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Skin disease in pregnancy

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Skin problems are common during pregnancy, but accurate diagnosis can be difficult. Skin changes in pregnancy can be broadly divided into physiological (box 1),[1] specific dermatoses of pregnancy, and other common skin diseases in pregnancy.

In our experience of pregnancy skin clinics, approximately 50% of women present with an exacerbation of a common inflammatory skin disease (for example, eczema, psoriasis, acne, rosacea) or a skin infection. Around 30-50% of women present with one of the specific dermatoses of pregnancy (pemphigoid gestationis, polymorphic eruption of pregnancy, or atopic eruption of pregnancy).[2] Pregnancy causes specific management issues, and there is often confusion over which treatments can be used safely for treating skin disease in pregnancy. Itching can occur in up to 1 in 5 normal pregnancies (physiological pruritus) but is also the presenting symptom of many of the pregnancy dermatoses (box 2).

This review aims to familiarise readers with the clinical presentations of common skin diseases in pregnancy, outline the steps for confirming an accurate diagnosis, and evaluate the safest and appropriate treatments.

Why is skin disease common in pregnancy?

To prevent rejection of the fetus during pregnancy, profound changes occur in the woman's immune system, with a shift from a predominantly T helper 1 lymphocyte profile to a T helper 2 profile.[3] This transition changes the cytokines that are produced by the placenta, so that levels of interleukin 12 and y interferon are reduced and levels of interleukins 4 and 10 are increased. These changes influence a woman's susceptibility to skin disease, increasing the risk of autoimmune disease and reducing cell mediated immunity (thereby increasing the risk of skin infections). Diseases such as psoriasis that are driven by the T helper 1 immune response tend to improve, whereas those driven by the T helper 2 immune response, such as atopic eczema and systemic lupus erythematosus, may be exacerbated.[4]

SUMMARY POINTS

- Pregnancy causes changes in the immune system that result in an increase in autoimmune disease and reduction in cell mediated immunity
- The two commonest skin conditions in pregnancy are atopic eruption of pregnancy and polymorphic eruption of pregnancy
- Pemphigoid gestationis is a rare autoimmune bullous disease that can cause reduced fetal growth and prematurity
- Many common skin diseases may flare in pregnancy and treatment may need to be modified for the safety and wellbeing of the mother and fetus
- Pemphigoid gestationis, pemphigus vulgaris, and systemic lupus erythematosus can all lead to neonatal involvement from passive transfer of maternal antibodies across the placenta
- Emollients are the mainstay of treatment in reducing pruritus and giving women relief of symptoms

SOURCES AND SELECTION CRITERIA

We searched Medline, Embase, the Cochrane Database of Systematic Reviews, and Clinical Evidence online using the terms "skin and pregnancy" and "pregnancy dermatoses". When possible, we used evidence from randomised controlled trials and systematic reviews. In the absence of higher level evidence (as trials are lacking in pregnant women) we included case series. We also referenced review articles by experts and included expert opinion based on clinical experience.

Box 1 | Physiological skin changes in pregnancy

- Hyperpigmentation—linea nigra, areolae, melasma, naevi, vulvar melanosis
- Striae distensae—increased in third trimester
- Pruritus gravidarum—common in the first and second trimester (affects 1 in 5 women)
- Hair changes—telogen effluvium (post partum)
- Nail changes—ridging, splitting, distal onycholysis, longitudinal melanonychia
- Vascular changes—telangiectasia, varicosities, pyogenic granulomas, haemangiomas, peripheral oedema
- Eccrine glands—activity increased (increased sweating)
- Apocrine glands—activity reduced (reduced sweating and apocrine secretion)
- Sebaceous glands—activity increased (in third trimester)
- Immune system—shift from T helper 1 to T helper 2 lymphocyte profile

What are the specific dermatoses of pregnancy?

The specific dermatoses of pregnancy represent a heterogeneous group of severely pruritic inflammatory dermatoses associated exclusively with pregnancy or the immediate postpartum period. These dermatoses have been reclassified recently.[2] Atopic eruption of pregnancy, a new term, describes a disease complex that includes women with a former diagnosis of atopic eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy. A large retrospective two centre study of over 500 pregnant women with pruritus showed considerable overlap both clinically and histopathologically among these entities (together accounting for 50% of the cohort).[2]

The pruritus associated with polymorphic and atopic eruption of pregnancy is distressing to the mother, but pemphigoid gestationis may also be associated with prematurity and small for date babies, and intrahepatic cholestasis of pregnancy increases the risk for fetal distress, prematurity, and stillbirth. Itching in intrahepatic cholestasis is often nocturnal and affects the palms and soles (unlike physiological pruritus). In patients with pruritus and absence of skin lesions other than excoriations it is important to exclude a diagnosis of intrahepatic cholestasis of pregnancy by carrying out a

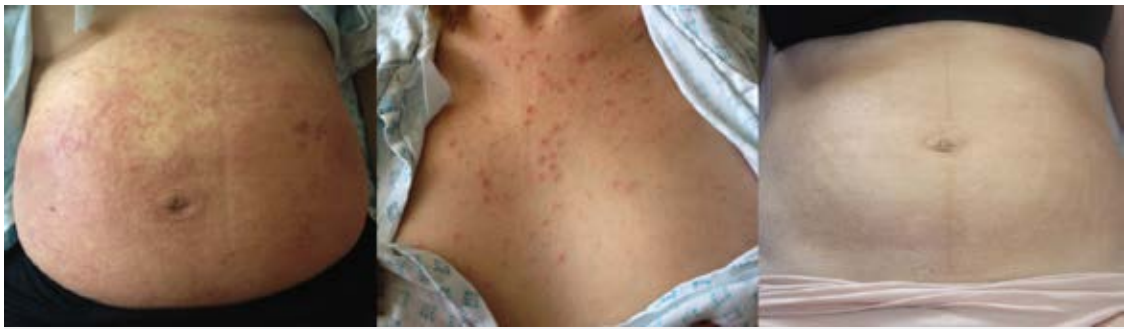

Fig 1 | Polymorphic eruption of pregnancy on abdomen and upper chest of woman with triplet pregnancy at 34 weeks' gestation and at four weeks after delivery following treatment with prednisolone

clinical assessment for signs of liver disease and performing liver function tests.[5] As intrahepatic cholestasis of pregnancy has been discussed extensively,[5] this review concentrates on the other three conditions.

Pemphigoid gestationis

Pemphigoid gestationis is a rare, self limiting autoimmune bullous disorder of mainly late pregnancy but can occur in any of the three trimesters. Its incidence varies from 1 in 2000 to 1 in 50 000-60 000 pregnancies, depending on the prevalence of the HLA haplotypes DR3 and DR4.[6]

Circulating complement fixing IgG antibodies bind to a 180 kDa protein, BP-180 or bullous pemphigoid antigen 2, in the hemidesmosomes of the basement membrane zone of the skin, leading to tissue damage and blister formation. These antibodies can be detected by direct immunofluorescence of perilesional skin as well as by indirect immunofluorescence of the serum in 30-100% of cases.[7] Pemphigoid gestationis presents with intense pruritus followed by urticarial papules and plaques, which typically develop on the abdomen and mostly within the umbilical region. Lesions may involve the entire body surface and usually progress to tense blisters.[6] Improvement in late pregnancy is often followed by postpartum flare (75% of cases) after which lesions usually resolve within weeks to months. Recurrence may occur with menstruation and hormonal contraception and should be expected in subsequent pregnancies. There is an increase in prematurity and small for date babies, which correlates with the severity of disease, as represented by early onset and blister formation.[8] As a result of passive transfer of antibodies from the mother to the fetus, about 10% of newborns may develop mild skin lesions, which resolve spontaneously within days to weeks.[6]

Box 2 | Causes of itching in pregnancy

Skin rash present

- Atopic eruption of pregnancy
- Polymorphic eruption of pregnancy
- Pemphigoid gestationis
- Scabies
- Urticaria
- Drug eruptions
- Allergy

Skin rash absent

- Intrahepatic cholestasis of pregnancy
- Exacerbation of underlying liver disease—for example, primary biliary cirrhosis

Polymorphic eruption of pregnancy

Polymorphic eruption of pregnancy usually affects primigravidas in the last few weeks of pregnancy or immediately post partum.[9] It occurs in about 1 in 160 to 1 in 200 pregnancies. Polymorphic eruption of pregnancy has been linked to excessive maternal weight gain and multiple pregnancy (fig 1).[9 10] The pathogenesis of the condition remains unclear, although theories include abdominal distension and hormonal and immunological factors.[10 11] Polymorphic eruption of pregnancy starts within the striae distensae on the abdomen, with severely pruritic urticarial papules that coalesce into plaques, spreading to the buttocks and proximal thighs and in severe cases becoming generalised. In contrast with pemphigoid gestationis, the umbilical region is typically spared (fig 2). Subsequently, skin lesions become more polymorphic, with small vesicles, widespread non-urticated erythema, and targetoid and eczematous lesions.[9] Maternal and fetal outcomes are not affected and neither is the neonate. Lesions are self limiting, usually resolving within 4-6 weeks, independent of delivery,[9] and recurrence is unusual, except in multiple pregnancy.

Atopic eruption of pregnancy

Atopic eruption of pregnancy is the most common dermatosis of pregnancy, accounting for 50% of patients seen in a typical pregnancy skin clinic. It includes eczematous or papular lesions in patients with a history of atopy and usually develops early in gestation, in 75% of cases before the third trimester.[2] Atopic eruption of pregnancy is thought to be triggered by the dominant T helper 2 immune response in pregnancy.[12] About 20% of women experience an exacerbation of pre-existing eczema in pregnancy, whereas 80% experience atopic skin changes for the first time or after a long remission

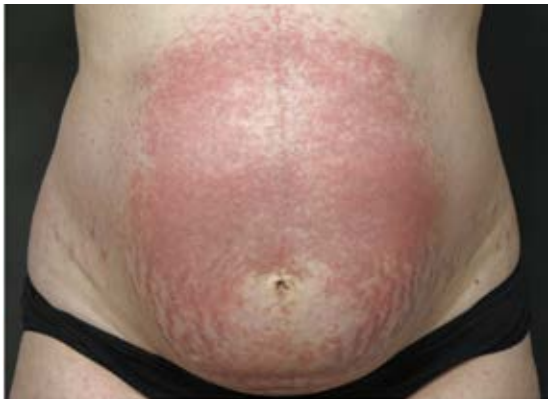

Fig 2 | Diffuse erythema and sparing of umbilical region in woman with polymorphic eruption of pregnancy

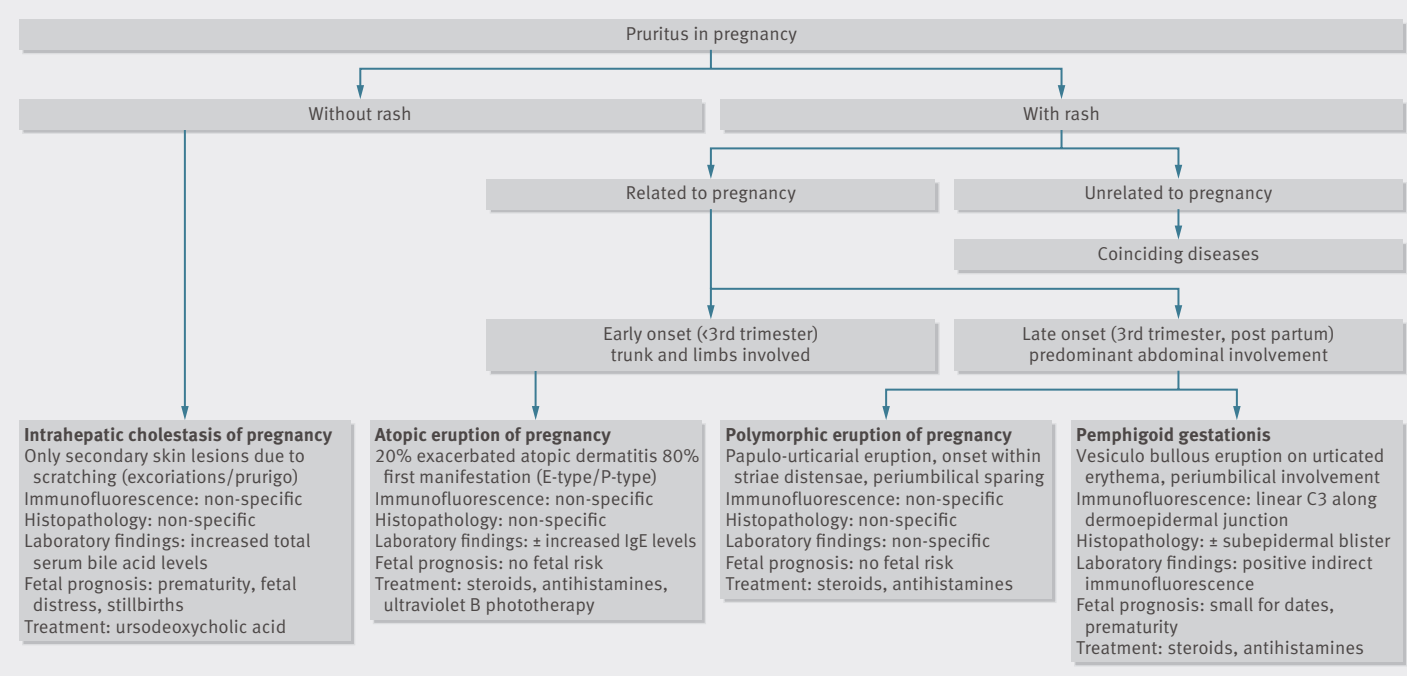

Fig 3 | Algorithm to help distinguish various pruritic dermatoses of pregnancy

(for example, since childhood). Of these, about two thirds present with widespread eczematous changes (so called E-type atopic eruption of pregnancy) often affecting typical atopic sites such as the face, neck, décolleté, and flexural surfaces of the arms and legs, whereas one third have papular lesions (P-type atopic eruption of pregnancy).[2] The papular lesions include small erythematous papules disseminated on the trunk and limbs, as well as typical prurigo nodules, mostly located on the shins and arms. Severe dryness of the skin is a key finding. Maternal prognosis is good even in severe cases, as skin lesions usually respond quickly to treatment; recurrence in subsequent pregnancies is common because of the atopic background. The fetus is unaffected but is at increased risk of atopic skin disease in infancy.

Algorithmic approach to the specific dermatoses of pregnancy

A retrospective analysis of a large patient sample showed important differences that are helpful for differential diagnosis.[2] The algorithm in figure 3 may facilitate discrimination between the various pruritic dermatoses in pregnancy and highlights their appropriate investigation and management.

How are the specific dermatoses of pregnancy treated?

Treatment of the specific dermatoses of pregnancy depends on the stage and severity of the disease and aims to control pruritus and skin lesions. In all cases treatment with corticosteroids, both topically and systemically, and systemic antihistamines can be effective. In the case of mild pemphigoid gestationis, topical corticosteroids with or without oral antihistamines may be sufficient. All other cases of pemphigoid gestationis generally require systemic corticosteroids (prednisolone, usually started at a dose of 0.5-1 mg/kg/day).[6] When the disease improves, the dose can usually be reduced, but should be increased in time to prevent the common disease flare that occurs at delivery. Cases that are severe or unresponsive to systemic corticosteroid treatment may benefit from other agents (pulsed methylprednisolone or intravenous immunoglobulins, see box 3, bmj.com).[6] After delivery, if necessary, the full range of immunosuppressive treatment may be administered. In polymorphic eruption of pregnancy, symptomatic treatment with topical corticosteroids with or without antihistamines is usually sufficient to control pruritus and skin lesions. In severe generalised cases, a short course of systemic corticosteroids (prednisolone, 40-60 mg/day, for a few days in tapering doses) may be necessary and is usually effective.[10] Also in atopic eruption of pregnancy, basic treatment together with topical corticosteroids for several days will usually lead to rapid improvement of skin lesions. Severe cases may require a short course of systemic corticosteroids and antihistamines; bacterial and viral superinfection needs to be treated accordingly (box 3, see bmj.com) and ultraviolet B phototherapy is a safe additional tool that can be used under specialist supervision, particularly for severe cases in early pregnancy.[13]

What are the other common skin diseases in pregnancy?

Inflammatory skin diseases

Psoriasis vulgaris

Pregnancy has a variable effect on psoriasis. Patients typically improve because of changes in immunity, although in 10-20% of women psoriasis can worsen and they require a more advanced/complex treatment.[14] A life threatening severe form of generalised pustular psoriasis exists that requires systemic treatment. A large Taiwanese study showed an increased risk of women with severe psoriasis delivering low birthweight infants, whereas mild psoriasis was not associated with an excess risk of adverse birth outcome.[15]

Impetigo herpetiformis is thought to be a severe variant of pustular psoriasis, and debate still continues as to whether this should be regarded as a separate disease. It typically presents with a flexural pustular eruption associated with fever, tetany, and hypocalcaemia. Recurrence in subsequent pregnancies is characteristic, with earlier onset and increased severity.

Safety of commonly used drugs for dermatological conditions in pregnancy

Safety of drugs	Adverse effects
Unsafe:	
Isotretinoin, acitretin	Teratogenic: face, central nervous system defects
Methotrexate	Teratogenic: fetal death (folate antagonist)
Cyclophosphamide	Teratogenic
Mycophenolate mofetil	Teratogenic: congenital malformations, especially ear
Rituximab	Teratogenic: potential fetal B cell depletion
Trimethoprim	Teratogenic in animal studies (folate antagonist)
Safe:	
Penicillins and cephalosporins	None known
Azithromycin	None known
Aciclovir	None known
Chlorpheniramine	Sedation of infant in late third trimester
Cetirizine, loratadine	None known
Can be used (under specialist guidance):*	
Prednisolone	Risk maternal diabetes and hypertension
Azathioprine	Risk bone marrow suppression
Ciclosporin	Hypertension
Anti-tumour necrosis factor drugs (adalimumab, etanercept, infliximab)	Avoid live vaccinations (for example, BCG) in infant for six months

* When benefits outweigh risk.

Topical corticosteroids can be used to treat psoriasis in pregnancy (and calcipotriol for localised disease). No studies have shown prenatal toxicity.[16 17] The preferred treatment for mild psoriasis is with emollients and topical corticosteroids. Severe cases of psoriasis can be treated effectively in secondary care with prednisolone and phototherapy using narrowband ultraviolet B light.[18] Ultraviolet B light should be used in preference to psoralen combined with ultraviolet A light, and systemic drugs such as methotrexate, hydroxyurea, and acetretin should be avoided during pregnancy as they are all teratogenic. Ciclosporin and biological drugs (tumour necrosis factor alpha inhibitors) can be used under specialist supervision for more severe disease.

Acne vulgaris

Acne vulgaris often improves in early pregnancy but worsens in the third trimester as maternal androgen levels increase. Mild acne vulgaris can be treated with topical treatments such as benzoyl peroxide or azelaic acid. Systemic and topical retinoids are teratogenic and should be avoided.[19] Oral erythromycin would normally be the first choice of antibiotic for acne vulgaris or acne rosacea in pregnancy after the first trimester. Two recent Swedish studies showed an increased risk (1.8%) of cardiovascular defects (atrial and ventricular septal defects) in the neonates of pregnant women who had taken erythromycin in early pregnancy. In these studies it is not clear whether these cardiac defects were due to confounding factors (such as the underlying disease or condition) or a true effect of the drug.[20 21] As a result, azithromycin or clarithromycin are preferred treatments in the first trimester. Erythromycin estolate has also been shown to cause hepatotoxicity, so this salt should be avoided during pregnancy.[16] In secondary care, narrowband ultraviolet B phototherapy can be used as second line treatment for acne vulgaris.[22]

Severe acne conglobata may require treatment with systemic corticosteroids in addition to oral antibiotics. Acne neonatorum may occur as a result of passive transfer of maternal androgens across the placenta during the third trimester.

Acne rosacea

Acne rosacea often worsens during pregnancy and may require systemic treatment. Topical azelaic acid and metronidazole can be used in pregnancy for mild disease. High doses of metronidazole should be avoided during pregnancy. Oral tetracyclines should be avoided owing to their effect on the development of fetal bones and teeth.

Pityriasis rosea

Pityriasis rosea is another inflammatory skin condition that can present during pregnancy and may be misdiagnosed as guttate psoriasis or tinea corporis. It classically presents with oval scaly plaques on the trunk, often preceded by a "herald patch." It has been associated with human herpesvirus 6 infection. A previous study of 38 women presenting with pityriasis rosea in pregnancy associated with active human herpesvirus 6 infection showed that nine delivered preterm and five miscarried.[23] Treatment is normally conservative as the rash fades rapidly within a few weeks in most cases.

Urticaria

Urticaria (or hives) presents commonly during pregnancy and can mimic other pregnancy dermatoses, particularly the prebullous phase of pemphigoid gestationis or polymorphic eruption of pregnancy. Oral antihistamines are the treatment of choice. Chlorpheniramine is known to be safe and should be the treatment of choice in the first trimester.[24 25]

Skin infections and infestations

Herpes simplex virus

Primary herpetic infection (herpes simplex viruses 1 or 2) occurs in 2% of pregnancies and is often more severe than in non-pregnant women. Primary or recurrent genital infection with herpes simplex virus is an indication for caesarean section and drug treatment. Systemic aciclovir is safe in

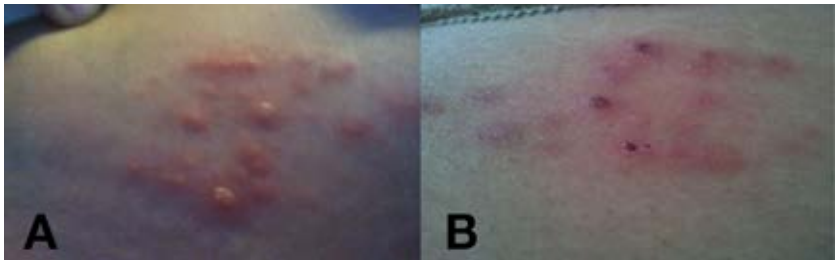

Fig 4 | Herpes zoster infection on lower trunk presenting in pregnancy (36 weeks' gestation) showing intact vesicles and an excoriated patch of skin secondary to scratching as affected area of skin resolves

Box 4 | Topical corticosteroid potency classes

- Mild: 1% hydrocortisone
- Moderate: betamethasone valerate 0.025% (Betnovate-RD) and clobetasone butyrate 0.05% (Eumovate), Trimovate, Daktacort
- Potent: betamethasone valerate 0.1% (Betnovate, hydrocortisone butyrate 0.1% (Locoid), mometasone furoate 0.1% (Elocon, Fucibet, Lotriderm)
- Ultrapotent: clobetasol propionate 0.05% (Dermovate)

The information in this box is from box 3 in *BMJ* 2012;345:e4770

TIPS FOR NON-SPECIALISTS

- Consider referral for skin biopsy where diagnosis is unclear (and request histopathology and direct immunofluorescence)
- Mild to moderate topical corticosteroids can be used in the management of several common dermatoses in pregnancy
- Avoid using potent topical corticosteroids as they may affect fetal growth
- Aqueous cream with 1-2% menthol can be effective in reducing pruritus
- Systemic antihistamines can be a useful adjunct to treatment
- Emollients and bath emollients are useful to reduce itch in the pruritic dermatoses of pregnancy
- Many women are anxious about the safety of treatments and potential adverse effects on the fetus, so supplying patient information leaflets and giving appropriate counselling can be helpful to reassure, educate, and improve compliance

QUESTIONS FOR FUTURE RESEARCH

- What are the causes and pathogenesis of polymorphic eruption of pregnancy?
- What causes the high prevalence of atopic eruption of pregnancy and is this partly due to the increasing prevalence of atopic eczema?
- Do melanomas behave differently during pregnancy and, if so, why?
- Are biologicals safe for the treatment of psoriasis in pregnancy?

pregnancy and has been used extensively without adverse effects. Three studies in animals did not show any teratogenic effects.[16] Prophylactic treatment with aciclovir can be used from 36 weeks' gestation in women with recurrent herpes genitalis. Intravenous treatment is indicated for life threatening disseminated infection to reduce maternal and fetal mortality. Aciclovir has been used most frequently in humans compared with similar antiviral agents (valaciclovir and famciclovir) during pregnancy and is therefore still the preferred treatment.[16]

Varicella zoster virus

Herpes zoster in pregnancy (reactivation of latent varicella zoster virus infection) is not associated with viraemia and does not pose a risk for the fetus (fig 4). Primary infections (chicken pox) occur in 5 of 10 000 pregnancies and may put both the mother and the fetus at risk (of pneumonia and encephalitis). Infection during weeks 1-20 can lead to fetal varicella syndrome in 1-2% of pregnancies, with major neurological and growth defects. Passive immunisation with varicella zoster immunoglobulin to seronegative mothers within 72 hours after exposure to the virus may prevent or ameliorate maternal infection. Women with confirmed varicella should be treated early for pneumonia or other complications with aciclovir either orally or intravenously. High dose intravenous aciclovir is used to treat varicella in neonates.[27]

Scabies

Infestation with scabies (*Sarcoptes scabiei*) is common during pregnancy. The preferred treatment is topical permethrin 5%, the treatment of choice for pregnant women with scabies in both the United Kingdom and the United States. Permethrin 5% is highly active in treating scabies infection, with systemic absorption occurring with less than 2% of the dose and no known adverse effects.[28] Second line treatment is with benzoyl benzoate 25%.[28] Treatment must be repeated after a week to kill eggs and persistent mites and all potentially infectious close contacts should also be treated. Antihistamines and mild to moderately potent topical steroids may be needed to control the irritant dermatitis that often follows treatment.

What drugs can be used systemically in pregnancy?

Many commonly used dermatology drugs are safe in pregnancy, but the potential benefit of any drug should be carefully balanced against possible risks to the mother and fetus. When doubt exists over the safety of any drugs during pregnancy and lactation, reliable sources should be consulted.[16 17]

A multinational survey indicated that 86% of women take an average of 2.9 drugs during pregnancy.[45] Drugs have the greatest potential to cause harm in the first trimester, during the period of organogenesis. Women may be unaware that they are pregnant at this stage, so careful counselling and prescribing is necessary in those of childbearing age. Equally, much harm can result if drugs necessary for disease control are omitted or discontinued precipitously, and as such an individual risk-benefit analysis is essential. Topical and oral retinoids (isotretinoin and acitretin),[19] methotrexate, and mycophenolate mofetil are teratogenic and should be avoided in women planning pregnancy. They should not be given to young women of childbearing age without specific advice to avoid pregnancy.[46 47] Oral steroids should be used under specialist supervision. The table lists the potential adverse effects of commonly used systemic drugs to treat dermatological conditions. A recent review of this topic was published in the American literature, highlighting the safety of dermatological drugs in pregnancy and lactation.[24]

What are the recommendations for use of topical corticosteroids?

Recent evidence based guidelines have been published on the use of topical corticosteroids in pregnancy.[48] This systematic review showed no association between maternal use of topical steroids and orofacial cleft, preterm delivery, or fetal death. However there was a significant association between fetal growth restriction and maternal use of potent or ultrapotent topical corticosteroids. Analysis of these data in a more recent study[49] showed that the risk of a low birthweight infant was significantly increased in women where the dispensed amount of potent or very potent topical corticosteroid exceeded 300 g during the whole pregnancy (P=0.02). By contrast, the risk of growth restriction was not increased with the use of less than 200 g of topical corticosteroid. Thus, guidance when prescribing topical corticosteroids either in pregnancy or in women of potential childbearing age should be to use the mildest effective formulation required for clinical improvement. If a potent topical corticosteroid is required to treat a more severe inflammatory dermatosis in pregnancy, then the dose prescribed should be kept to a minimum (<200 g during the entire pregnancy) and fetal growth should be monitored closely (box 4).

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