PREGNANCY PLUS

Eczema in pregnancy

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Introduction

Atopic eczema has a reported lifetime prevalence of 8-17% in adults aged under 60.¹ It is more common in women, affecting 16% in the United Kingdom, and in adults has its highest prevalence between the ages of 16 and 24.² The incidence of eczema seems to be generally increasing, particularly in children.^{3 4} Moderate to severe eczema can be particularly difficult to manage, and second line treatments are often needed to control it.⁵

As the scenario suggests, treatment options become limited when a patient decides to try to conceive, and disease control is often suboptimal. This article discusses management of eczema in pregnancy.

SCENARIO

A 26 year old woman with lifelong moderate to severe atopic eczema had been unable to achieve good disease control with topical drugs. She received narrow band ultraviolet B phototherapy in 2001 but relapsed within a short time. As part of a randomised controlled trial she received 12 weeks of azathioprine,⁶ on which she greatly improved. She subsequently failed to respond to topical tacrolimus but received two further courses of azathioprine, both with an excellent response.

Six months after stopping azathioprine she became pregnant, and her eczema quickly flared. This was managed with potent topical steroids, although her disease remained troublesome throughout the pregnancy. After the birth of her child, her eczema was managed with methotrexate with a good response.

Methods

We searched national health information sources, the Cochrane database and PubMed up to March 2007. Key search words used included "atopic dermatitis", "eczema", "pregnancy", "maternal", and "breastfeeding". We used our personal archive of references and sought advice from the National Teratology Information Service, Drug Information Department, Royal Victoria Infirmary, Newcastle upon Tyne and from colleagues.

How common is eczema in pregnancy?

Eczema is the most common dermatosis of pregnancy, accounting for between a third and a half of all cases.^{7 8} Only 20-40% of patients are estimated to have a pre-existing history of eczema; the rest develop symptoms for the first time during pregnancy.^{7 8} Three quarters of these patients develop symptoms within the first two

trimesters. The total prevalence of eczema in pregnancy is unknown.

Does pregnancy affect eczema?

Eczema has a fluctuating course in most patients and is influenced by environmental and internal triggers. However, pregnancy does seem to have an effect on eczema in most women with the condition—approximately 25% improve, and more than 50% experience a deterioration.⁹ Although available data are limited, pre-existing eczema may deteriorate at any stage of pregnancy, and a slightly higher rate is seen in the second trimester.^{7 9} About 10% of cases flare in the postpartum period.

In most cases, pregnancy biases T cell immunity towards a type 2 T helper response, and this is thought to be important for continuation of a normal pregnancy.¹⁰ However, a type 2 response is also associated with atopy, and this bias may explain why eczema can deteriorate during pregnancy. Whether skin barrier function or expression of filaggrin (a protein needed for terminal differentiation of cells within the epidermis, which is commonly mutated in eczema^{11 12}) changes during pregnancy is unknown.

Does eczema affect the outcome of pregnancy?

Little or no evidence exists to suggest that eczema directly affects fertility or rates of miscarriage, birth defects, or premature birth. However, secondary skin infection with herpes simplex virus causes eczema herpeticum. Although eczema herpeticum has not been reported to cause intrauterine infection to date, herpes simplex virus is associated with premature delivery, intrauterine growth restriction, and miscarriage.¹³ Aciclovir seems to be safe in pregnancy,¹⁴ so prompt treatment is warranted if eczema herpeticum is suspected clinically. Infection can be confirmed by a viral swab taken before treatment.

Little evidence suggests that eczema is associated with illnesses such as depression. With the exception of infected eczema, the condition should not affect a woman's birth plan or her obstetric outcome after delivery.

Good evidence suggests that both genetic and environmental factors are important in determining whether a child will develop eczema. Studies have shown a higher concordance of eczema in monozygotic twins (risk=0.86) than in dizygotic twins (risk=0.21).¹⁵ Moreover, recent genetic evidence indicates that an

Advice for eczema patients before conception**Eczema treatments in pregnancy***Safe*

Emollients

Topical steroids (mild, moderate, or potent)

Ultraviolet B

Relatively safe (caution)

Very potent topical steroids (small quantities)

Oral steroids (in third trimester)

Ciclosporin*

(Azathioprine)

Topical calcineurin inhibitors (small quantities)

Avoid

Methotrexate*

Psoralens plus ultraviolet A (PUVA)*

Recommended minimum systemic drug-free interval before conception

Methotrexate—three months (men and women)

PUVA—no minimum time but stop before conception

*Avoid in breastfeeding mothers

important proportion of atopic eczema is caused by non-functioning filaggrin that results in a primary skin barrier defect.^{11 12} This could potentially allow abnormal cutaneous penetration of environmental allergens and chemicals leading to increased immune activation. Some studies suggest a greater heritability of eczema maternally rather than paternally, although others do not.¹⁶ Maternal gene imprinting or transplacental fetal exposure to allergen could possibly contribute to this. A recent systematic review examined whether maternal dietary avoidance of cows' milk or egg during pregnancy affects the subsequent development of eczema in the child, but the evidence did not support an effect.¹⁷

How is a patient with eczema managed in pregnancy?

Where possible, advice before conception should include strategies to minimise disease activity at baseline, as eczema may deteriorate during pregnancy. This should include advice about avoiding irritants and allergens, the use of emollients (see below), and how to apply topical treatments. A patient who is receiving systemic treatment for eczema should be made aware of the minimum time interval between stopping their treatment and safely getting pregnant, without increased risk to the child (box).

Emollients remain an integral part of eczema management in all patients. Taking tepid baths, using emollients, and avoiding soap can minimise barrier disruption, which may otherwise increase transepidermal water loss and exacerbate eczema. Moderate to potent topical steroids combined with moisturisers remain the mainstay of treatment for mild to moderate eczema and, with the exception of very potent topical steroids, can continue to be used relatively safely throughout pregnancy.¹⁸ Bacterial infections are an important cause of exacerbations and should be treated promptly to avoid further deterioration. *Staphylococcus aureus* colonises more than 90% of eczema lesions,¹⁹ but active infection may be suggested by the presence of increased pain or swelling, impetigo-like crusting, or inflammatory papules.

Moderate to severe eczema may need second line treatments when not controlled by the above measures. Systemic steroids are used only rarely by dermatologists for the treatment of eczema, and they may be associated with a rebound flare of disease when stopped. Oral steroids have been associated with cleft lip and palate defects in mice, but little evidence supports this occurring in humans.^{18 20-24} Oral steroids may also be linked to fetal growth restriction, although much of the evidence for this comes from their use in patients with asthma, and separating the effects of maternal disease from treatment is difficult. When eczema remains uncontrolled despite optimisation of topical steroids, narrowband ultraviolet B has been shown to reduce disease severity by more than 30% in a randomised controlled trial and is probably the safest second line treatment in pregnancy.²⁵

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are increasingly used as second line agents in primary and secondary care. The manufacturers advise avoidance of topical calcineurin inhibitors during pregnancy. Although systemic tacrolimus is teratogenic, the bioavailability of the topical form is limited (<5%) and its use has not been associated with fetal anomalies.²⁶ No epidemiological studies of pregnancy after use of systemic tacrolimus exist, and congenital malformations are not reported, although intrauterine growth restriction may occur. Therefore, if eczema remains poorly controlled despite optimal first line treatment and ultraviolet B is ineffective or contraindicated, topical calcineurin inhibitors may be considered after appropriate discussion; however, accepted practice is to restrict use to localised areas.

Patients who continue or start systemic treatment during pregnancy will need close monitoring in the hospital setting, by both dermatologists and obstetricians. If systemic agents are needed, the safest option is likely to be ciclosporin, although this should be used for the shortest duration possible (typically less than six months) to avoid the increasing risk of renal impairment in the mother. In a double blind randomised crossover trial, ciclosporin improved eczema by 59% over eight weeks,²⁷ although no specific data exist for pregnant patients. Ciclosporin does cross the placenta, but information from organ transplantation suggests that it is relatively safe. Fetal growth restriction has been reported in this group but probably relates to underlying maternal disease.

Another important second line treatment is azathioprine. A recent randomised controlled trial in non-pregnant patients showed that this reduced disease severity by approximately 37%.¹ It readily crosses the placenta, and its use during pregnancy has been associated with miscarriage, preterm delivery, and fetal growth restriction.²⁸ However, the fetus seems to be protected from teratogenic effects, as its liver lacks the enzyme needed to convert azathioprine into active metabolites,²⁹ and no compelling evidence of an association with congenital malformations in humans exists. The case reports of azathioprine in pregnancy come from its use in pregnant transplant recipients, and current advice to these patients is to continue its use; no reports exist of patients taking azathioprine for eczema becoming pregnant. Rarely, it

has been associated with neonatal leucopenia, pancytopenia, or inhibition of neonatal haematopoiesis, although this should be predictable by maternal leucopenia in the third trimester.^{30,31} Use of azathioprine in severe eczema must be decided on a case by case basis.

Methotrexate, although likely to be effective in moderate to severe atopic eczema,³² is contraindicated in pregnancy and breastfeeding mothers. Patients established on ciclosporin or azathioprine before pregnancy will need careful counselling and liaison with obstetricians. Furthermore, those taking ciclosporin need regular monitoring of full blood count, renal function, and blood pressure, and those taking azathioprine need regular full blood count and liver function tests.

How is eczema managed in the postpartum period?

Mild to moderate eczema is managed routinely with emollients and topical steroids or topical calcineurin inhibitors. In breastfeeding women, topical calcineurin inhibitors are not recommended by the manufacturers, although early reports of women taking oral tacrolimus after transplantation suggest that minimal amounts (approximately 0.1%) of tacrolimus pass into milk.³³ Further studies are needed to assess its safety.

Up to 2% of breastfeeding mothers develop eczema of the areola or nipple.³⁴ About 50% of these will have atopic eczema; other causes include food contact sensitivity or irritation as the baby is weaned on to solids. Moderate to low potency topical steroids and emollients are used to treat eczema in this area, although these should be applied after breast feeding and washed off thoroughly before the next feed.

Ultraviolet B is safe while breast feeding, but safety data are lacking for other second line treatments. However, in a recent cohort of 10 women receiving azathioprine while breast feeding, no adverse effects were seen in the babies, and it was not detected in most of the breast milk collected.³⁵ Ciclosporin and methotrexate should be avoided.

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