Chapter 5
Acne in Women

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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).

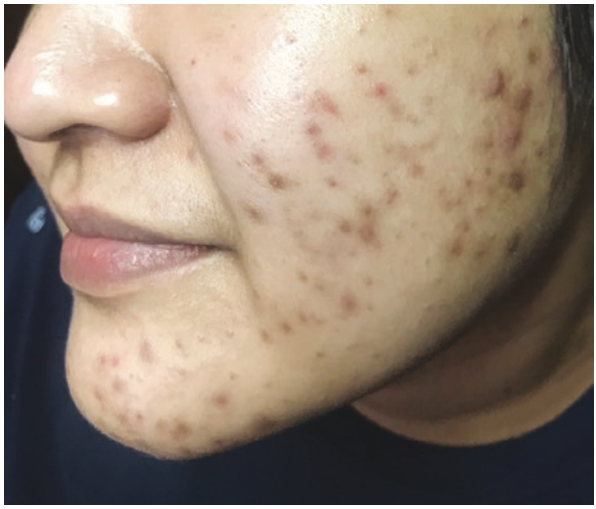

Fig. 5.1 Adult female acne in a 34-year-old single Asian female (Courtesy of Dr. Maria Juliet Macarayo)

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).

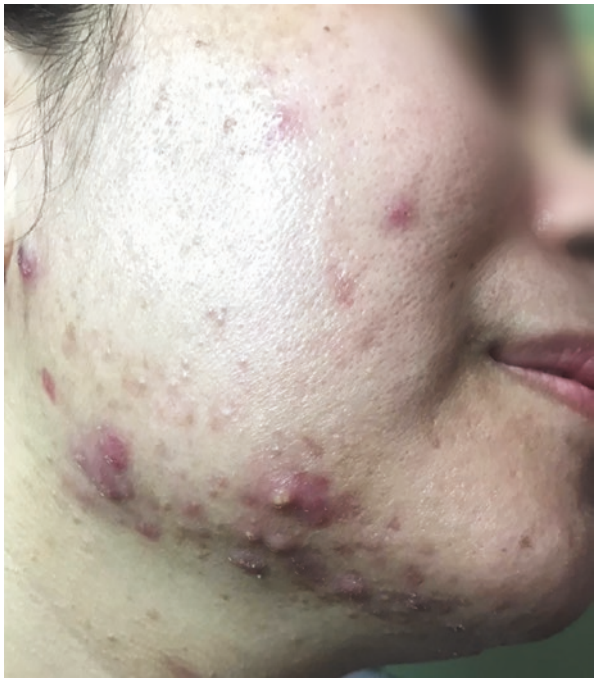

Fig. 5.2 Acne with PCOS in a 40-year-old married Asian female (Courtesy of Dr. Maria Juliet Macarayo)

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],

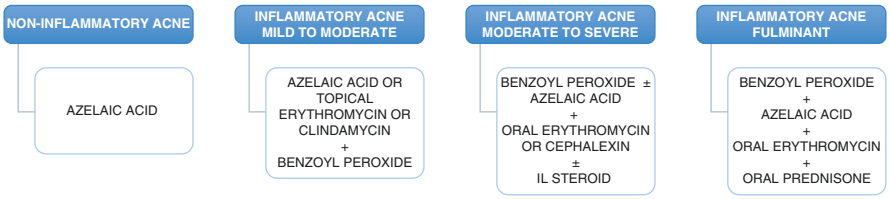

Fig. 5.3 Treatment options for acne in pregnancy. (Adapted from Chien AL, Qi J, Rainer B, et al. Treatment of acne in pregnancy. J Am Board Fam Med 2016;29:254–62)

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.