A comprehensive review on the pregnancy dermatoses

Mohammad Adil, Tasleem Arif and Syed Suhail Amin

Abstract
Pregnancy results in cutaneous changes in more than 90% of women. This is the result of the altered endocrine, metabolic and immunological state in the female. Many cutaneous changes are common and benign; these are referred to as the physiological changes of pregnancy. They may be of cosmetic concern to the patient and seldom require intervention. These changes are so well recognized that they act as contributory evidence of pregnancy. Many pre-existing dermatological conditions tend to change in pregnancy; some are aggravated while others may be relieved. Knowledge of these conditions is important to forewarn the patient and to prepare for upcoming complications. There are a group of dermatoses specific to pregnancy and there has been much confusion in the literature about their classification and nomenclature. Atopic Eruption of Pregnancy is the most common pregnancy specific dermatoses followed by Polymorphic Eruption of Pregnancy. These are benign conditions with no risk to the mother or baby. Pemphigoid Gestationis and Intrahepatic Cholestasis of Pregnancy carry fetal risk and require antepartal surveillance. This article discusses the current knowledge of the various cutaneous changes of pregnancy with emphasis on their clinical features, diagnosis, management and prognosis.

Keywords: Dermatoses, endocrine, physiological changes, pregnancy.
Abbreviations: Melanocyte Stimulating Hormone (MSH), Systemic Lupus Erythematosus (SLE), Pemphigoid Gestationis (PG), Herpes Gestationis (HG), Polymorphic Eruption of Pregnancy (PEP), Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), Prurigo of Pregnancy (PP), Pruritic Folliculitis of Pregnancy (PF), Intrahepatic Cholestasis of Pregnancy (ICP), Atopic Eruption of Pregnancy (AEP), Bullous Pemphigoid Antigen 2 (BPAg2)

INTRODUCTION
The state of pregnancy results in a multitude of cutaneous changes in the female. These are a reflection of the profound alterations in the endocrine, metabolic and immunological profiles that occur during this period. Skin manifestations occur due to the production of a number of proteins and steroid hormones by the fetoplacental unit and also by the maternal pituitary, thyroid and adrenals. The placenta, a new endocrine organ in the woman, produces progesterone. Dehydroepiandrosterone is produced by the fetal adrenals from pregnenolone and this is aromatized to estriol. At term, the level of progesterone is 7 times, estradiol is 130 times and prolactin level is 19 times of that present at 8 weeks of gestation. There occurs an overall preference for the Th2 cytokine profile, which helps in fetal protection from the immune system. This is due to the high levels of progesterone, which promotes Th2 cytokines like IL-4, IL-5 and IL-10 and has inhibitory effects on TNF alpha production. Oestrogen suppresses IL-2 production. The postpartum period is marked by withdrawal of hormones and consequent elevation of Th1 cytokine levels.

Cutaneous changes develop in more than 90% of all pregnant females. These include common cutaneous changes that occur in most cases to severe diseases, some of which are seen exclusively in the pregnant and postpartum state. Cutaneous manifestations can be grouped into three broad categories: physiological cutaneous changes related to pregnancy; diseases modified by pregnancy and specific dermatoses of pregnancy.

PHYSIOLOGICAL CHANGES IN PREGNANCY
These changes are so common that they are not considered abnormal. Rather, they provide contributory evidence of a pregnant state. This however, does not mean they are cosmetically acceptable to all patients. The various physiological changes during pregnancy have been summarized in Table 1.

Pigmentation:
Hyperpigmentation is one of the most common and early signs of pregnancy, seen in more than 90% of patients. High levels of Melanocyte Stimulating Hormone (MSH), oestrogen and progesterone are believed to be responsible for hyperpigmentation. Progesterone augments the oestrogen mediated melanin output, the levels of which correlate with pigmentedary changes.

Generalized hyperpigmentation is seen which is more marked in the dark haired skin. Pigmented areas of the body, namely the genitalia, perineum, areolae and upper medial thighs, demonstrate more pronounced pigmentation. Linea nigra, a hyperpigmented line extending from the pubic symphysis to umbilicus and further up to the xiphisternum, replaces the linea alba. Chloasma, also termed as mask of pregnancy, is the well marginated brownish pigmentation of the face like melasma. It...
is seen in 45-75% of pregnant women in western literature but in less than 10% cases in women with pigmented skin.\textsuperscript{5,10,11} Pigmentary demarcation lines appear on the limbs with borders of abrupt transition; freckles, naevi and scars tend to darken and enlarge.\textsuperscript{12}

The pigmentation gradually fades after delivery, though the resolution of skin colour is usually incomplete. Chloasma tends to persist in 30% cases postpartum.\textsuperscript{13} Sun protection and reassurance is all that is needed. Topical formulations containing hydroquinone and tretinoin are avoided in pregnancy and can be added after delivery.

Table 1: Physiological changes in pregnancy

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<tr>
<th>Pigmentation</th>
<th>Connective tissue changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized hyperpigmentation</td>
<td>Striae distensae (Striae gravidarum)</td>
</tr>
<tr>
<td>Pigmentation of inner thigh, genitalia, axilla</td>
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</tr>
<tr>
<td>Secondary areola</td>
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<tr>
<td>Linea nigra</td>
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<td>Prominence/ appearance of pigmentary demarcation lines</td>
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<td>Enlargement and darkening of freckles, naevi and scars</td>
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<thead>
<tr>
<th>Vascular changes</th>
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<tr>
<td>Oedema of distal extremities and hands</td>
<td>Miliaria</td>
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<tr>
<td>Spider angiomatas</td>
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<tr>
<td>Palmar erythema</td>
<td>Montgomery’s tubercles</td>
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<tr>
<td>Leg varicosities</td>
<td>Aggravation of acne</td>
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<tr>
<td>Rectal haemorrhoids</td>
<td></td>
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<tr>
<td>Cutis marmorata</td>
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<td>Capillary haemangioma</td>
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<table>
<thead>
<tr>
<th>Oral mucosal changes</th>
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<tr>
<td>Oedema and hyperaemia of gingivae</td>
<td>Hirsuitism</td>
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<table>
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<tr>
<td>Brittle nail plate</td>
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<td>Onycholysis</td>
<td></td>
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<tr>
<td>Beau’s lines after delivery</td>
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| Physiological connective tissue changes: |

Gross distension of abdomen with adrenocortical activities are responsible for the red-blue depressed streaks seen on abdomen and breasts in 70-90% pregnancies, called stria distensae.\textsuperscript{5,14} These usually develop in the second trimester. Females with pre-existing striae on breasts and thighs are more likely to develop striae gravidarum\textsuperscript{11}, seen in White women more than Asian and African-American.\textsuperscript{14} Preventive therapies are controversial and postpartum treatment options include topical tretinoin, excimer laser or surgery.\textsuperscript{10}

Soft tissue fibromas of pregnancy are called molluscum fibrosum gravidarum. They appear in the second trimester on the neck, face and beneath the breasts. These disappear after delivery.\textsuperscript{16}

Physiological vascular changes:

Vascular growth factors released during pregnancy by the pituitary, adrenals and placenta are believed to be causative and this has been demonstrated in vitro as well.\textsuperscript{17} Non-pitting oedema of the face, hands and feet is present in around half of all females in the later part of pregnancy.\textsuperscript{13} This is probably due to sodium and fluid retention and pressure of the gravid uterus on the inferior vena cava. Spider naevi or spider angiomas are small raised lesions with a central pulsatile punctum and radiating telangiectatic vessels frequently present over the area drained by the superior vena cava. They are present in 67% of White women and 11% Black women during the second trimester.\textsuperscript{5} Palmar erythema is seen in two-thirds of White and one-third of Black women.\textsuperscript{6} Other vascular changes include varicosities of legs and anus (40%)\textsuperscript{15}, cutis marmorata (0.7%)\textsuperscript{10} and capillary haemangioma (5%)\textsuperscript{9}. These changes revert after the postpartum period.

Physiological glandular changes:

Eccrine gland activity is usually increased but the palms show decreased sweating. Thus, the incidence of miliaria and dishidrotic eczema is increased. There is inconclusive evidence to suggest that apocrine gland activity is decreased during pregnancy.\textsuperscript{19} Sebaceous activity increases in the third trimester leading to acne and enlargement of Montgomery’s tubercles.\textsuperscript{14} One-third to half of all pregnant women develop these tubercles, which are modified sebaceous glands.\textsuperscript{5,8} However, sebum excretion has not been found to decrease in lactating females post-delivery.\textsuperscript{20}

Oral mucosal changes:

Oedema and hyperaemia of the gingivae in pregnancy is attributable to local irritation and nutritional deficiencies and is seen in around 80% women.\textsuperscript{5} Gingivitis not related to poor oral hygiene may occur. Granuloma gravidarum or pregnancy epulis might occur that regresses postpartum.

Hair changes:

Hair changes are seen in 3-12% of pregnant females.\textsuperscript{21} Hirsuitism and hypertrichosis occurs due to oestrogen. This leads to an increase in the percentage of hair in anagen.\textsuperscript{2} Approximately 2-3 months after delivery, loss of telogen hair occurs.\textsuperscript{22} This is termed as late anagen release as the hair follicles are no longer stimulated to stay in anagen phase by the maternal hormones. The hair recovery occurs in 3-12 months. A small number of females may experience episodic shedding of hair for long periods. This has been proposed to be due to the inability of some hair follicles to revert to...
asynchronous shedding. Rarely, male pattern baldness may occur in women. Nail changes:

Nail growth increases during pregnancy. Britleness of the nail plate and distal onycholysis may be seen. Beau's lines may develop after delivery. Reassurance is all that is needed for these benign nail problems.

DISEASES MODIFIED BY PREGNANCY

Many pre-existing dermatoses may be exacerbated or ameliorated by pregnancy. Certain tumours may also show remission or exacerbation. This is due to the shift in pregnancy to the Th2 state and a return to Th1 state in the postpartum period and also the discontinuation of some drugs due to their teratogenic potential.

Infections:

Depressed cell-mediated immunity makes the pregnant woman susceptible to more severe and frequent infections. Candidiasis is quite common and was found to be the commonest cause of white discharge per vagina, being present in 22% pregnant females. Half of all neonates born to infected mothers are positive for Candida and some may show signs of infection. Pityrosporum folliculitis, caused by Pityrosporum ovale, is more common in pregnancy. Genital warts are the commonest sexually transmitted disease seen in 4.7% subjects, these increase in size during pregnancy. Prophylactic caesarian section to prevent laryngeal papillomas in the neonate is not recommended now. Herpes simplex virus infection carries 50% risk of transmission to neonate in the primary episode and 5% risk in recurrent episode, caesarean section might be warranted to prevent such transmission. Verruca vulgaris infection has been reported to cause pneumonia in 14% of mothers and death in 3%. Bowenoid papulosis, caused by human papilloma virus appears first during pregnancy or may get aggravated. Pregnancy preposes the clinical manifestations in HIV infected females, possibly due to additive immune suppression. Pneumocystis pneumonia or listeriosis may prove to be fatal. Kaposi’s sarcoma may occur in these females. Kaposi’s sarcoma may occur in these females. 20-30% women present with leprosy for the first time in pregnancy and the postpartum period. The disease tends to downgrade towards the lepromatous pole in pregnancy and upgrades during lactation. Type 1 lepra reactions are more frequent in the first trimester and after delivery, whereas type 2 lepra reactions peak in third trimester. Trichomania is diagnosed in 60% of pregnant women. Autoimmune diseases:

Systemic Lupus Erythematosus (SLE) is associated with a better prognosis than previously thought, if the disease is in remission and nephropathy and cardiomyopathy are not present. If the disease is active, half of the patients’ disease will get worse and there might be fatalities. SLE tends to be more severe if it first presents in pregnancy. Babies of such mothers are likely to develop neonatal lupus.

Patients with scleroderma are usually unafflicted and some are improved in pregnancy. However, occasional reports of renal crisis, hypertension and pre-eclampsia are reported. Course of dermatomyositis is usually unaltered but the disease may worsen in some patients. Pemphigus tends to be exacerbated or present for the first time in pregnancy. The clinical presentation in pregnancy is similar to that of the regular presentation. Differentiation from herpes gestationis is important.

Metabolic diseases:

Effect of pregnancy on porphyria cutanea tarda is not clear, though some females show biochemical and clinical deterioration. Acrodermatitis enteropathica shows clinical worsening. Connective tissue diseases:

Pregnancy can lead to bledding, uterine lacerations and wound dehiscence in patients of Ehlers-Danlos syndrome. Pseudoxanthoma elasticum patients may suffer massive gastrointestinal bleeds. Lichen sclerosis et atrophicus of the vulva usually improves in pregnancy and a normal delivery is mostly possible.

Disorders of glands:

Acne can aggravate during pregnancy. Hidradenitis suppurativa and Fox-Fordyce disease become better as a result of decreased apocrine gland activity. Keratinization diseases:

The course of psoriasis remains unaltered in 40% females during pregnancy while it improves in a similar percentage of females and worsens in the remaining. It is more likely to deteriorate in the postpartum period. Psoriasis arthritis has been found to worsen or present for the first time in pregnancy. Generalized pustular psoriasis of Von Zambusch may rarely occur. Though most patients have a preceding or family history of psoriasis, some may develop the disease without ever having a preceding episode. Peak incidence is seen in the last trimester and the disease tends to recur. Multiple, discrete, sterile pustules at the margins of erythematous macules on the umbilicus, medial thigh, axillae, inframammary folds, gluteal creases and sides of neck are seen. These break to form erosions and crusts. Painful, circinate mucosal erosions may form. Prednisolone is used for management. Von Zambusch pustular psoriasis of pregnancy was earlier termed ‘Impetigo Herpetiformis’ but the term is best avoided as it is impossible to differentiate it from the former, both clinically and surgically.
histologically.6 Erythrokeratoderma variabilis is reported to worsen during pregnancy.27

Tumours:
A melanoma that develops during pregnancy carries worse prognosis but if pregnancy occurs after the tumour is resected, the prognosis is unaltered.39 Metastasis in the fetus has been seen and a minimum period of two years following tumour resection is recommended.52 A female with neurofibromatosis may develop neurofibroma for the first time in pregnancy or older neurofibromas may grow in size. Rupture of major vessels may occur.5 Pregnancy may worsen mycosis fungoides and eosinophilic granuloma.6

Miscellaneous diseases:
Prognosis of atopic dermatitis is unpredictable in pregnancy, with reports of both improvement and worsening.22 Predisposed patients may first develop atopic dermatitis during pregnancy.40 Allergic contact dermatitis may improve in pregnancy.12 Hand eczema may worsen in the puerperal period.4 Erythema multiforme may be precipitated by pregnancy.4 Autoimmune progesterone dermatitis has been described in pregnancy.12 This disease is characterized by hypersensitivity to progesterone demonstrated by a positive intradermal skin test and cutaneous lesions resembling urticaria, eczema, erythema multiforme and dermatitis herpetiformis.41 The disease is associated with fetal mortality and recurs in subsequent pregnancies.12

PREGNANCY SPECIFIC DERMATOSES
These are a heterogeneous group of inflammatory skin diseases specific for pregnancy.42 Most of these conditions are benign and resolve spontaneously in the postpartum period but a few of these are associated with fetal complications.54 Almost all of them present with pruritus and a cutaneous eruption of varying severity.3

Classification:
The first attempt to classify these conditions was made by Holmes and Black in 1982-83 who classified them into: a) Pemphigoid Gestationis (PG) or Herpes Gestationis(HG), b) Polymorphic Eruption of Pregnancy (PEP) or Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP), c) Prurigo of Pregnancy (PP) and d) Pruritic Folliculitis of Pregnancy (PF).43,44 Shornick was of the view that all patients with PF also had papular dermatitis, so he included PF in the PP group. He included Intrahepatic Cholestasis of Pregnancy (ICP) in his classification for dermatoses where secondary skin lesions due to scratching are produced. He proposed that failure to consider ICP in the classification has led to confusion in terminology of pregnancy specific diseases. Thus, his classification included PG, PEP, PP and ICP.45 Ambros-Rudolph et al carried out a retrospective review of 505 pregnant patients over a 10 year period and gave a more rationalised classification system in 2006. They clubbed PP, PF and eczema of pregnancy in one group called Atopic Eruption of Pregnancy (AEP) due to their overlapping features and found this group to be the most common pruritic condition in pregnancy. Thus, they proposed four conditions: a) AEP, b) PEP, c) PG and d) ICP.46 The various specific pregnancy dermatoses have been elaborated in Table 2.

Atopic eruption of Pregnancy (AEP): (Syn: Besnier’s prurigo, prurigo gestationis, Nurse’s early onset prurigo of pregnancy)

It is the most common pregnancy specific dermatoses that includes eczematous or papular lesions in females with personal or family history of atopy and elevated IgE - accounting for nearly half of all patients.66 The disease tends to recur in subsequent pregnancies with 75% of all cases occurring before the start of the third trimester.57 It carries no risk for the mother or baby however, infant may develop atopy later in life.67 Treatment is symptomatic with antihistamines and corticosteroids.

E-type AEP: This group comprises of 67% of AEP patients and includes patients with eczematous features; previously referred to as Eczema of Pregnancy (EP). It was not until 1999 that a high prevalence of atopic eczema was noted in pregnancy.48 80% of pregnant women develop the first episode of atopic dermatitis during pregnancy.46 This is attributed to the Th2 cytokine profile in pregnancy and a dominant humoral immunity.4 It is more common in primigravida, in single gestation, begins in early pregnancy and affects whole body including face, palms and soles.46

P-type AEP: This group includes what was referred to previously as Prurigo of Pregnancy and Pruritic Folliculitis of Pregnancy. Prurigo of Pregnancy (PP) is seen in one out of 300 to 450 pregnancies and occurs predominantly in the second to third trimester.50 Excoriated or crusted papules are seen over the extensors of extremities and abdomen and are associated with some eczematization. The eruption lasts up to 3 months after delivery and recurrences in subsequent pregnancies are common.51 PP is associated with ICP with the differentiating feature being the absence of a primary lesion in the latter.50 Personal and family history of atopic dermatitis or raised IgE may be seen in PP.52 Serology is normal. There are no specific changes on histopathology and immunofluorescence results are found to be negative.50 There appears to be no maternal or fetal risk.45

Pruritic Folliculitis of Pregnancy (PF), first described by Zoberman and Farmer, is now believed to be as common as PG or PP, though only a few cases have been reported.59 It begins in the latter two trimesters and affects roughly one in 3000 pregnancies.51 Pruritus is not a defining feature, despite what the name suggests.3 Multiple, follicular papules and pustules occur on the shoulders, arms, chest, upper back and abdomen and are aceniform in nature.43 The lesions tend to resolve in a couple of months following delivery. Histopathological examination reveals non-specific features with sterile folliculitis
Polymorphic Eruption of Pregnancy (PEP): (Syn: Pruritic Urticarial Papules and Plaques of Pregnancy or PUPPP, Bourne’s Toxaemic Rash of Pregnancy, Toxic Erythema of Pregnancy, Nurse’s Late Prurigo of Pregnancy)

With a prevalence of a case in every 130-300 pregnancies, this disease is the second most common pregnancy specific dermatoses and was seen in 21.6% pregnancies reviewed by Ambros-Rudolph et al. They found it began in late pregnancy in 83% cases and 15% in the postpartum period. The disease occurs predominantly in primigravida and a familial predisposition is present. Lesions are pleomorphic, usually urticarial but purpuric, vesicular, polycyclic and targetoid lesions may be present. The striae on the abdomen are the first to be involved and there is a characteristic periumbilical sparing. The lesions seldom occur on the body above the breast and on hands and feet. The lesions resolve with scaling and crusting in six weeks. The disease is more common in excessive weight gain during pregnancy and in multiple gestation.

Table 2: Comparison of different pregnancy specific dermatoses in relation to clinical characteristics, prognosis, investigations and treatment.

<table>
<thead>
<tr>
<th></th>
<th>AEP</th>
<th>PEP</th>
<th>PG</th>
<th>ICP</th>
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<tbody>
<tr>
<td>Pruritus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Primary cutaneous involvement</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Eczematous or papular</td>
<td>Papules, vesicles and urticarial lesions</td>
<td>Vesiculo bullous lesion on urticarial base</td>
<td>Excoriations, papules secondary to scratching</td>
</tr>
<tr>
<td>Site of lesions</td>
<td>Trunk, extensors of limbs, rest of the body also involved</td>
<td>Abdominal involvement, in striae distensae, periumbilical sparing</td>
<td>Abdominal, particularly periumbilical involvement</td>
<td>Palms and soles followed by rest of the body</td>
</tr>
<tr>
<td>Time</td>
<td>First trimester</td>
<td>Third trimester, Post partum</td>
<td>Second and third trimester, post partum</td>
<td>Second and third trimester</td>
</tr>
<tr>
<td>Risk with primigravidae</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>Association with multiparity</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Flare at delivery</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Recurrence</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Family history</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Histopathology</td>
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<td>Specific, sub epidermal vesicle</td>
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<tr>
<td>Immunofluorescence</td>
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<td>-</td>
<td>Linear deposition of C3</td>
<td>-</td>
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<tr>
<td>Other lab findings</td>
<td>Ig E elevated</td>
<td>-</td>
<td>Indirect IMF +</td>
<td>Increased serum bile acids</td>
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<tr>
<td>Maternal risk</td>
<td>-</td>
<td>-</td>
<td>Progression to pemphigoid, thyroid dysfunction</td>
<td>Gallstones, Jaundice</td>
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<tr>
<td>Fetal risk</td>
<td>-</td>
<td>-</td>
<td>Prematurity, Small for age baby, neonatal blistering</td>
<td>Premature births, fetal distress, stillbirth</td>
</tr>
<tr>
<td>Treatment</td>
<td>Steroids, antihistaminics</td>
<td>Steroids, antihistaminics</td>
<td>Oral steroids, antihistaminics</td>
<td>Ursodeoxycholic acid</td>
</tr>
</tbody>
</table>

Pemphigoid Gestationis (PG): (Syn: Herpes Gestationis or HG, Gestational Pemphogoid, Dermatitis Herpetiformis of Pregnancy)

in severe cases. There are no associated maternal or fetal complications, although infants may later develop atopic dermatitis.

The pathogenesis is unknown however, the abdominal distension leading to collagen and elastic fibre damage in striae is hypothesized, leading to formation of antigens and triggering inflammatory cascade. The role of progesterone has been suggested by the increased progesterone receptor immunoreactivity in skin lesions of PEP. The discovery of fetal DNA in skin lesions of women with PEP has furthered the hypothesis that abdominal distension leads to increased permeability of vessels and permit chimeric cell migration in the maternal skin. Linear IgM dermatosis of pregnancy is an entity characterized by pruritic, red, follicular papules and pustules on the abdomen and proximal extremities seen after 36 weeks gestation and a linear band of IgM deposition on basement membrane zone. It has been characterized as a variant of PEP or PP by different authors.

and immunofluorescence studies are negative. No maternal or fetal risk is described except for low birth weight neonates in a single study. Pathogenesis of PF is unknown with no definite role of androgens or immunologic abnormalities. There is no evidence to suggest that it is a hormonally aggravated acne as proposed by some workers.
PG is the most clearly characterized pregnancy dermatosis and the one which also affects the fetal skin.\textsuperscript{63} It is a rare, self-limiting, autoimmune bullous disease with an incidence of 1:1700 to 1:50000 pregnancies.\textsuperscript{64} Mean onset occurs at 21 weeks gestation, though it occurs in the postpartum period in a fifth of all cases.\textsuperscript{64} Constitutional symptoms, burning and itching herald the onset of the disease. Half of patients develop urticarial lesions on the abdomen, particularly in the periumbilical region, that change rapidly to a generalized bullous eruption usually sparing the face, palms, soles and mucosae. Vesicles may arise in herpetiform or circinate distribution. Face is involved in 10% cases and oral mucosa in 20%.\textsuperscript{12} The disease shows spontaneous improvement in late gestation but flares may occur at the time of delivery in 75% of the cases.\textsuperscript{64} Though the disease may remit after a few weeks after delivery, a protracted course, conversion to bullous pemphigoid or recurrence with menstrual cycle and use of oral contraceptive pills has been reported.\textsuperscript{50} PG tends to recur in subsequent pregnancies in a more severe form and at an early stage with longer stay in postpartum.\textsuperscript{50} Skipped pregnancies have been described.\textsuperscript{63,65} The disease is also linked with hydatidiform mole and choriocarcinoma.\textsuperscript{66}

The classical histopathological finding is the presence of a subepidermal vesicle, spongiosis and an infiltrate consisting of lymphocytes, histiocytes and eosinophils.\textsuperscript{64} An inverted tear drop appearance due to oedema in the dermal papilla is seen in early urticarial lesions.\textsuperscript{13} Direct immunofluorescence reveals a linear deposition of C3 along the dermo-epidermal junction in 100% cases and is diagnostic of the disease, while a salt split skin shows an epidermal staining.\textsuperscript{67} Antithyroid antibodies may be present but thyroid dysfunction is not common.\textsuperscript{63} Systemic corticosteroids are the mainstay of management. About one in ten children born to women with PG develop blisters due to passive transfer of antibodies, this resolves on its own. Severity of the disease has been correlated with the risk of prematurity and small for gestational age babies.\textsuperscript{68}

Pathogenesis of PG involves the production of IgG1 antibodies against NC16A domain of carboxyl terminus of Bullous Pemphigoid Antigen 2 (BPAg2), leading to activation of complement, recruitment of eosinophils to the local site and damage of the basement membrane and consequent blistering.\textsuperscript{2} The aberrant expression of MHC class II antigens of paternal haplotype is believed to stimulate an allogenic response to placental basement membrane and this is believed to cross react with the skin in PG.\textsuperscript{63,69}

**Intrahepatic Cholestasis of pregnancy (ICP):** (Syn: Obstetric Cholestasis, Pruritus Gravidarum, Icterus Gravidarum, Recurrent Jaundice of Pregnancy, Idiopathic Jaundice of Pregnancy)

Pruritus in pregnancy is fairly common and can be due to various reasons like pregnancy specific dermatoses and other co-existing dermatoses such as scabies, urticaria, atopic dermatitis, drug reactions etc. It was found to be present in more than half of 170 pregnant women in an Indian study.\textsuperscript{70} This must be differentiated from ICP where the skin lesions arise secondary to itching.

ICP was first described by Kehr in 1907.\textsuperscript{63} ICP being referred to Pruritus Gravidarum (for pruritus without skin changes occurring early in pregnancy and related to atopic diathesis and no cholestasis) and Prurigo Gravidarum (for pruritus associated with PP like skin lesions and associated with cholestasis) lead to much confusion regarding nomenclature.\textsuperscript{69} The disease has an incidence of 10-150 cases per 10,000 pregnancies\textsuperscript{71}, being more common in South America and Scandinavia, probably due to dietary factors.\textsuperscript{50} Patients complain of sudden onset pruritus beginning from the palms and soles and later generalizing to the whole body. Skin lesions are secondary to itching and range from excoriations to prurigo nodularis, extensors are more severely involved. Jaundice is seen in 20% cases only.\textsuperscript{72} Clay coloured stools, dark urine and haemorrhage secondary to vitamin K malabsorption can occur. Family history can be elicited in half of the cases and an association with multiple gestation is described.\textsuperscript{73} Resolution of ICP occurs soon after delivery. Recurrence in subsequent pregnancies is seen in 45-70% cases and routinely with the use of oral contraceptive pills, though no detectable abnormalities are seen in the duration between two pregnancies.\textsuperscript{63} Histopathology is non-specific and immunofluorescence is negative. Diagnosis is made by increased serum bile acid levels, transaminases are elevated. Prothrombin time may be prolonged. A 2.7 times increased risk of gallstones is reported in primigravida with ICP compared to non-pregnant women.\textsuperscript{74} ICP is associated with significant fetal morbidity including premature births in 20-60% cases, intrapartum fetal distress including meconium aspiration in 20-30% and fetal mortality in 1-2%.\textsuperscript{71} Risk is particularly more if serum bile acid levels exceed 40 micromoles per litre.\textsuperscript{79} Meconium may cause umbilical vein compression and induction of labour at 36 weeks gestation has been recommended in severe cases.\textsuperscript{70} The goal of treatment is reduction of serum bile acids. Ursodeoxycholic acid, given in the dose of 15mg/kg orally daily is the only proven therapeutic agent that decreases fetal mortality.\textsuperscript{63,76} Cholestyramine reduces vitamin K absorption and increases the risk of haemorrhage. Other agents like S-adenosylmethionine, dexamethasone, silymarin, phenobarbitone, epomediol and activated charcoal are not that effective and do not affect fetal risk.\textsuperscript{63} Topical emollients and antipruritic agents offer symptomatic relief but antihistamines are not that effective.\textsuperscript{50}

The key event in the pathogenesis of ICP is elevation of bile acids. Oestrogens are said to have cholestatic properties by reducing hepatocyte bile acid uptake and also by inhibiting basolateral transport proteins.\textsuperscript{50} Progesterone may additionally saturate the transport capacity of these transport proteins in hepatocyte.\textsuperscript{73} Genetic predisposition occurs due to mutation in genes encoding bile transport proteins, with cholestasis developing in pregnancy as their capacity to secrete substance is exceeded.\textsuperscript{63} Bile acids passing through the placenta produce...
vasoconstriction of placental veins, fetal cardiomyocyte dysfunction and also abnormal uterine contractility, all leading to fetal hypoxia.71

CONCLUSION

Pregnancy is associated with a wide variety of cutaneous changes. These may range from common, benign changes termed physiological or more severe, posing significant risk to the mother as well as the baby. Physiological pregnancy changes may be of cosmetic concern to the patient and seldom need anything more than counselling. Pre-existing dermatoses may aggravate during this period, posing a challenge to the treating physician. Women suffering from such diseases need to be warned of complications and risks before trying to conceive. A strict watch for possible complications and appropriate management at an early stage is warranted. Women should also be looked for pregnancy specific dermatoses and their complaints should not be lightly overlooked as non-specific or physiological. Careful history and examination with a judicious use of investigations will help to arrive at a diagnosis and in prompt institution of treatment.

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