Chapter 3
Skin in Pregnancy

Shital Poojary and Kavya Badireddy

3.1 Physiological Skin Changes in Pregnancy

3.1.1 Introduction

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

3.1.2 Pigmentation

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

S. Poojary (✉)
Department of Dermatology, K. J. Somaiya Medical College, Mumbai, India

K. Badireddy
King George Hospital, Vishakapatnam, India

R. Sarkar, S. Sinha (eds.), *Skin Diseases in Females*,
https://doi.org/10.1007/978-981-16-6065-8_3

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

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

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

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

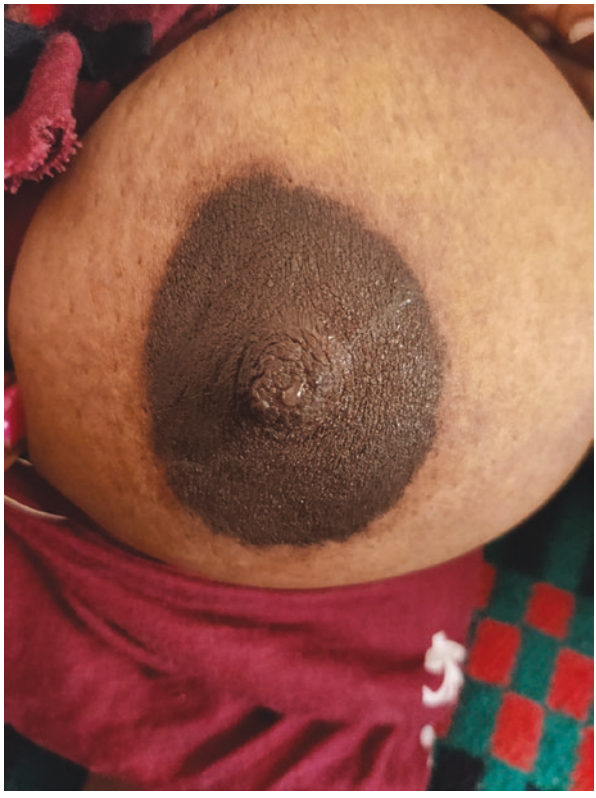

Fig. 3.1 Pigmentation of areola in pregnancy

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

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

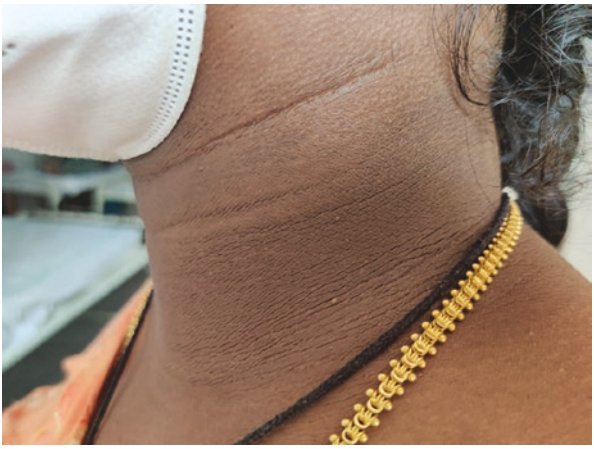

Fig. 3.2 Acanthosis nigricans in pregnancy

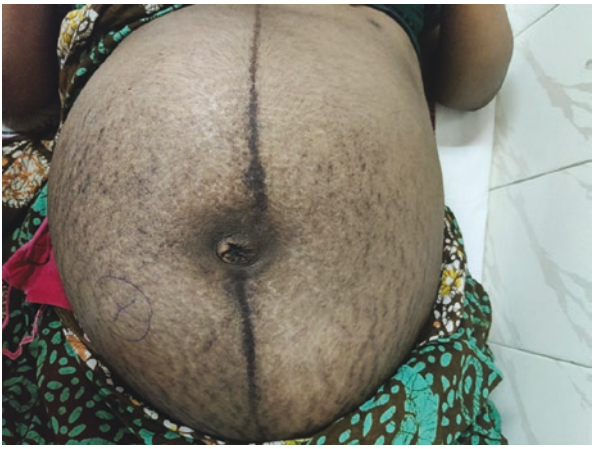

Fig. 3.3 Linea nigra, pigmentation of umbilicus and striae gravidarum

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

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

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

3.1.2.1 Melasma

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

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

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

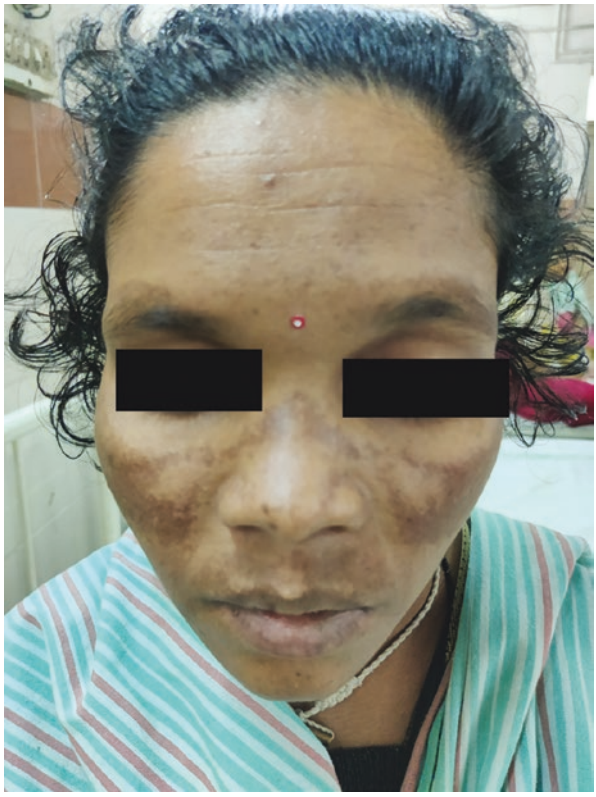

Fig. 3.4 Melasma in pregnancy

3.1.3 Vascular Changes

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

3.1.3.1 Varicosities

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

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

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

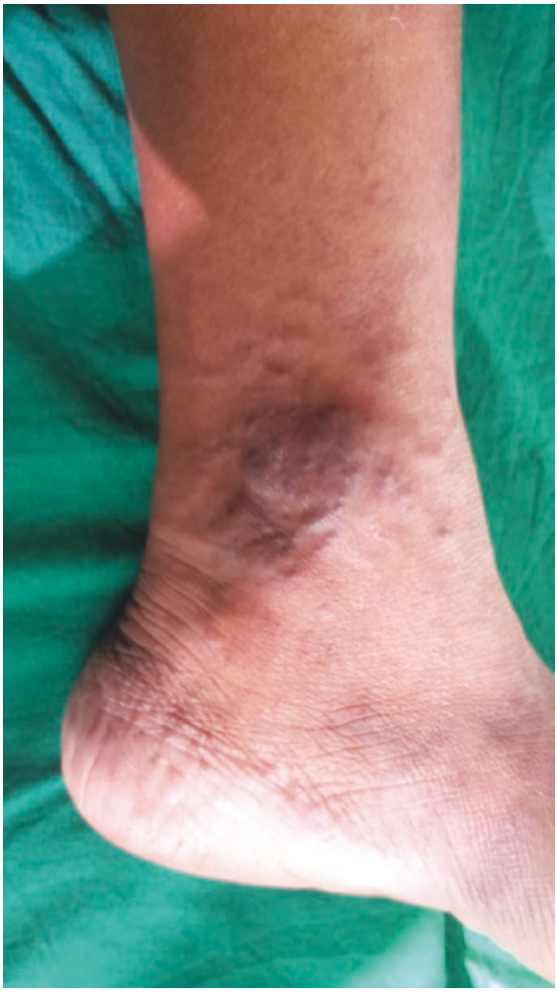

Fig. 3.5 Varicosities around ankle in pregnancy

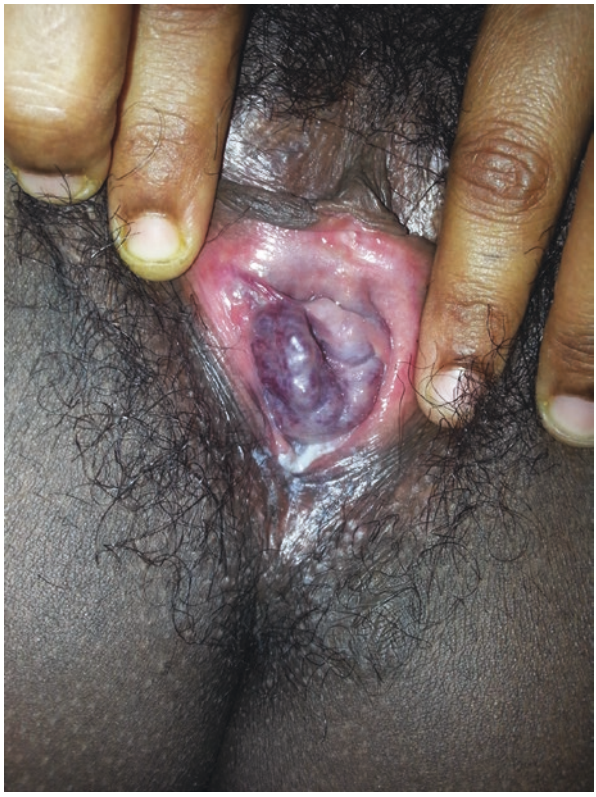

Fig. 3.6 Vulvar and vaginal varicosities in pregnancy

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

3.1.3.2 Edema of Pregnancy

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

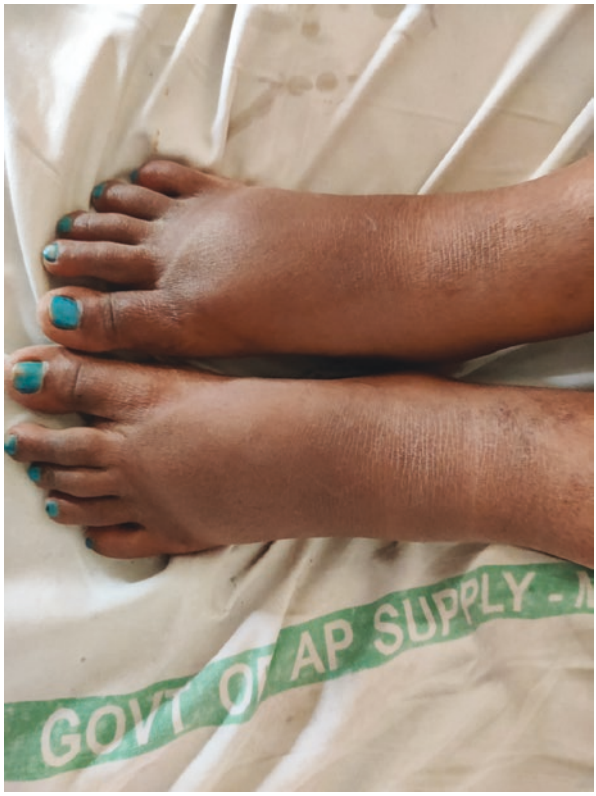

Fig. 3.7 Pitting edema, both legs in pregnancy

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

3.1.3.3 Spider Angioma

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

3.1.3.4 Palmar Erythema

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

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

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

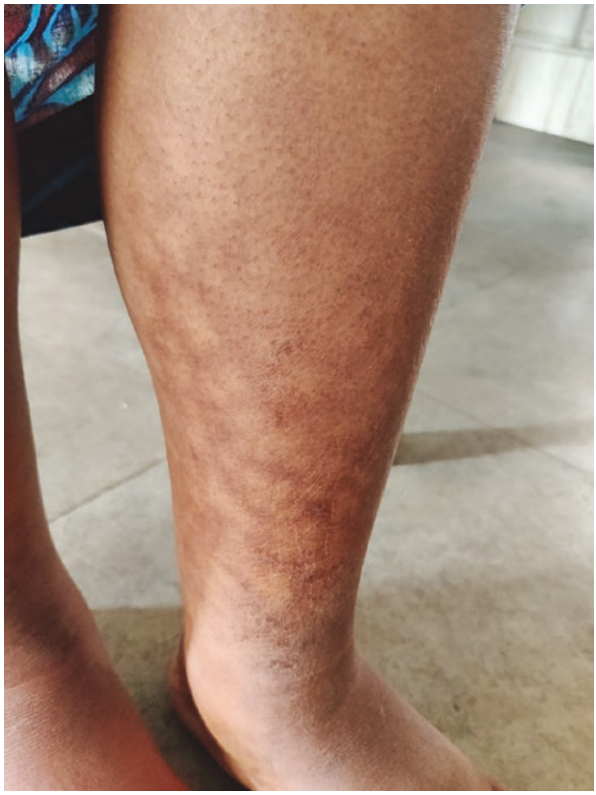

Fig. 3.8 Cutis marmorata in pregnancy

3.1.4 Connective Tissue Changes

3.1.4.1 Striae Distensae

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

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

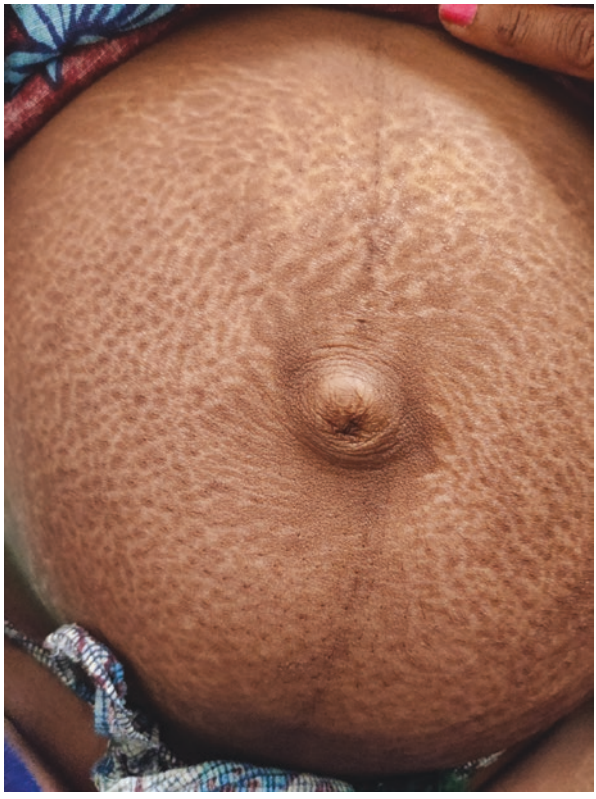

Fig. 3.9 Striae distensae

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

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

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

3.1.5 Glandular Activity

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

3.1.5.1 Eccrine Glands

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

3.1.5.2 Sebaceous Glands

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

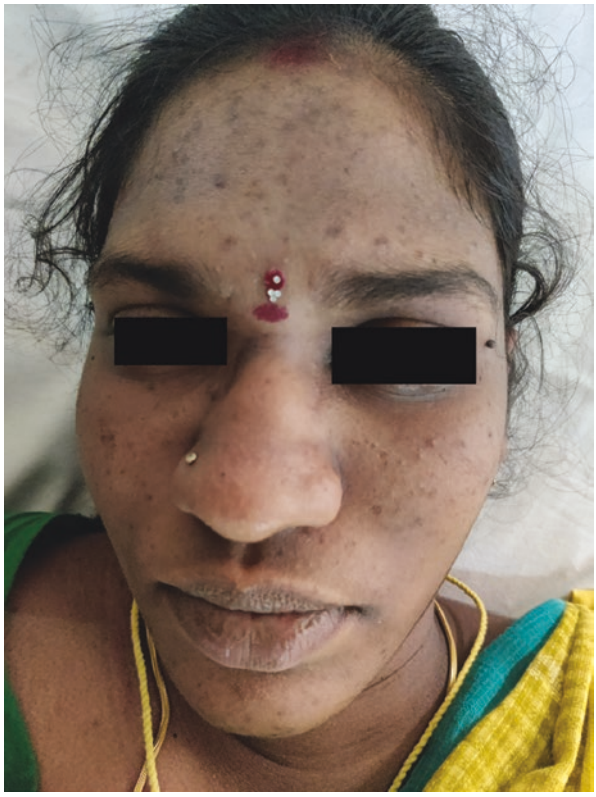

Fig. 3.10 Acne aggravated in pregnancy

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

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

3.1.5.3 Apocrine Glands

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

3.1.6 Hair Changes

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

3.1.6.1 Hirsutism

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

3.1.7 Nail Changes

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

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

3.1.8 Breast

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

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

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

Fig. 3.11 Enlargement of nipple and areola

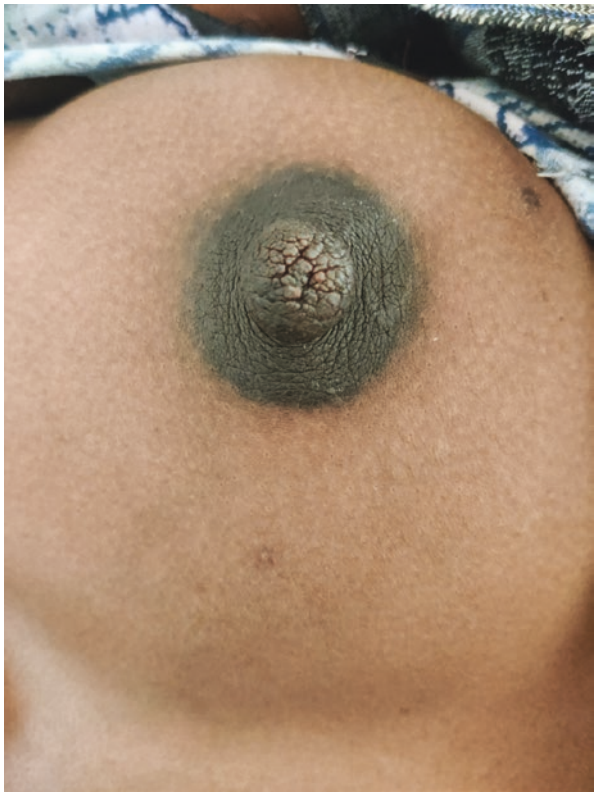

Fig. 3.12 Severe nipple hyperkeratosis with fissuring

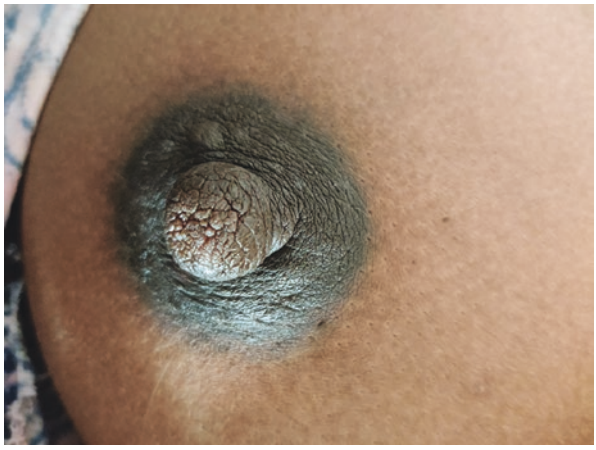

Fig. 3.13 Montgomery tubercles with nipple hyperkeratosis

3.1.9 Mucosa

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

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

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

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

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

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

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

3.2 Dermatologic Drugs in Pregnancy

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

Factors affecting use of drugs in pregnancy:

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

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

Table 3.1 Pregnancy categories according to the FDA

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

Table 3.2 New pregnancy and lactation labeling rule (PLLR)

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

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

3.2.1 Topical Dermatology Drugs in Pregnancy

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

Table 3.3 Topical dermatology drugs in pregnancy

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

(continued)

Table 3.3 (continued)

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

Table 3.3 (continued)

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

3.3 Systemic Dermatologic Drugs in Pregnancy

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

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

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

Table 3.4 Systemic dermatology drugs in pregnancy

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

Table 3.4 (continued)

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

(continued)

Table 3.4 (continued)

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

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

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

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

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

Table 3.5 Biologicals in pregnancy [65–74]

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

(continued)

Table 3.5 (continued)

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

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

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

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

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

3.3.2 Cosmetic Procedures in Pregnancy: Table 3.6 [76]

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

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

Table 3.6 Cosmetic and surgical procedures in pregnancy

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

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

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

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

References

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

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

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

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