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An Overview of Dermatoses of Pregnancy

Pathiraja L*[1,2] and Pathiraja PDM[1,3]

[1]Ministry of Health, Nutrition and Indigenous Medicine, Sri Lanka

[2]Department of Dermatology, St George Hospital, Australia

[3]Department of Obstetrics and Gynecology, St John of God Hospital, Australia

***Corresponding author:** Dr. Lakmali Pathiraja, Department of Dermatology, St George Hospital, Australia, Email: pathirajaknl@gmail.com

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Abstract

Pregnancy results in cutaneous changes in more than 90% of women. It may be either physiological, changes in pre-existing skin diseases or the development of new pregnancy dermatoses. Better understanding and proper management of these conditions will lead to a good outcome in both the mother and the fetus. This article discusses pregnancy specific dermatoses with emphasis on their clinical features, diagnosis, management and prognosis.

Current classification of pregnancy dermatoses includes atopic eruption of pregnancy, polymorphic eruption of pregnancy, pemphigoid gestationis and intrahepatic cholestasis of pregnancy. While atopic eruption of pregnancy and the polymorphic eruption of pregnancy are without significant adverse effect on the mother and the fetus, pemphigoid gestationis and intrahepatic cholestasis of pregnancy carry fetal as well as maternal risks, thus necessitate careful surveillance.

Keywords: Dermatoses; Skin; Pregnancy

Abbreviations: PG: Pemphigoid Gestationis; PEP: Polymorphic Eruption of Pregnancy; PUPPP: Pruritic Urticarial Papules and Plaques of Pregnancy; ICP: Intrahepatic Cholestasis of Pregnancy; UVB: Ultraviolet B; UDCA: Ursodeoxycholic Acid.

Introduction

Pregnancy is a condition which profound immunological, metabolic and vascular changes which may affect the skin in various ways. Dermatological manifestations of pregnancy may be physiological, exacerbation of a pre-existing dermatological disease or pregnancy-specific dermatoses. These may have a profound psychological impact on the patient and the family. Like all the other organs in the body, the skin changes during pregnancy (Table 1) with pigmentary and vascular changes being the most common. Although these may cause significant concerns, the majority of these resolve after the delivery.

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Pigmentary	Generalized hyperpigmentation
	Localized hyperpigmentation (e.g., linea nigra, areolae)
	Chloasma
	Increased size and pigmentation of freckles, scars and naevi
	Gingival hyperplasia
Vascular	Pyogenic granuloma
	Varicosities
	Palmar erythema
Glandular	Increased sweating
	Increased seborrhoea
Connective tissue	Striae gravidarum
Hair	Hirsutism
	Postpartum telogen effluvium
Nails	Brittle nails
	Onycholysis
	Subungual hyperkeratosis

Table 1: Physiological changes during pregnancy.

The incidence and severity of some common dermatological problems, such as atopic dermatitis, melasma, perioral dermatitis and pustular psoriasis increase in pregnancy. Pregnancy dermatoses consist of a heterogeneous group of cutaneous diseases with confusing nomenclature [1, 2]. Ambros-Rudolph CM has proposed a newer classification [3]. These include the following diseases: pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis and the atopic eruption of pregnancy (Table 2). The most common pregnancy dermatoses are the atopic eruption of pregnancy followed by the polymorphic eruption of pregnancy. Both of which are not associated with any maternal or fetal complications. However, pemphigoid gestationis and intrahepatic cholestasis of pregnancy are associated with fetal risks such as prematurity, fetal distress and stillbirth. Early diagnosis, prompt treatment and antenatal surveillance are needed to improve the pregnancy outcome.

Pemphigoid gestationis	Herpes gestationis
Polymorphic eruption of pregnancy	Pruritic urticarial papules and plaques of pregnancy, Toxic erythema of pregnancy
Intrahepatic cholestasis of pregnancy	Obstetric cholestasis
Atopic eruption of pregnancy	Prurigo of pregnancy, Eczema of pregnancy
This article will focus only on the detailed description of pregnancy dermatoses.	

Table 2: Classification of the dermatoses of pregnancy & their synonym(s) [3].

Pemphigoid Gestationis

Pemphigoid gestationis (PG) is an autoimmune bullous disease. It is the only pregnancy dermatoses that may cause cutaneous manifestations in the newborn. PG is rare, affecting only 1 in 50 000 to 60 000 pregnancies. There is an association with HLA-DR3 and DR4. Patients with PG also have a higher risk of other autoimmune diseases, particularly Graves' disease. Circulating IgG antibodies against skin basement membrane hemidesmosomal protein BP-180 is present in the serum of patients with PG.

These autoantibodies also bind to the placenta, which is the primary site of autoimmunity [4]. Aberrant expression of MHC class 11 molecules of the placenta, suggested being paternal. It is believed that pathogenesis is due to cross-reactivity of the placenta and the skin [4]. These autoantibodies also bind to fetal ectodermal structures, which are antigenically similar to skin, causing transient cutaneous manifestations in the newborn.

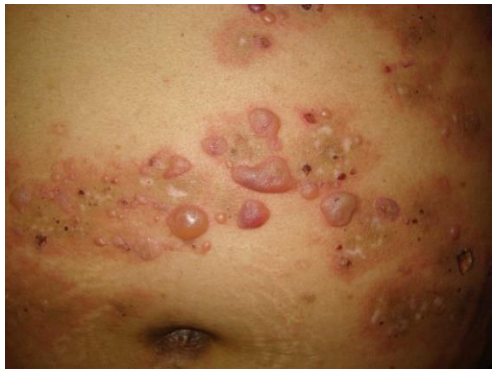

Figure 1: Classically PG presents during late pregnancy.

In initial "pre-bullous" stage, multiple erythematous urticarial papules and plaques develop on the abdomen, often within or immediately adjacent to the umbilicus (Figure 1). In this stage, it is clinically and histologically difficult to differentiate PG from the polymorphic eruption of pregnancy. This is followed by clustered vesicles and tense bullae may become generalized, resembling bullous pemphigoid. Mucous membranes are usually spared.

Ten per cent of the newborns may have transient cutaneous lesions, which spontaneously resolve within weeks. Due to chronic placental insufficiency, there is an increased risk of prematurity and small for gestational age. Though it may not develop during the first pregnancy, once it occurs, it usually recurs in subsequent pregnancies, often with earlier onset and more severe disease, but rarely (5%) skip pregnancies. Furthermore, flares reported with menstruation and oral contraceptives.

Histopathological features of the pre-bullous stage are dermal edema and mixed cellular infiltrate predominately eosinophils. Histopathological findings from early intact bullae reveal classic histological findings of a sub-epidermal split. Histopathological diagnosis can be confirmed with 100% sensitivity by direct immunofluorescence of perilesional intact skin, which shows linear deposition of C3 along the dermo-epidermal junction. Linear IgG deposition is only seen in 30% of patients. Circulating IgG antibodies are detected by indirect immunofluorescence in 30% of patients. Disease activity can be monitored by antibody levels using ELISA and immunoblot techniques.

Management

Symptomatic management of pruritus is antihistamines. Topical steroids may be helpful in the pre-bullous stage. However, systemic steroids are the treatment of choice in PG [5]. Oral prednisolone can be started at a dose of 0.5/kg/day dose and can be reduced as the disease improves, but should be increased at the time of delivery to prevent flaring of the disease. The refractory disease may be responded to plasmapheresis [6]. Although the persistence of the disease after delivery is uncommon, in those rare cases immunosuppressive treatment can be given.

Polymorphic Eruption of Pregnancy

Polymorphic eruption of pregnancy (PEP), also known as pruritic urticarial papules and plaques of pregnancy (PUPPP) is a common and benign, self-limiting pregnancy dermatoses. Incidence is about 1 in 160 pregnancies, and it is the second most common dermatoses in pregnancy. PEP is commonly seen is primigravidae in their last weeks of pregnancy and is associated with increased maternal weight gain and with multiple pregnancies.

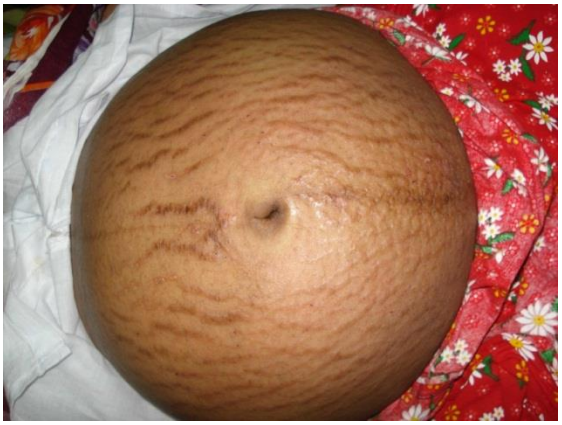

Figure 2: Polymorphic eruption of pregnancy.

The exact cause of PEP is unknown, but several theories suggest that rapid stretching of the abdominal skin, causing connective tissue damage (Figure 2), may lead previously inert structures to act as antigens, triggering an allergic reaction. These theories are supported by PEP starting within striae distensae at the time of maximum abdominal distention and commonly associated with pregnancy conditions with large abdomens such as twin pregnancies and polyhydramnios.

PEP usually starts during the last few weeks of pregnancy (85%) or during the immediate postpartum period (15%). Lesions typically start within the striae distensae and characteristically spare the umbilical region. PEP consists of severely pruritic papules, which coalesce to form pruritic plaques. Lesions may spread to upper thighs and buttocks, may be generalized in severe cases, but

usually spares face, palms and soles. Usually, the rash resolves in four to six weeks. Both maternal and fetal prognosis is excellent and usually, there are no skin manifestations in the newborn [7]. PEP usually does not recur except for subsequent multiple pregnancies. Histopathology is usually non-specific and changes with the stage of the disease.

Both direct and indirect immunofluorescence is negative. Routine investigations are always normal.

Management

Patients should be reassured regarding the benign nature of the disease. The majority of patients benefit from corticosteroid application and oral antihistamines. In severe or generalized cases, a short course of systemic corticosteroid (oral prednisolone) is very effective.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a rare form of hormone-induced cholestasis that develops in predisposed individuals in their late pregnancies. Unlike other pregnancy dermatoses, ICP presents with severe pruritus leading to secondary cutaneous lesions, but no primary skin lesions. There is a striking geographical difference in ICP. It is most common in South America with the highest incidence in Chile (15-28%) [8] and interestingly, ICP can run in families.

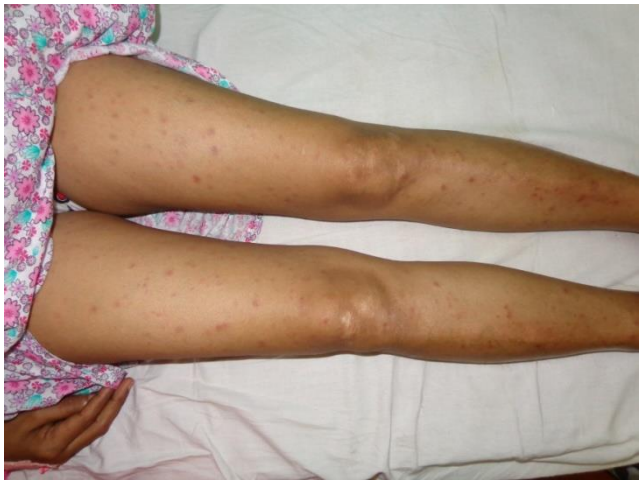

Figure 3: Intrahepatic cholestasis of pregnancy.

The key feature is the reduction of bile acid excretion, leading to increased serum bile acids levels, which is multifactorial in origin (Figure 3). Genetic, hormonal and external factors are involved in the pathogenesis of the disease. Genetic factors include mutations of genes that encode bile transporter proteins [9]. Levels of sex hormones are high in pregnancy and with hormonal contraception and may exceed the capacity of the transporters, leading to cholestasis. Furthermore, metabolites of estrogen and progesterone with cholestatic effects are high during pregnancy, contributing to the pathogenesis [10].

Patients are usually in their last trimester and present with severe generalized pruritus, which starts on the palms and soles. Characteristically the onset is sudden. Although there are no primary skin lesions, secondary skin lesions develop rapidly and range from scratch marks to severe nodular prurigo. The extensor surfaces of limbs, buttocks and abdomen are most severely affected. Jaundice is seen only in only10% of patients, usually associated with severe and prolonged ICP and is associated with steatorrhea, which can be complicated by malabsorption of fat-soluble vitamins including vitamin K, causing vitamin K deficiency, leading to the risk of intra and postpartum haemorrhage. ICP has the risk of premature births (19-60%), fetal distress (22-33%), and stillbirths (1-2%).

Pruritus persists till delivery and resolves spontaneously within days to weeks after the delivery.

ICP recurs in subsequent pregnancies in 45-70 % of patients and usually recurs with oral contraceptives. ICP is diagnosed when there is an unexplained pruritus in pregnancy with elevated liver function tests and or raised bile acid. Serum transaminases levels are elevated in 70% of patients. Direct bilirubin levels may be high and prothrombin time may be prolonged in patients with ICP with jaundice. Histopathology of skin and liver are non-specific.

Management

Early diagnosis and proper management are important, as fetal prognosis depends on disease activity. The aim is to reduce total serum bile acid levels. Ursodeoxycholic acid (UDCA) is the only available effective treatment to improve symptoms of severe pruritus as well as to improve fetal outcome. The usual dose is 15mg/kg, and should be started as early as possible and must be continued until the delivery.

Atopic Eruption of pregnancy

Atopic eruption of pregnancy (AEP) is either the first appearance or exacerbation of eczematous changes in pregnancy in mothers with atopic predisposition. AEP is the most common pregnancy dermatoses. The incidence is about 1in 120- 240 pregnancies. Pregnancy is characterized by changes in the immune system to

prevent fetal rejection. In pregnancy, cell-mediated immune function and Th1 cytokine (interferon gamma, IL -12) production depressed and humoral immune response and Th2 cytokine (IL -4, IL -10) production dominate. This switch towards predominant Th2 response worsens the imbalance already present in atopic individuals, leading to the atopic eruption, which is Th2 mediated [11].

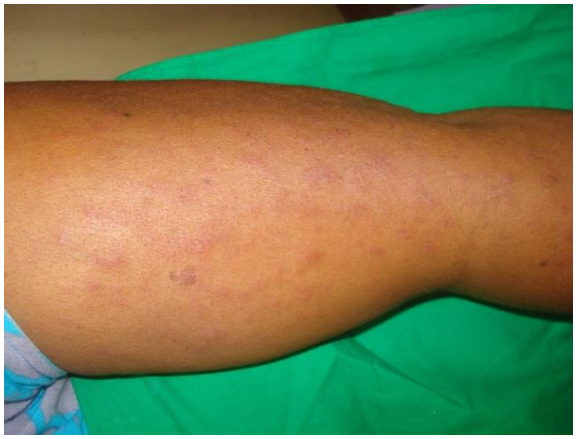

Figure 4: Atopic eruption of pregnancy

In contrast to other pregnancy-specific dermatoses, AEP occurs in early pregnancy, usually during the first trimester (Figure 4). Twenty per cent of women suffer from worsening of pre-existing atopic dermatitis, while the remaining 80% experience atopic dermatological manifestations for the first time during pregnancy or after a long remission (e.g. following childhood atopic dermatitis). One third develop papular lesions (P-type AEP) over the trunk and extremities, while other two thirds present with eczematous lesions (E-type AEP) over atopic sites such as the face, neck and the flexural aspects of the limbs. Extremely dry skin is a key feature, and other manifestations of skin atopy are present. Maternal and fetal outcomes are excellent, but infants may have atopic tendencies. Recurrences are common in subsequent pregnancies. Histopathological features may vary, depending on the stage of the lesion and often are non-specific. Serum IgE levels may be elevated in 20 to 70 % of patients, often to a mild degree.

Management

Regular application of emollients is essential, often with urea (3-10%) or with an antipruritic agent such as menthol. Both urea and menthol are considered safe in pregnancy (FDA category B). Lesions rapidly respond to topical corticosteroids. Severe disease may need systemic therapy with a short course of pregnancy appropriate oral corticosteroids (oral prednisolone) and antihistamines (e.g. Chlorpheniramine). Ultraviolet B (UVB) phototherapy is also an option in severe disease, which is considered safe during pregnancy. Antibiotics (topical and/or systemic) may be required to treat secondary bacterial infections.

	PG	PEP	ICP	AEP
Incidence	1/3000-50000	1/250	2/1000	1/120-240
Onset	Second and third trimester, post-partum	Third trimester	Second and third trimester	First and second trimester
Skin lesions	Vesicles and bullae form at the center or periphery of plaques. Begins periumbilically and spread to trunk and extremities.	Red papules and plaques begins related to abdominal striae, Umbilical sparing	Excoriation and papules secondary to scratching.	Multiple excoriated papules on abdomen and limbs. No urticarial lesions
Pruritus	+	+	+	+
Resolution	Few weeks to one year after delivery	Within two weeks after delivery	Few weeks after delivery	Several months after delivery
Histology	Subepidermal blisters	Epidermal edema	Non specific	Perivascular infiltration Patchy keratosis
Immunofluorescence	+	-	-	-
Management	Topical/Systemic steroids, Antihistamines	Calamine Lotion, Antihistamine	Ursedeoxy cholic acid	Aqueous cream
Fetal effect	Prematurity, Neonatal blisters	-	Premature births, fetal distress, Meconium stain liquor, Still birth	-
Recurrence	+	-	+	+

Table 3: Summary of Pregnancy Dermatoses.

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