 27.5 Patient evaluation for NVR [1, 10, 11]

Patient evaluation prior to non-vaginal rejuvenation	
History	
Genitourinary syndrome of menopause (GSM)	• Menopausal women
	• Laxity, dryness, itching, urinary incontinence, pain
	• Vulvovaginal Symptom Questionnaire
	– Quality of life impact of physical vulvovaginal symptoms (like dryness, pain, burning, and itching)
	– Emotional and sexual concerns associated with GSM
Vaginal laxity (VL) and vulvar changes	• Self-reported vaginal laxity during intercourse
	• Pre-menopausal women with history of vaginal childbirth
	• Not all patients with VL will have vulvar change (atrophy, pigmentation, labia majora hypotrophy, labia minora hypertrophy) and vice versa
	• Vaginal Laxity Questionnaire—7-point Likert scale from 'very loose' to 'very tight'
Urinary incontinence	• Previous assessments of urinary incontinence and a history of urodynamic testing in the past should be obtained
	• A surgical history including any specific uro-gynaecologic or vaginal procedures should be documented
	• Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7)
Sexual or orgasmic dysfunction	Assess for any concomitant diagnoses of sexual disorders:
	• Nonspecific pelvic pain
	• Vulvodynia
	• Vaginismus
	These patients may not tolerate NVR procedures
	• Patients with isolated orgasmic dysfunction may be suitable candidates
	• Female Sexual Function Index (FSFI)—assesses the domains of desire, arousal, lubrication, orgasm, satisfaction, and pain
	• Female Sexual Distress Scale Revised (FSDS-R)—assesses patients' distress with sexual activity
Sexual history	• History of active sexually transmitted diseases
	• Documentation of medications that are known to affect sexual function
Oncologic history	History of
	• Breast cancer
	• Treatment status
	• Endocrine therapy
	• Surgical menopause
Others	• Hormone supplement use
	• Oral contraceptive use
	• Pregnancy history
	• Current pregnancy

Table 27.5 (continued)

Patient evaluation prior to non-vaginal rejuvenation	
Examination and Investigations	
Pelvic organ prolapse	• Should be ruled out
	• Internal organs will be found to push on the vaginal walls
Vulva	• Signs of atrophy
Vaginal pH	• pH increases outside the range of normal (pH 3.5–4.5) in atrophy
Pregnancy	• Urine pregnancy test must be done to rule out pregnancy
Biopsy	• Abnormal or suspicious lesions

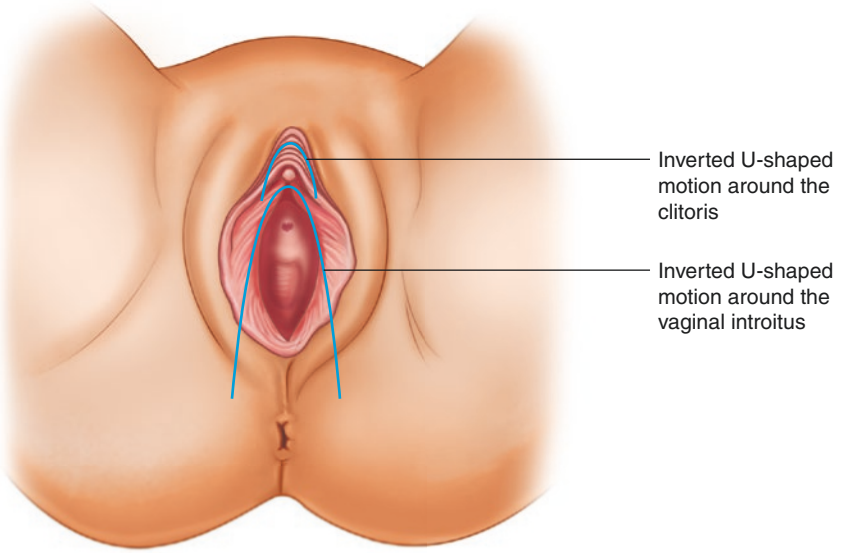

Fig. 27.5 The handpiece is moved in two semi-circular or inverted U-shaped motions around the clitoris and around the vaginal introitus while avoiding direct energy delivery to the clitoris and the urethra. The focused thermal energy disrupts collagen fibres causing them to unwind and the natural healing process stimulates fibroblasts to produce new collagen

vaginal canal and the labial area. An aqueous gel is first applied to the external genital area to be treated. RF energy (80–90 J/cm^2) is delivered in pulses for 12 min. The hand piece is moved in two semi-circular or inverted U-shaped motions around the clitoris and around the vaginal introitus while avoiding direct energy delivery to the clitoris and the urethra (Fig. 27.5). The focused thermal energy damages the collagen fibres causing them to unwind and the natural healing process stimulates neocollagenesis and increases tissue vascularity to the pubic mound, labia, clitoris, and perineum leading to rejuvenation and heightened sensitivity [6, 11–13].

When targeting the vaginal canal, a different tip is used and inserted to access the entire vaginal canal. Internal therapy utilizes a single-use applicator tip that directs the energy towards the entire circumference of the vaginal wall simultaneously. The patient feels the insertion of the probe, then a comfortable warmth as it is introduced and withdrawn from the apex to the hymenal ring at the introitus. The tip comes in

two sizes (24 and 30 mm diameter) ensuring complete contact with the vaginal wall for a complete treatment of the lamina propria, providing a homogeneous distribution of heat throughout tissue. The therapeutic temperature remains maintained (between 40 and 43 °C) during the treatment duration of 8 min. No pain or irritation is experienced during the procedure; however a warming sensation is felt. One treatment session lasts around 20–30 min, inclusive of the external and internal rejuvenation. Mild redness and swelling may occur in the treatment area, which usually disappears within a few hours. Patients can return to their normal activities immediately after the procedure. However, it is recommended to avoid from sexual intercourse for a week after treatment.

Three to four such sessions, scheduled 1–2 weeks apart, are recommended to attain the best results. Some improvement can be perceived immediately after treatment, with the complete results being achieved around a month after the last treatment session, as the collagen continues to rebuild. Maintenance treatments may be recommended in every 6 months or annually, depending on the patient's individual need [1, 6, 11–13]. Important features of RF-based NVR have been summarized in Box 27.2.

Box 27.2 Summary: Salient Features of Radiofrequency-Based Nonsurgical Vulvovaginal Rejuvenation

Salient features of RF devices for NVR
Patients who benefit most include those with:
• Mild-to-moderate SUI
• Overactive bladder
• Vaginal dryness
• Decreased lubrication
• Orgasmic dysfunction
• Grade 1 prolapse
• Vaginal laxity
Outpatient procedure
Device size and portability
Monopolar Devices—large and non-portable
Bipolar and Other RF Devices—portable
Small disposable handpiece
Monopolar—same handpiece for vulva and vagina
Bipolar—separate handpieces for vulva and vagina
Requires no anaesthesia
No pain during the procedure
Mild sensation of heat/mild discomfort
Procedure duration is 15–30 min
No downtime
Daily activities can be resumed immediately
Effects last for 12 months
Sittings
Monopolar: 3–4 sittings at monthly intervals
Bipolar: 4–6 sittings at 2–3-week intervals
Multipolar: 3 sittings, each a week apart

Results

The procedure improves the vascularity of the treated areas and stimulates production of collagen and elastin, resulting in the tightening of the vaginal introitus, increase in the natural lubrication and enhanced genital sensation. Similar enhancement in tautness and firmness are also observed in the labia. Many patients also experience significant improvement in stress incontinence and relief from pruritus, dryness, and dyspareunia. Various studies report statistically significant improvement in vaginal laxity (including improvement in tightening, lubrication, and sensitivity), sexual function and/or satisfaction (assessed using various questionnaires or sexual scores and average time to orgasm), vulvar appearance, and relief in symptoms of stress urinary incontinence [1, 4, 6].

Based on our experience with monopolar RF-based NVR, amongst ten women we observed that the pigmentation and skin texture improved after the second session; appreciable improvement in urinary continence was also observed after the first session, while sexual function improved after the second or third session (Table 27.4). One patient underwent a maintenance session at 10 months follow-up, as she reported reappearance of symptoms associated with VVL (Fig. 27.6).

Complications

Probable complications of vaginal burns, scarring, dryness, infection, altered sensation, dyspareunia, adhesions, chronic pain, or vaginal stenosis over time may occur leading to sexual dysfunction or worsening of quality of life [1, 4].

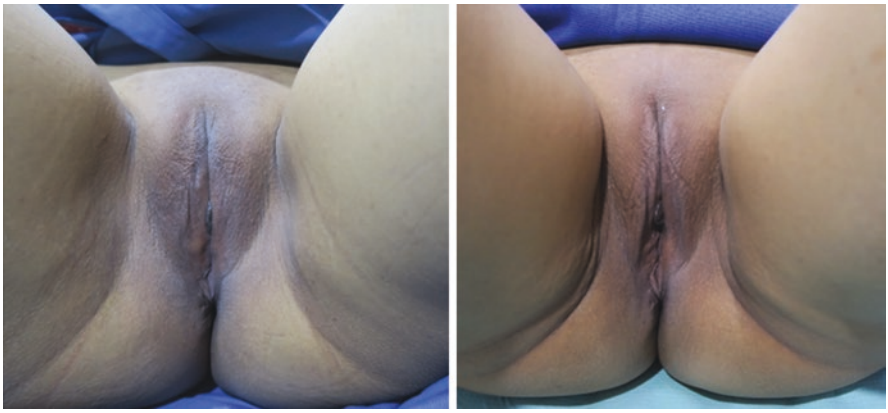

Fig. 27.6 Results of NVR using 3 sessions of Monopolar RF. Improvement in the vulvar appearance, firmness, and tautness along with relief in symptoms associated with vulvovaginal laxity was observed

27.3.5.1.2 Lasers

Several lasers have emerged including microablative fractional CO_2 (10,600 nm), nonablative Er:YAG (2940 nm), and hybrid fractional lasers (2940 and 1470 nm) and provide a noninvasive means for treating NVR. Salient features of lasers for NVR have been outlined in Box 27.3 and Table 27.6.

Box 27.3 Salient Features of Laser Devices for NVR

Salient features of laser devices for NVR
Outpatient procedure
Device size and portability
Large and non-portable
Handpiece
• Large, barrel-shaped hand pieces with disposable sleeves that are attached to an articular arm
• Separate probe for vulva
Requires no anaesthesia
Pain near introitus; hence, need to decrease energy in that area
Procedure duration is 8–20 min
Downtime
Sexual intimacy after 3 days
Effects last for 12 months
Sittings
CO_2 Laser: 3–4 sittings at 4–6-week intervals
Er-YAG laser:
• 2 sessions at 8 weeks interval
OR
• 3 sessions at 2 weeks interval

CO_2 Laser (Ablative)

Principle

Fractional CO_2 laser (10,600 nm) provides targeted energy delivery and utilizes water as a chromophore. These devices can penetrate approximately 20–30 μm of tissue in less than 1 ms and generate controlled and confined thermal damage to a 100- to 150-μm-thick section of tissue known as the microthermal zone, while preserving the surrounding healthy tissue. The energy causes heating up of underlying tissues to 45–50 °C and these ablated areas undergo wound healing which stimulates neocollagenesis and neovascularization. Superpulsed CO_2 lasers are associated with a more precise depth of ablation because they combine short pulse duration and higher power. The depth of penetration ranges from 20 up to 125 μm. It thus improves vaginal aesthetics and function by rejuvenating and replenishing the elasticity and lubrication of the female lower genital tract mucosa. Fractional CO_2 has also been found to restore the age-related loss of vaginal rugae with reported improvement in sexual function [1, 6, 23, 24].

Table 27.6 Radiofrequency devices for nonsurgical vaginal rejuvenation

Device	Mechanism and Regimen	Study Details	Technique	Results	Complications
I. Radiofrequency Devices					
1. Trans-mucosal temperature controlled radiofrequency heating device	Transmucosal heating of the tissue to 40–47 °C promotes tightening of vaginal mucosa.	*Leibaschoff et al., Surg Technol Int 2016* [14]	1 Tx every 30 days for 3 months used for both arms	Marked improvement in VHI, ICIQ-UI, UDI6, IIQ7, VAS, punch biopsies	Nil reported
	At 460 kHz radiofrequency	Prospective RCT ($N = 20$):			
	Up to 30 min per area	• Vaginal function (n = 10)			
	3 Tx at 4–6 week intervals. Maintenance every 6 months	• Urethral muscle tone (n = 10)			
		Alinsod, Prime 2015	• 3 TX with a 4–6 week interval	• Statistically significant improvements in Vaginal Laxity and Sexual Satisfaction Questionnaire	Nil reported
		Prospective study ($N = 23$) [15]	• Endpoint temperature of 40–45 °C for 3–5 min per zone during a total of 30 min treatment	• Improvements in SUI, atrophic vaginitis, and orgasmic dysfunction	
		Mild-moderate vaginal laxity and SUI	• 3 sessions at intervals of 1 month	92% patients reported reduction in time to orgasm of 50% tightening effects, vaginal moisture improvements, and improved sensitivity of the vulva	Nil reported
		Alinsod, Lasers Surg Med 2016 [16]	• Slim S-shaped probe		
		Prospective study ($N = 25$)	• 25 min time		
		Patients with orgasmic dysfunction	• External treatment + full length treatment of the vagina		

(continued)

Table 27.6 (continued)

Device	Mechanism and Regimen	Study Details	Technique	Results	Complications
2. Cryogen-cooled monopolar radiofrequency	Reverse thermal gradient cools surface mucosa allowing for the application of high-energy RF at 6 MHz radiofrequency to promote submucosal neocollagenesis. Heats target tissue to above 50 °C at a depth of 3–5 mm	*Millheiser et al., J Sex Med 2010* [17]	1 treatment with reverse thermal gradient RF energy (60–90 J/cm^2)	Significant improvement in vaginal tightness and sexual function at 6 months	None reported
	20–30 min	Prospective for laxity; *N* = 24	1 treatment at 90 J/cm^2 for 30 min	Significant improvement in sexual function at 6 months, sustained through 12 months	None reported
	1 treatment	*Sekiguchi et al., J Womens Health 2013* [18]	1 treatment at 90 J/cm^2 for 30 min	Vaginal laxity was improved by 43.5% and 19.6% (p = 0.002) in the active and sham groups, respectively	None
	Maintenance annually	Prospective for laxity; *N* = 30			
		Kryhman et al., J Sex Med 2017 [19]			
		Randomized, placebo sham controlled multicentre study; *N* = 1742			

Table 27.6 (continued)

Device	Mechanism and Regimen	Study Details	Technique	Results	Complications
3. Bipolar RF	Employs bipolar RF energy that utilizes three distinct RF frequency channels (0.8, 1.7, and 2.45 MHz) and an additional fourth multichannel mode, combining all three RF frequencies to improve labial skin laxity and texture using the unit's V-ST handpiece.	*Steven et al. NJ. 2014* [20]	The V-ST handpiece emits RF energy fluency of up to 130 J/cm^3 with pulse duration of up to 200 ms and includes an integral cooling mechanism that cools the electrodes to 6 °C.	Moderate improvement in labial skin laxity and texture	None reported
	4–6 Tx at 2–3 week intervals	Single-centre study *N* = 14 For labial skin laxity and texture	Each session: 30 min	67% of patients reported great satisfaction	
4. Monopolar RF	Four weekly sessions, each taking approximately 20 min	*Clark, J Cosm Laser Ther 2018* [21]	Starting energy set to 90 points and 100% duty factor	Statistically significant improvement in vulvar appearance and sexual function at 1- and 12-month follow-up.	None reported
		Prospective for aesthetic appearance; *N* = 19	Conducted using slow circular motions in a cranial–caudal direction		
	An external and internal monopolar radio frequency device	*Lalji and Lozanova, J Cosmet Dermatol 2017* [22]	For intravaginal treatment	Improvement in all evaluated areas of SUI and vaginal laxity	None reported
	3 once-a-week sessions	Mild/moderate SUI and vaginal laxity; *N* = 27	Starting power—30 points and 80% duty factor; repetitive movement of the intravaginal tip for 5 min		
			For extra-vaginal treatment		
			Initial power—90 points and 100% duty factor. The extra-vaginal tip was applied to the labia majora using circular motions for 3 min on each side		

Technique

Ideal candidates are women above 18 years of age, with a normal cervical cytology on Papanicolaou smear, with no injuries of the introitus or the vaginal canal. Patients with history of previous vaginal reconstructive surgery or vaginal tightening procedures within the past 1 year, active urinary tract infections, active genital infections, and hormonal imbalance are not considered suitable for undergoing this procedure. There is wide variation between CO_2 lasers marketed and studied for NVR. A large number of parameters exist including power delivered, dwelling time, and interval between treatment sessions among other variables. The number of treatments and specifics of the protocol vary and largely depend on the device. The protocol for the (Lumenis FemTouch TM) CO_2 fractional laser has been elucidated below. This is an outpatient procedure, lasts for around 20–30 min, requires no anaesthesia, and is not associated with any pain. Treatment of the vaginal canal is performed **using** a specific vaginal handpiece, utilizing the square pattern and deep mode, fractional density of 5–15% and energy level of 7.5–12.5 mJ. The handpiece is inserted up to 11 cm in the vaginal canal and baby oil may be used to facilitate insertion into the introitus. The handpiece is placed in contact with the vaginal wall and pulses applied at each 1 cm marking and then retracted. The probe is then rotated 45–90° to allow uniform energy delivery. Three to four treatments sessions at 4–6-week intervals are recommended. The procedure is not associated with any downtime; however patients are advised to abstain from sexual activity for at least 7 days after treatment [24].

Results

After 1 month following the third treatment, more than 90% women report an improvement in sexual function, enhanced vaginal tightening, and improvement in dryness and atrophy. Considerable improvement in dyspareunia after the third session of treatment is seen and continued improvement is noted 1–2 months after follow-up. Majority of the women report significant improvement in vaginal dryness and burning sensation after the third session. More than 50% patients also experience an improvement in urinary symptoms. Restoration of the vaginal pH also occurs leading to an improvement in symptoms of dysuria, vaginal itching, and recurrent infections [1, 23, 24].

Post-treatment biopsies demonstrate renewal and thickening of the vaginal epithelium, with enhanced storage of glycogen in the epithelial cells, resembling the pre-menopausal vaginal mucosa. Fibroblast activation, neocollagenesis, and neovascularization were also noted. Compared to erbium lasers, which are known to cause tissue contraction as a normal part of the wound healing process, CO_2 lasers may also stimulate neocollagenesis via heat-induced collagen fibre contraction and fibroblast activation. Atrophy and thinning of the vaginal epithelial layer may also exhibit improvement with CO_2 laser treatment [1, 6, 24].

Side Effects and Complications

Burning sensation, itching, pain with probe insertion, tingling sensation, numbness, and discharge are mild, transient post-procedure responses which tend to resolve in 1–2 days. CO_2 laser causes superficial mucosal microablation, and potential

complications including vaginal burns, scarring, dryness, infection, altered sensation, dyspareunia, adhesions, chronic pain, or vaginal stenosis over time may occur [23, 24].

Er-YAG Laser (Nonablative)

Principle

The nonablative erbium:YAG laser leads to tissue resurfacing by emitting light at a wavelength of 2940 nm. The depth of penetration is approximately 1–3 μm of tissue per J/cm^2, enabling targeted skin ablation with negligible thermal damage to surrounding tissue. Various modes such as the 'smooth mode' (fast sequence of low-fluence laser pulses inside a superlong pulse of several hundred milliseconds) or a 'dual mode' (rapid sequential micropulses with long-pulse modes) in certain Er-YAG devices allow deep nonablative, controlled heating of the vaginal epithelium producing neocollagenesis, thus resulting in vaginal canal tightening, without causing surface tissue damage, reducing the risk of unwanted side effects [1, 4, 23].

Technique

Before the treatment, topical anaesthesia (10% lidocaine cream) is applied to the introitus and the distal portion of the vaginal canal left for 10 min and then wiped off. Before the procedure the area to be treated is cleaned with normal saline and carefully dried off. The 'smooth' mode consists of one pulse sequence which itself comprises a train of multiple micropulses, resulting in a controlled rise of temperature of the vaginal mucosa, and lamina propria to a range of 45 and 65 °C, optimal for collagen remodelling. In the first step, a full-beam handpiece is used along with a circular intravaginal adapter, enabling circumferential energy delivery to the vaginal canal. The entire length of the vaginal canal is treated by sequentially moving the handpiece outward by 0.5 cm, until the entrance to the vaginal canal has been reached. Two hundred and fifty joules of energy are delivered per pass, corresponding to 3 J/cm^2 of fluence per one pulse and two complete passes along the entire length of the vaginal canal are delivered in the first step. In the second step, a fractional handpiece is used to deliver laser pulses to the opening of the vagina. Three passes of 10 J energy each are delivered to the entire vestibule and introitus area. The patients receive 2–3 laser sessions at 4 weekly intervals. Post-procedure, the patients are advised to avoid sexual intercourse for at least 3 days [25].

Results

Studies assessing the effectiveness of nonablative Er:YAG laser for vaginal rejuvenation report significant improvement at 3 and 12 months follow-up, in vaginal laxity, sexual gratification, as well as other symptoms of vaginal atrophy and GSM, thus improving the overall quality of life. Studies report that the extent of improvement in symptoms due to vaginal laxity can range from 80% to 95%, a level of efficacy which is comparable to surgical interventions. Histology of vaginal mucosa treated with Er:YAG exhibited increased vaginal thickness and denser connective tissue with increased collagen and elastin [25].

Side Effects and Complications

Majority of the reported side effects including pain, discomfort, and oedema were mild and transient, lasting for 1–2 days. Uncommonly reported, transient side effects include vaginal discharge and urge incontinence. As compared to CO_2 laser, it has a lesser depth of penetration, leading to minimal thermal injury to adjacent tissue and less pain, discomfort, swelling, and erythema [23, 25].

Hybrid Fractional Lasers

Hybrid fractional lasers (HFL) utilize 2940 and 1470 nm wavelengths to target tissue. However, a paucity of studies exists with regard to the usefulness of HFL in vaginal tissue rejuvenation [1, 26].

27.3.5.1.3 Other Modalities for NVR

Various other nonsurgical, non-energy-based modalities (Table 27.7) have shown variable results in NVR.

No clear-cut or well-established protocols or guidelines exist for the use of these modalities in NVR, as a result of paucity of data. Further large-scale randomized control studies are required to establish the safety and efficacy of these techniques for vaginal rejuvenation (Tables 27.8 and 27.9).

Table 27.7 Parameters and duration of improvement after RF-based vaginal rejuvenation—an experience based on monopolar RF performed amongst ten patients

Parameters	Session after which improvement is observed
Pigmentation (vulva)	70–80% after II session
Skin texture (Tightening, firming, lifting of labia)	70–80% after II session
Stress urinary incontinence	30–40% after I
	70–80% after II
Sexual function (Vaginal tightening, lubrication, sensation)	70–80% after II–IV

Table 27.8 Summary—lasers for non-functional vaginal rejuvenation

Laser	Mechanism of action	Regimen used	Results	Adverse events
2940-nm Erbium Er:YAG laser system	Collagen contracture from wound healing response and pigmentation improvement	• 10–20 min • 1 treatment session • Maintenance unknown	Significant improvement in vaginal laxity, vaginal dryness, dyspareunia, SUI, sexual function	Mild burns Mild vulvar oedema
CO_2 RE digital pulsed fractional laser	Heat-induced ablation and coagulation leading to collagen contraction and elastin generation. Improves pigmentation and mucosa texture	• 10–15 min • 3 sessions at 4–6-week intervals • Maintenance unknown	Significant improvements in vaginal dryness, burning, itching, and dyspareunia, sexual function	Mild, transient events

Table 27.8 (continued)

Laser	Mechanism of action	Regimen used	Results	Adverse events
Er:YAG and Diode hybrid fractional laser	Fractional laser emits infrared light for ablation (2940 nm wavelength) and coagulation (1470 nm wavelength). Wavelengths are tuneable for hybrid or independent use	• 3–5 min • 3 sessions at 4–6-week intervals • Maintenance unknown	Significant improvement seen in symptoms of vaginal atrophy, sexual function. Significant histological changes were observed with increase in epithelial thickness of 61.8% at 3 months	No adverse events were reported

Table 27.9 Other nonsurgical modalities for nonsurgical vulvovaginal rejuvenation

Modality	Mechanism of action	Technique	Results	Advantages	Complications or adverse effects
Platelet-rich plasma [27]	Vaginal vascularity is increased, with a subsequent dramatic increase in sensitivity. In addition, the skin becomes thicker and firmer, making the vagina look much more youthful.	Patients' venous blood is collected in special tubes and centrifuged to obtain a supernatant of PRP	• Skin becomes thicker and firmer, making the vagina look much more youthful	• Minimally invasive	Pain during the procedure
	Moreover, the ligaments and muscles supporting the urethra become stronger, alleviating urinary incontinence	PRP acts by being very rich in and promoting growth factors with a fibrin	• Improvement in urinary incontinence	• No downtime	Temporary effects
		• PRP may be applied after microablative lasers as a rejuvenating liquid in the vagina	• Relief in symptoms of vaginal atrophy	• Safe procedure	Limited studies available
		• Application of autologous lipofilling mixed with PRP has also been tried	• Rejuvenated appearance of external genitalia		
	O-Shot amplification [28, 29]	PRP is injected in the clitoro-urethro-vaginal space for better orgasms and better urinary control for stress urinary incontinence after use of energy-based devices	Improves sexual gratification and urinary incontinence.	Minimally invasive means of improving sexual gratification and urinary incontinence. PRP immediately activates tissue regeneration, and the enhancement in sexual response is dramatic	Pain during the procedure
	Derived from the fresh blood of a patient and is rich in chemokines, growth factors, and cytokines that have been implicated in tissue repair and inflammation		Improved arousal, stronger orgasm, decreased dyspareunia, and increased natural lubrication		Temporary effects Limited studies available

(continued)

Table 27.9 (continued)

Modality	Mechanism of action	Technique	Results	Advantages	Complications or adverse effects
Fillers Hyaluronic acid [30]	Labia majora enhancement to disguise their existing anatomy of labia minora protruding past the labia majora. Hyaluronic acid dermal fillers are used to enhance the labia majora due to their effectiveness in restoring tissue volume, skin biocompatibility, and improving skin quality	In this procedure, both labia majora are injected with hyaluronic acid dermal filler to increase the overall tissue volume and improve surface skin texture and structural support	Improvement in shape, volume, firmness, and skin texture	• Immediate results	• Painful
			Improves self-esteem and sexual function	• Better skin hydration	• Bruising, swelling
				• Not permanent	• Infection
				• Can be repeated	• Unpredictable duration of effects
				• HA can be dissolved if needed	• Large quantities, expensive
				• Shorter downtime	• Migration of filler
				• No donor site aftercare as with fat grafting	• Unevenness
Silicone threads [31]	• The threads stimulate collagen production, leads to the development of the 'traction vector'	• Performed under local anaesthesia; incisions at the 3 and 9 o'clock positions; insertion of silicone threads under the vaginal submucosa	92.8% satisfied with the vaginal width correction	• Minimal anatomic injury which leads to minimal pain	Implant exposure (5%)
	• Preservation of effects, even after thread absorption		Significant improvement in sexual function	• Does not require considerable recovery time	Capsule contracture (3.9%)
					Infection (1.7%)
G-spot amplification [3, 6, 7]	Aims to improve female sexual gratification by increasing friction. Located inferior to the urethra, midway between the pubic bone and cervix	Injection of hyaluronic acid fillers into an erogenous zone on the anterior vaginal wall located 1–2 cm from the urethra. Other filler substances, such as collagen, autologous fat, PRP, silicone, and calcium hydroxyapatite, have also been used	Improvement in sexual function and gratification	Minimally invasive	Bleeding, infection, and urinary complications
	Bulking the sensitive area forward towards the vaginal lumen may lead to easier, longer, more frequent, and intense orgasm			No downtime The results of the G-shot may last 3–5 months	Most serious adverse event is intravascular injection
Mycromesh [32]	Biocompatible compound (expanded poly-tetrafluoroethylene) as a Gore-Mycromesh	Under local anaesthesia, a 2×4 cm^2 mesh was inserted under the posterior wall submucosa	Improvement in sexual function at 12-month follow-up	Elderly patients experience better outcomes using gore-mycromesh rather than silicone thread because the vaginal posterior wall with senile changes can be plicated simultaneously using an open technique	Foreign body sensation
					Infection

27.4 Conclusion

Ageing, menopause, pregnancy, obesity, and many other factors contribute to vulvovaginal laxity (VVL), changes which significantly affect a woman's quality of life. Vaginal rejuvenation (VR) is a treatment modality for women which includes procedures aimed at decreasing the width of the vagina in order to enhance vaginal aesthetics and functionality. VR therefore not only provides cosmetic enhancement, but also improves functionality and has been known to positively impact self-esteem. The term vaginal rejuvenation has evolved into an umbrella term that covers procedures that enhance vulvovaginal aesthetics and functionality. Common procedures include *surgical* (e.g. vaginal tightening, labia minoraplasty, labia majoraplasty, clitoral hood reduction, clitoral unhooding, lipofilling, and hymen reconstruction) or *nonsurgical* (e.g. energy-based treatments, platelet-rich plasma [PRP], and fillers) interventions. Existing studies suggest that these modalities and devices are promising nonsurgical alternatives, which can help enhance vaginal function and improve the quality of life for women. However, large-scale randomized trials with long-term follow-up are essential to compare these therapies with conventional modalities, and to ascertain the safety of these techniques. With the growing need for VR, minimally invasive alternatives have emerged in recent years. Novel technology is permitting us to use less invasive methods of treating VVL and atrophy without turning to traditional surgery, and numerous studies have reported the gaining interest and popularity of these procedures amongst women.

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References

1. Qureshi AA, Tenenbaum MM, Myckatyn TM. Nonsurgical vulvovaginal rejuvenation with radiofrequency and laser devices: a literature review and comprehensive update for aesthetic surgeons. Aesthet Surg J. 2018;38(3):302–11.
2. Lev-Sagie A. Vulvar and vaginal atrophy: physiology, clinical presentation, and treatment considerations. Clin Obstet Gynecol. 2015;58(3):476–91.
3. Vanaman M, Bolton J, Placik O, Fabi SG. Emerging trends in nonsurgical female genital rejuvenation. Dermatol Surg. 2016;42(9):1019–29.
4. Tadir Y, Gaspar A, Lev-Sagie A, et al. Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies. Lasers Surg Med. 2017;49(2):137–59.
5. Mehta A, Bachmann G. Vulvovaginal complaints. Clin Obstet Gynecol. 2008;51(3):549–55.
6. Desai SA, Kroumpouzos G, Sadick N. Vaginal rejuvenation: from scalpel to wands. Int J Womens Dermatol. 2019;5(2):79–84.

7. Iglesia CB, Yurteri-Kaplan L, Alinsod R. Female genital cosmetic surgery: a review of techniques and outcomes. Int Urogynecol J. 2013;24:1997.
8. The PMFA Journal. Revirgination is not the same as hymenoplasty. PMFA J. https://www.thepmfajournal.com/error-page/revirgination-is-not-the-same-as-hymenoplasty. Accessed 8 Feb 2021.
9. Ahluwalia J, Avram MM, Ortiz AE. Lasers and energy-based devices marketed for vaginal rejuvenation: a cross-sectional analysis of the MAUDE database. Lasers Surg Med. 2019;51(8):671–7.
10. Krychman ML. Vaginal laxity issues, answers and implications for female sexual function. J Sex Med. 2016;13(10):1445–7.
11. Hashim PW, Nia JK, Zade J, Farberg AS, Goldenberg G. Noninvasive vaginal rejuvenation. Cutis. 2018;102(4):243–6.
12. EMC Aesthetic Clinic. Intimate rejuvenation Ultra Femme 360. n.d.. https://www.emc-beauty.ru/en/cosmetology/Ultra_Femme_360. Accessed 30 Jan 2021.
13. Pure Medical Spa. Vaginal rejuvenation. n.d.. http://puremedspamd.com/index.php/vaginal-rejuvenation/. Accessed 8 Feb 2021.
14. Leibaschoff G, Izasa PG, Cardona JL, Miklos JR, Moore RD. Transcutaneous temperature controlled radiofrequency (TTCRF) for the treatment of menopausal vaginal/genitourinary symptoms. Surg Technol Int. 2016;29:149–59.
15. Alinsod RM. Temperature controlled radiofrequency for vulvovaginal laxity. 2015. https://www.prime-journal.com/temperature-controlled-radiofrequency-for-vulvovaginal-laxity/. Accessed 2019.
16. Alinsod RM. Transcutaneous temperature controlled radiofrequency for orgasmic dysfunction. Lasers Surg Med. 2016;48(7):641–5.
17. Millheiser LS, Pauls RN, Herbst SJ, Chen BH. Radiofrequency treatment of vaginal laxity after vaginal delivery: non-surgical vaginal tightening. J Sex Med. 2010;7(9):3088–95.
18. Sekiguchi Y, Utsugisawa Y, Azekosi Y, Kinjo M, Song M, Kubota Y, et al. Laxity of the vaginal introitus after childbirth: nonsurgical outpatient procedure for vaginal tissue restoration and improved sexual satisfaction using low-energy radiofrequency thermal therapy. J Women's Health (Larchmt). 2013;22(9):775–81.
19. Krychman M, Rowan CG, Allan BB, DeRogatis L, Durbin S, Yacoubian A, et al. Effect of single-treatment, surface-cooled radiofrequency therapy on vaginal laxity and female sexual function: the VIVEVE I randomized controlled trial. J Sex Med. 2017;14(2):215–25.
20. Karcher C, Sadick N. Vaginal rejuvenation using energy-based devices. Int J Women's Dermatol. 2016;2(3):85–8.
21. Clark Z. Labial tissue rejuvenation and sexual function improvement using a novel noninvasive focused monopolar radio frequency device. J Cosmet Laser Ther. 2018;20(2):66–70.
22. Lalji S, Lozanova P. Evaluation of the safety and efficacy of a monopolar nonablative radiofrequency device for the improvement of vulvo-vaginal laxity and urinary in- continence. J Cosmet Dermatol. 2017;16(2):230–4.
23. Preminger BA, Kurtzman JS, Dayan E. A Systematic review of nonsurgical vulvovaginal restoration devices: an evidence-based examination of safety and efficacy. Plast Reconstr Surg. 2020;146(5):552e–64e.
24. Pillai R, Rahim S. Fractional CO2 laser treatment for vaginal rejuvenation in post-menopausal Indian women. Trichol Cosmetol Open J. 2019;3(1):7.
25. Mitsuyuki M, Štok U, Hreljac I, Yoda K, Vižintin Z. Treating vaginal laxity using nonablative Er:YAG laser: a retrospective case series of patients from 2.5 years of clinical practice. Sex Med. 2020;8(2):265–73.
26. Guerette NL. Safety and efficacy of hybrid fractional laser (1470nm and 2940nm) for symptoms of genitourinary syndrome of menopause: 12 month prospective multi-center study. J Minim Invasive Gynecol. 2019;26(7):S70.
27. Kim SH, Park ES, Kim TH. Rejuvenation using platelet-rich plasma and lipofilling for vaginal atrophy and lichen sclerosus. J Menopausal Med. 2017;23(1):63–8.

28. Jain A, Bedi RK, Mittal K. Platelet-rich plasma therapy: a novel application in regenerative medicine. Asian J Transfus Sci. 2015;9:113–4.
29. Runels C, Melnick H, Debourbon E, Roy L. A pilot study of the effect of localized injections of autologous platelet rich plasma (PRP) for the treatment of female sexual dysfunction. J Women's Health Care. 2014;3:169.
30. Taylor-Barnes K. Using dermal fillers for vaginal skin rejuvenation. J Aesthet Nurs. 2018;7(9):464–70.
31. Park TH, Park HJ, Whang KW. Functional vaginal rejuvenation with elastic silicone threads: a 4-year experience with 180 patients. J Plast Surg Hand Surg. 2015;49(1):36–9.
32. Park TH, Whang KW. Vaginal rejuvenation with Gore-Mycromesh. Aesthet Plast Surg. 2015;39(4):491–4.