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REVIEW ARTICLE

Specific Dermatoses of Pregnancy: A Review

Dermatoses spécifique de la grossesse: Un Examen

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ABSTRACT

BACKGROUND: **Some dermatoses worsen during pregnancy, some improve, yet others have unpredictable course.**

OBJECTIVE: **To conduct evidence-based search, and review of current management of specific dermatoses of pregnancy.**

METHODS: **Comprehensive literature search was conducted, with Medline and Cochrane Database regarding skin diseases in pregnancy from 1990–2005. International pharmaceutical abstracts science search (1997–2003) was used for search references found in the articles. All articles selected for inclusion in this review were evaluated critically with regards to their impact factor, source, and evidence based contribution on this topic as measured by their citation index and the journals they were published in. This review was limited to specific dermatoses of pregnancy generally and some of the skin disorders modified by pregnancy.**

RESULTS: **Intrahepatic cholestasis of pregnancy should be managed as high risk pregnancies as several investigations have shown foetal complications. Recent randomised trials have demonstrated beneficial effects of ursodeoxycholic acid (UDCA) in intrahepatic cholestasis of pregnancy (ICP). Pruritic eruption of pregnancy is associated with multiple pregnancies. It has variable clinical features and has to be differentiated from pemphigoid gestationis, which is associated with an increased incidence of both prematurity and small for date's babies. Prurigo of pregnancy is extremely itchy with papules appearing on the extensor surfaces of the limbs and trunk. It has no maternal risk. The eruptions in pruritic folliculitis of pregnancy clear spontaneously in the postpartum period, with no associated morbidity either in the mother or baby.**

CONCLUSION: **Some skin diseases like obstetric cholestasis may have adverse foetal outcome, while other disorders like pruritic folliculitis of pregnancy have no significant effect on either the mother or baby. WAJM 2011; 30(4): 239–244.**

Keywords: **Skin diseases of pregnancy, Intrahepatic Cholestasis Pemphigoid Gestationis.**

RÉSUMÉ

CONTEXTE: Certains dermatoses s'aggraver pendant la grossesse, certains d'améliorer, d'autres encore ont évidemment imprévisible.

OBJECTIF: Pour effectuer la recherche fondée sur des preuves, et l'examen de la gestion actuelle des dermatoses spécifiques de la grossesse.

MÉTHODES: recherche documentaire exhaustive a été menée, avec Medline et Cochrane Database concernant les maladies de la peau pendant la grossesse de 1990 à 2005. International Pharmaceutical Abstracts sciences de recherche (1997-2003) a été utilisé pour les références de recherche dans les articles. Tous les articles sélectionnés pour inclusion dans cette étude ont été évalués de façon critique à l'égard de leur facteur d'impact, la source, et la contribution des preuves fondées sur ce sujet tel que mesuré par leur indice de citation et les journaux qu'ils ont été publiés po Cet examen a été limitée à des dermatoses spécifiques de la grossesse en général, et quelques-uns des problèmes de peau modifié par la grossesse.

RÉSULTATS: cholestase intrahépatique de la grossesse doivent être gérés comme des grossesses à risque élevé comme les enquêtes l'ont démontré plusieurs complications fœtales. De récents essais randomisés ont démontré des effets bénéfiques de l'acide ursodésoxycholique (UDCA) dans la cholestase intrahépatique de la grossesse (ICP). Éruption prurigineuse de la grossesse est associée aux grossesses multiples. Il a des caractéristiques cliniques variables et doit être différenciée de pemphigoïde gestationis, qui est associée à une incidence accrue de prématurité et deux petites pour les bébés de ce jour. Prurigo de la grossesse est extrêmement irritante avec papules apparaissant sur la surface des extenseurs des membres et du tronc. Il n'a pas de risque pour la mère. Les éruptions de folliculite prurigineuse de la grossesse disparaître spontanément dans la période post-partum, sans morbidité associée soit à la mère ou le bébé.

CONCLUSION: Certaines maladies de peau comme obstétriques cholestase peut avoir des effets issue fœtale, tandis que d'autres troubles comme la folliculite prurigineuse de la grossesse n'ont pas d'effet significatif ni sur la mère ou le bébé. **WAJM 2011; 30 (4): 239–244.**

Mots-clés: grossesse, dermatoses, Gestationis intrahépatique Cholestase Pemphigoïde.

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Abbreviations: AIED, Autoimmune Oestrogen Dermatitis; **AIPD,** Autoimmune Progesterone Dermatitis; **BMZ,** basement membrane zone; **HCH,** Human chorionic gonadotrophins; **ICP,** Intrahepatic cholestasis of pregnancy; **PEP,** Polymorphic Eruption of Pregnancy; **PFP,** Pruritic Folliculitis of Pregnancy; **PG,** Pemphigoid Gestationis; **PP,** Prurigo of Pregnancy; **PUPPP,** Pruritic urticarial papules and plaques of pregnancy; **UDCA,** Ursodeoxycholic acid.

INTRODUCTION

Pregnancy dermatoses are a group of disorders that occur as a consequence of immune, endocrine, metabolic and vascular changes during pregnancy. The dermatoses of pregnancy are divided in to three groups: dermatoses that are exclusive to pregnancy, specific dermatoses of pregnancy and dermatoses that are modified during pregnancy. This review will outline recent developments with greater emphasis on specific dermatoses of pregnancy, disease entities almost exclusively related to pregnancy or the puerperuim. These include pemphigoid gestations, prurigo of pregnancy, pruritic folliculitis of pregnancy, and polymorphic eruptions of pregnancy. Current treatment and foetal complications of intraheaptic cholestasis are also described.

Physiological Skin Changes

Pregnancy, childbirth and the puerperium are associated with profound physiological and endocrine changes. The physiological events of pregnancy can modify a number of concomitant dermatoses, while some pathological skin conditions are virtually pregnancy specific.

Hyperpigmentation, pigmentory demarcated lesions and chloasma are some of the localised and generalised skin changes that develops during the second half of pregnancy and can occur in up to 90 percent of pregnant women.[1,2] These are thought to be due to increase in the melanin pigment under the skin. Palmer erythema may present as mottled erythema distributed on the entire surface of the palm, or as a diffuse redness which is more prominent over the thenar and hypothenar eminences.

These changes are most prominent in the patients with darkly pigmented skin, although they also occur to some degree in pregnant women with fair skin. Perhaps the most familiar example to obstetricians is the darkening of the lower midline called the linea nigra; a midline streak, which usually extends from the symphysis pubis to the umbilicus and can sometimes extend to the xyphoid process.

Pruritus is the principle cutaneous symptom during pregnancy, with and estimated incidence of 17%. Pruritis gravidarum refers to the intense, which occurs late in pregnancy in the absence of any associated (apart from excoriations secondary to scratching) or clinincal jaundice. It is important to exclude other possible causes of pruritus such as scabies, pediculosis eczema drug eruptions and most importantly obstetric cholestasis.

Some dermatoses worsen during pregnancy, some improve, and many are unpredictable, yet others like papular dermatitis are less well define. In addition there are certain autoimmune conditions that do not even fit into any of the classifications, yet they may have adverse outcome in pregnancy. These are the Autoimmune Progesterone Dermatitis (AIPD) and the Autoimmune Oestrogen Dermatitis (AIED).[3–5]

This review will look at the current acceptable classification of dermatoses in pregnancy and their effect on the foetal outcome. A brief mention will be made of AIPD and AIED.

There is no entirely satisfactory method of classification of skin diseases. Traditionally dermatologists have used morphological classification where the condition was often described in Latin. At present modern dermatologist are doing their best to described skin diseases according to bio chemically defined functional or genetic abnormalities.[6,7]

While the terminology of specific dermatoses of pregnancy continues to be confusing and misleading, a number of attempts have been made in literature to resolve them. A number of eponyms have been used for Intrahepatic Cholestasis of Pregnancy, including Obstetric Cholestasis, Recurrent Jaundice of Pregnancy and Icterus Gravid arum. Holms and Black[8–10] published their proposal in 1982[11] and 1993 of a simplified clinical classification of the specific dermatoses of pregnancy and is now widely accepted.

Unfortunately, except for Pemphigoid Gestationis no reliable criteria exist to differentiate the specific dermatoses of pregnancy.[11] Nevertheless the proposed simplified clinical classification appears to have gained International acceptance.[12,13] It is clear that there is still much to be done to elucidate the pathogenesis of specific dermatomes of pregnancy.

Obstetric Cholestasis (Intrahepatic Cholestasis of Pregnancy)

Incidence: Obstetric cholestasis is manifested by pruritus in pregnancy with or without laboratory evidence of cholestasis. The incidence of ICP in Europe varies from 100–150 per 10,000 pregnancies. In the United States the incidence is approximately 70 in 10,000 pregnancies. The disorder is a genetically

Table 1: Classifcation of Specific Dermatoses of Pregnancy

Dermatosis	Special Features
Obstetric cholestasis	Manifests with intense itching associated with multiple pregnancy recurrence in over 60% typically presents in the 3rd trimester. Increase of still birth and preterm delivery.
Polymorphic Eruptions of Pregnancy	Most common predominantly found in primigravidas lesion overlie the striae, on the abdomen tends to occur in 3rd trimester.
Pemphigoid gestationis	Associated with GTD Lesion confine to preiumblicus small for date babies.
Prurigo of pregnancy	Predominantly in 2nd &3rd trimester papules appear on the extensor surfaces of extremities and trunk lesion extremely itchy tend to occur in subsequent pregnancies
Pruritic folliculitis	Strongly resembles steroid-induces acne clears spontaneously after delivery. No risk of recurrence

linked oestrogen-dependent condition, which results in cholestasis with or without jaundice. It usually begins in the latter half of pregnancy. There is a family history of jaundice in 50% of cases and an association with multiple pregnancies. Recurrence in subsequent pregnancy occurs in 60–70% of cases.[14, 15]

Aetiology: The exact aetiology is unknown. It is thought to be multifactorial.[15]

Recent studies indicate higher incidence of ICP in mothers of patients with progressive familial intrahepatic cholestasis or benign recurrent intrahepatic cholestasis.[16,17]

Clinical Features: The disorder typically presents in the last trimester of an otherwise normal pregnancy, although initial presentation as early as 8 weeks has been reported.[18,19] Intense generalised itching occurs, which is invariably worse at night, and presents throughout the duration of the pregnancy. Pruritus may often be localised particularly to the palms and soles.

The result of physical examination is usually normal apart from the widespread excoriation, and skin biopsies are unhelpful. A typical biochemical finding is of a markedly increased level of total serum bile acids. Others may include moderately raised levels of conjugated bilirubin and alkaline phosphatase,. Liver transaminases are usually only slightly raised, to differentiate it from the significantly raised levels that are found in infectious hepatitis.

Hepatic ultrasound scan is normal and liver biopsy is not indicated in ICP.. *Foetal risk* in ICP includes foetal distress, stillbirths and preterm delivery,[18, 19] which are all the result of placental anoxia. Decreased foetal elimination of toxic bile acids may cause vasoconstriction of placental chorionic veins *in vitro,*[20] and meconium passage. Stillborn infants in ICP often lie in meconium stained amniotic fluid and can cause acute umbilical vein constriction. Most authors recommend intensive foetal surveillance and induction of labour at 38 weeks gestation or after the demonstration of mature lecithin-sphingomyelin ratio. This may result in increased foetal survival. In postpartum, foetal intracranial haemorr-hage are particular risks, due to malabsorption of fat soluble vitamin K. The latter is therefore recommended.

Treatment: Mild ICP may respond to symptomatic treatment with emollients and topical antipruritics. Ursode-oxycholic acid (UDCA), a naturally occurring hydrophilic bile acid is now used to treat this disorder. It enhances the excretion of hydrophobic bile acids and other hepatotoxic compounds and sulphated progesterone metabolites.[21,22] UDCA reduces the bile acids levels in cord blood, amniotic fluid and colostrums. The recommended dose is 15mg/kg/day both to reduce symptoms and improve foetal outcome. It has been shown to reduce premature labour, foetal distress and foetal deaths.[23]

Polymorphic Eruption of Pregnancy (PEP)

Incidence: Polymorphic eruption of pregnancy also known as pruritic urticarial papules and plaques of pregnancy (PUPPP) is probably the most common of the gestational dermatoses It affects about one in 160 to 240 pregnancies. The condition occurs predominantly in primigravidas in the third trimester and exceptionally postpartum It rarely recur in subsequent pregnancy, but when it does it is often less severe.[23]

There is still no consensus on which name to use. In the UK as proposed by Holmes and Black,[24] the term polymorphic eruption of pregnancy is favoured. Elsewhere the lengthy descriptive phrase PUPPP is widely used especially in the USA as suggested by Lawley *et al.* [25]

Pathology: Polymorphic eruption of pregnancy is an imflammatory dermatosis associated solely with pregnancy. It is an ill-defined entity because of its variable clinical presentation, lack of pathognomic diagnostic features and of laboratory abnormalities. Direct immuno-flourescence is negative in the great majority of patients. However some investigators have reported equivocal findings such as minimal C3 deposition along the basement membrane zone (BMZ), perivesicular C3 and fibrin deposition in the dermis. Scurat [34] has stressed the importance of performing DIF in patients with PEP.

Aetiology: The cause remains obscure, although the condition has been related to abnormal weight gains in the mother and newborn and to twin pregnancy. It has been postulated that excessive abdominal distension may acts a trigger for the skin changes. [27]

The association of PEP with multiple pregnancies is further supported by a recent study of Elling *et al* [23] The author reported a prevalence of 7.89 cases out of 200 multiple gestation pregnancies compared with one case out of 200 singleton pregnancies. It has been shown that serum cortisol levels are low in patients with PEP, while human chorionic gonadotrophins (HCG) and oestradiol are normal.

Clinical Features: Polymorphic eruption of pregnancy may have variable clinical morphology and may be confused with several disorders. The most important differential diagnosis is Pemphigoid Gestationis (PG) and the following points should be considered.

- Examination of striae distension is important because lesions overlying the striae are found in 90% of patients with PEP, but are seldom prominent in PG.
- Vesicles in PEP patients are unlikely to be larger than 2–3 in diameter; however once they occur in PG, they evolve rapidly into larger tense bullae.
- Involvement of periumbilical skin is a common finding (84%) in PG, but observed only in 10% of PEP patients.
- The most striking feature however is the distribution of the lesions. They usually begin and predominate on the abdomen, often closely following the lines of the striae where present.

Treatment: Apart from the discomfort of pruritus, the maternal prognosis is

unaffected. It is generally agreed foetal prognosis is normal.[28,29] The disease is self-limiting, and the rash disappears at or soon after birth.. Most patients can obtain relief with the use of moderate potent topical corticosteroids cream, topical calamine and systemic sedatives.

Pemphigoid Gestationis

Incidence: The incidence of pemphigoid gestationis (PG) is estimated between 1 in 40,000–60,000 pregnancies, and the disease most commonly manifests itself in the second and third trimester.[31] A flare at the time of delivery is a typical feature seen in 75% of cases.[32, 33] Initial presentation postpartum may be "explosive" and occurs in approximately 14% of women. The disease is likely to recur with an earlier onset and more flaccid expression, although subsequent pregnancies may occasionally be unaffected. Such "skip pregnancies" have an incidence of approximately 8% but remain unpredictable on a prospective basis using available data.[35,36] Foetal and neonatal disease presenting as cutaneous lesion may be found in 5–10% of infants born to PG mothers.

Aetiology: Pemphigoid Gestationis is a rare autoimmune bullous disease that occurs during pregnancy and puerperium, being associated occasionally with trophoblastic tumour, hydatidiform mole and choriocarcinoma.[31]

Clinical Features: The clinical features of the disease are pruritic, erythematous, urticarial papules and plaques, which may become target-like, developing into annular wheals or they become polycyclic. In 90% of patients the eruption is initially confined to the periumbilical areas, before spreading to the entire abdomen, palms and soles. There is a controversy about whether or not PG is associated with an increased in foetal morbidity or mortality rates. Recent large study found no evidence of spontaneous abortion or significant mortality, but did demonstrate an increased incidence of both prematurity and small for date babies.[37,38]

Diagnosis: Differential diagnosis of PG from other cutaneous lesions is usually not difficult; once the typical blisters have begun to develop. The vesicles and bullous distinguish from other dermatosis of pregnancy such as prurigo of pregnancy. In most clinical setting the most important differential diagnosis is between PG and PEP, and the key to differentiate the two is immunofluorecence.

Pathogenesis: Recent studies involving tissue typing have supported earlier suggestion of a genetic predisposition. Immunoflourescence revealed a linear band of immunoglobilinG (IgG) at the basement membrane, identical to that seen in bullous Pemphigoid.

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Treatment: The aim of therapy in patients with PG is to relieve pruritus, suppress blister formation, and prevent erosions, secondary infection, and scarring of lesion sites.

Early urticarial lesion may respond to topical corticosteroids[39,40] but more advanced lesions require oral corticosteroids. Refractory cases during the postpartum period may respond to adjunct therapy with cyclophosphamide, pyridoxine, gold or methotrexate. Experience with each has been variable.[41,42] Chemical oophorectomy with goserelin has been used in exceptionally chronic PG with some success in the postpartum period.[43, 44]

Prurigo of Pregnancy

Incidence: In 1907, Besnier first introduced the term "prurigo of pregnancy" (PP). The incidence of PP varies from 1 in 300 to 1 in 450 pregnancies[45–47] and occurs pre-dominantly in the second or third trimester of pregnancy and can persist for up to three months postpartum.

Aetiopathogenesis: The histopathology is non-specific and immunoflourescence negative.

Clinical Features: The clinical lesions are discrete erythematous or skin-coloured papules, which are extremely pruritic. Characteristically the papules appear on the extensor surfaces of the extremities and trunk and do not progress to vesicle formation There are no maternal risks, and the outcome is favourable, but prurigo of pregnancy may occur in successive pregnancies which can cause significant distress to the pregnant woman.

Treatment: Treatment is symptomatic, and this is rather unsatisfactory. Occasional use of tapering doses of prednisolone has been tried.[48,]

Pruritic Folliculitis of Pregnancy (PFP)

Incidence: The term Pruritic folliculitis of pregnancy was first described by Zoberman and Farmer in 1981.[43]

Aetiopathogenesis: Histology reveals a non-specific folliculitis and Immunoflourescence is negative. Further studies are necessary to define PFP as a separate entity and establish its pathogenesis

Clinical Features: The eruption consists of masses of itchy red follicular papules. It strongly resembles steroid-induced acne .there is no associated significant morbidity either in the mother or fetus.

Treatment: There is no specific treatment required as the disorder clear spontaneously after delivery, and in the postpartum period.

Skin Diseases Modified by Pregnancy

Certain more common dermatoses may be affected by pregnancy. These include psoriasis, eczema, scabies and melanomas.

Psoriasis

The fact that psoriasis is one of the commonest of all skin conditions accounts for its apparent high incidence during pregnancy. There are conflicting opinions regarding the effect of pregnancy on psoriasis. Flex oral psoriasis is liable to be aggravated during pregnancy.

Treatment is generally aimed at soothing the inflammatory reaction, relieving irritation and prescribing suitable remedies for the monolial or pyogenic infection if present. It is important to explain to the patient the chronic nature of the disease and the fact that currently available treatment control rather than cure the disease.

Eczema and Scabies

The areola and nipple are common site for eczema in a pregnant woman. Eczematous Lesions on the breast may also be due to scabies and if there is any reason to suspect this, a search should be made for scabetic burrows in the body.

The possibility of scabies should always be considered in any eruption associated with pruritis in pregnancy, which has nocturnal exacerbations even when urticarial lesions are present. Treatment includes a warm bath with soap and application of benzyl benzoate.

Malignant Melanoma

The malignant melanoma, while fortunately not so common, tends to be activated by pregnancy. It is highly malignant, dangerous and unpredictable neoplasm. It is known that moles become darker during pregnancy and that benign *naevi* may sometimes become malignant at these times. The pigmented lesion may be present, although invisible as a result of increased pigmentation, which normally occurs in the skin during pregnancy. The general consensus is that cases of suspected *melanoma* should be referred to, immediately to surgeons for wide and deep excision under general anaesthesia irrespective of the stage of pregnancy.

Pruritis of Pregnancy

Pruritis generally means itching. It is a symptom for most of the specific dermatoses related to pregnancy discussed above; and can be a manifestation of metabolic illness such as diabetic, uraemia or a symptom of some psychiatric states such as melancholic depression or drugs. During pregnancy it is quite common and although usually mild, may be severe enough to interfere with sleep and exhaust the patient mentally and physically. Careful history is mandatory to arrive at diagnosis. Where no definitive cause can be found, antipruritics and corticosteroids could be cautiously prescribed.

Other Dermatoses

Autoimmune Progesterone Dermatitis of Pregnancy

The term was introduced in 1964 by Shelly *et al.* A case in the literature was reported of a patient who developed an odd acne form rash on the extremities and buttocks in two successive pregnanacies.[49,50] There was an associated arthritis and a positive skin test reaction to progeaterone.Onset of worsening of eruptions during pregnancy has been reported in two cases.[50] This may not be unexpected as progesterone level rises steadily during pregnancy.

Prurigo Annularis

Persistent scaly annular lesion has been reported in two patients in the postpartum period. It is difficult to say whether they have anything to do with pregnancy.

Papular Dermatitis

A lot of controversy surround this entity .which was first described by Spangler *et al* in 1962.[52,53] Essentially is a 3–5mm, intensely itchy widespread papular eruption with a smaller central crust estimated to occur only once in every 2400 pregnancies. There were several laboratory abnormalities, including markedly raised gonadotrophins and *low* urinary oestriol. Most importantly was observation that there appeared to be a 30% foetal mortality with this eruption. However there, have been no other convincing reports and a recent review of 85 patients found no evidence of increased foetal loss.[51]

It is generally accepted that the changes reported as papular dermatitis of pregnancy are probably those of prurigo of pregnancy.

Conclusion

Pregnancy results in immunologic, endocrine, metabolic and vascular changes in the pregnant woman which modify her response to skin disease. Both the obstetrician and dermatologist need to be aware of this potential, if they are to provide optimal management during pregnancy. Major advances have contributed to a better understanding of the classification, pathogenesis and treatment of the specific dermatosis of pregnancy.

At present difficulty still exists in distinguishing ICP from PP, PFP from PEP and protracted postpartum PG from conversion to Bullous Pemphigoid. The current clinical diagnostic criteria of these disorders may be insufficient to make these distinctions.

Biopsy for direct immunofluorescence is necessary when PG is a consideration and biochemical tests like LFT's, bile salts are important when ICP is suspected, because these two dermatoses are associated with foetal risks. When the diagnosis of PEP, PFP or PP is evident by history and physical examination, a work up may not be necessary, because these dermatoses are mostly benign for mother and fetus. Potential foetal and maternal risk associated with PG and ICP must be discussed with the patient.

It is clear that, there is still much to be done in elucidating the pathogenesis of the specific dermatoses of pregnancy. A team approach that involves dermatology, paediatrics and obstetrics is the optimal way to treat the potential maternal, foetal and neonatal complications of these dermatoses.

REFERENCES

1. Vaughan-Jones SA, Black MM, Pregnancy dermatoses. *J Am Dermatol.* 1999; **40:** 233–241.
2. Worjnarwska F, Greows MW, Pearches RD. Progesterone induced erythema multiforme. *J R Soc Med.*1988; **78:** 407–408.
3. Black MM, Maou SC. Skin diseases in Pregnancy. In: de SweitM, ED Medical Disorders in Obstetrics Practice, 2nd edn. Oxford: Blackwell Scientific Publications. 1989; 808–29.
4. Stephens CJM, Wojnanowska FT, Wilkinson JD. Autoimmune progesterone dermatitis responding to tamoxifen. *B J Dermatol.* 1989; **121:** 135–137.
5. Farah FS, Shabaklu Z. Autoimmune progesterone urticaria. 1971, *J Allergy Clin Immunol.* 1971; **48:** 357–361.
6. Georgouras K, Autoimmune progesterone dermatitis. *Aust J Dermatology.* 1981; **22:** 109–11.
7. Lee AY, Lee KH, Lim YG. Oestrogen urticaria associated with pregnancy. *Br J Dermatology.* 1999; **141:** 774.
8. Black MM, Vaughan-Jones. In Obstetric and Gynaecologic Dermatology. Second edition. 2002; Mosby International Ltd.
9. Lammert F, Marshall H-U, Glantz A, Matern, Intrahepatic cholestasis of pregnancy: molecular pathogenesis,

diagnosis and management. *Hepatol.* 2001; **3:** 1012–21.
10. Kroumpouzos G. Intrahepatic cholestasis of pregnancy: What's new? (Editorial) *J Eur Acad Dermatol Venerol.* 2002; **16:** 316–8.
11. Fisk M, Storey GNB. Foetal outcome in obstetric cholestasis. *Br J Obstet Gynaecol.* 1998; **95:** 1137–43.
12. Sepulveda WH, Gonzalez C, Crus MA, Rudolph, MI Vasocontrictive effect of bile acids on isolated human placental chorionic vein. *Eur J Obstet Gynecol Reproduct Biol.* 1991; **42:** 211–5.
13. Shaw D, Frohlich J, Wittmann MA. Prospective study of 18 patients with cholestasis of pregnancy. *Am J Obstet Gynecol.* 1982; **4:** 621–5.
14. Campos GA, Guerra FA, Israel EJ. Effects of cholic acid infusion in foetal lambs. *Acta Obstet Gynecol Scand.* 1986; **65:** 23–6.
15. Kroumpouzos G, Cohen LM. Specific dermatosis of pregnancy. An evidence-based systematic review. *Am J Obstet Gynecol.* 2003; **188:** 1083–92.
16. Kroumpouzos G, Cohen LM. Dermatosis of pregnancy. *A Am Acad Dermatol.* 2001; **45:** 1–22.
17. Vaughan-Jones, S. A., Hem, S., and Black M.. M. Neutrophil folliculitis and serum androgen levels. *Clinical and Exp Dermatology.* 1999; **24:** 392–395.
18. Shornick JD. Dematosis of Pregnancy. *Semin Cutan Med Surg.* 1998; **17:** 172–81.
19. Hayes PM, Sonelzer JS. Multiple gestation. *Clin Obstet and Gynecol.* 1986; **29:** 264–85.
20. Charles-Holmes, Wade TR. Polymorphic eruption of pregnancy. Serum Dermatol. 1989; **8:** 18–22.
21. Holmes RC, Black MM. The specific dermatoses of pregnancy towards a comprehensive view? Arch. Dermatol. 1994; **130:** 778–780.
22. Alcalay J, Wolf JE. Pruritic Urticarial papules and plaques of pregnancy: the enigma and the confusion. *J Am Acad Dermatol.* 1988; **65:** 1115–1116.
23. Elling SV, Yee KC, Cunliffe WJ. Progesterone-induced urticaria: response to buserelin. *Br J Dermatol.* 1994; **130:** 121.
24. Alger LS, Farley JJ, Robinson BA, Hines SE, Borchin JM, Johnson JP. Interactions of human immunodeficiency virus infection in pregnancy. *Obstet Gynecol.* 1993; **82:** 787–96.
25. Lawley TJ, Hertz KC, Wade TR. Pruritic urticarial papules and plaques of pregnancy. *J Am Med Assoc.* 1979; **241:** 1696–1699.
26. Yancey KB, Hall RP, Lawley TJ. Pruritic urticarial papules and plaques of pregnancy. *J Am Acad Dermatol.* 1984; **10:** 473–480.
27. Alcalay J, Tugher A, Kafri B. Hormonal evaluation and autoimmune background in pruritic urticarial papules and plaques of pregnancy. *Am J Obstet Gynecol.* 1988; **158:** 417–420.
28. Jenkins RE, Sharick JK, Black MM. Pemphigoid gestationis associated with choriocarcinoma. *Arch Dermatol.* 2000; **136:** 129–30.
29. Kolodny RG, Herpes gestationis: a new assessment of incidence and foetal prognosis. *Am J Obstet Gynecol.* 1969; **1054:** 39–45.
30. Engineer L, Bhol K, Ahmed AR. Pemphigoid gestationis: A review. *Am J Obstet Gynecol.* 2000; **183:** 483–491.
31. Jenkins RF, Hern S, Black MM. Clinical features and management of 87 patients with pemphigoid gestationis. *Clin Exp Dermatol.* 1999; **24:** 255–259.
32. Shornick JK, Black MM. Foetal risks in herpes gestationis. *J Am Acad Dermatol.* 1992; **26:** 63–68.
33. Chimanovitch I, Schmidt E, Mesier G, Dôpp R, Partscht K, Brôker EB. IgG 1 and IgG 3 are the major immunoglobulin subclasses targeting epitomes within the NC16A domain of BP180 in pemphigoid gestationis. *J Inves Dermatol.* 1999; **113:** 40–42.
34. Kelly SE, Cerio R, Bhogal BS, Black MM. The distribution of IgG subclasses in pemphigoid gestationis. PG factor is an IgG antibody. *J Invest Dermatol.* 1989; **92:** 695–8.
35. Lin MS, Ghavia M, Fu CL, Olague-Marchou M, Hacker M, Harman KE. Molecular mapping of the major epitopes of BP180 recognised by herpes gestationis autoantibodies. *Clin immunol.* 1999; **92:** 285–92.
36. Yancey KB. Herpes gestationis. *Dermatol Clin.* 1990; **8:** 727–34.
37. Hashimoto T, Amagai M, Murakam H. Specific detection of anti-cell surface antibodies in herpes gestationis. *Ser Exp Dermatol.* 1996; **5:** 96–101.
38. Nurses DS. Prurigo of Pregnancy. *Australus J Dermatol.* 1968; **9:** 258–67.
39. Roger D, Vaillant L, Fignon A, Pierre F, Baig Y, Brechot JF. Specific pruritus dermatoses of pregnancy; a prospective study of 3192 women. *Arch Dermatol.* 1994; **130:** 734–39.
40. Kasdon SC. Abdominal Pruritus in Pregnancy. *Am J Obstet Gynecol.* 1953; **65:** 320–324.
41. Bos JD. Reappraisal of Dermatitis of Pregnancy. *Lancet.* (2) 1999; **354:** 1140–2.
42. Holmes RC, Black MM. The specific dermatoses of pregnancy. *J Am Acad Dermatol.* 1983; **8:** 405–12.
43. Zoberman E, Farmer ER. Pruritic folliculitis of pregnancy. *Arch Dermatol.* 1981; **117:** 20–22.
44. Wilkinson SM, Buckler H, Wilkinson N. Androgen levels in pruritic folliculitis of pregnancy. *Clin Exp Dermatol.* 1985; **20:** 234–236.
45. Vaughan Jones SA, Hern S, Black MM. Pruritic folliculitis and serum androgen levels. *Clin Exp Dermatol.* 1999; **24:** 392–395.
46. Reed, J., George, S. Pruritic follicules of pregnancy treated with narrow band (TL–01) Ultraviolet B phototherapy (letter) *Br J Dermatol.* 1999; **141:** 177–179.
47. Black MM. Prurigo of pregnancy, papular dermatitis of pregnancy and pruritic folliculitis of pregnancy. *Semin Dermatol.* 1989; **8:** 23–5.
48. Beltrani VP, Beltrani VS. Pruritic urticarial papules and plaques of pregnancy: a severe case requiring early delivery for relief of symptoms. *J Am Acad Dermatol.* 1992; **26:** 266–267.
49. Vaughan Jones SA, Hens S, Nelson-Piercy C, Seed PT, Black MM. A prospective study of 200 women with dermatosis of pregnancy correlating clinical findings with hormonal and immunopathological profile. *Br J Dermatol.* 1999; **141:** 71–81.
50. Borrego L. Follicular lesions in polymorphic eruption of pregnancy (letter) *J Am Acad Dermatol.* 2000; **43:** 146.
51. Gouzales MC, Reyes H, Ribalta J. Intrahepatic cholestasis of pregnancy in twin pregnancies. *J Hepatol.* 1989; **9:** 84–90.
52 Sprangler AS, Reddy W, Bardonil WA, Roby CC, Emerson K. 1962, *JAMA* **181:** 577.
53. Cunningham FG, Gant NF, Leveno KJ, Gistrap111 LC, Hauth JC, Wenstrom KD, 2001, Williams Obstetrics 21st ED. McGraw Hill Co. Inc. 1429.