European Dermatology Forum

Guideline on Steroids in Pregnancy

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European Dermatology Forum

EDF CONSENSUS RECOMMENDATIONS FOR USE OF TOPICAL STEROIDS IN PREGNANCY

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Disclaimer: These recommendations reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from these recommendations in special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligent.

Abstract

Women with inflammatory dermatoses and dermatoses of pregnancy may need topical corticosteroids during pregnancy. However, little is known about the effects of topical corticosteroids on the foetus. Pharmacology references such as the British National Formulary do not give specific advice on prescribing topical corticosteroids in pregnancy and topical corticosteroids are given prescribing information such as: **"should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus"**

This lack of knowledge may lead to adverse effects on the mother and foetus as treatment decisions are a trade-off between potential benefits and harms. Lack of information and clarity regarding the risks of topical corticosteroids may result in non-prescribing; and pregnant women's excessive concerns of possible foetal harm may result in weakened adherence compromising therapeutic effectiveness and lessening the woman's wellbeing during pregnancy. Conversely there may be over-prescribing of topical steroids with adverse effects on the foetus.

The evidence from a Cochrane Review and data mining of the World Health Organisation International Database of Adverse Drug Reactions suggested that the major possible adverse effects on the foetus of topical corticosteroids were orofacial clefts when used preconception and in the first trimester of pregnancy, and foetal growth restriction and preterm delivery especially when potent/very potent topical corticosteroids were used during pregnancy. A large population-based cohort studies (84,133 pregnant women from the UK General Practice Research Database) found a significant association of foetal growth restriction with maternal exposure to potent/very potent topical corticosteroids, but not with mild/moderate topical steroids. No associations of maternal exposure to topical corticosteroids of any potency with orofacial cleft, preterm delivery, and foetal death were found. However, antibiotic-containing topical corticosteroid preparations were associated with an increased risk for foetal growth restriction and foetal death, but further studies are required to determine if the topical antibiotic was the culprit.

The current evidence is sufficient for doctors and pregnant women to a well-informed decision as to whether to use topical corticosteroids in pregnancy. The evidence suggests that mild/moderate topical corticosteroids

are preferred to potent/very potent ones in pregnancy, because of the risk of foetal growth restriction.

Plan of guideline

- **Introduction**
- **Need for guideline**
- **Development process of recommendations**
- **Evidence for harm in animal studies**
- **Pharmacology and pharmacokinetics in the mother**
    - **Skin absorption of topical steroids in pregnancy**
    - **Metabolism of steroids**
    - **Placental metabolism**
- **Review of evidence from human studies**
- **Recommendations**
- **Summary and conclusions**

Introduction

Topical corticosteroids are the principal therapy for eczematous dermatoses [1] and are also effective in treating inflammatory dermatoses such as discoid lupus erythematosus [2], bullous pemphigoid [3], and chronic palmoplantar pustulosis [4]. Women with these chronic inflammatory dermatoses may continue to need topical corticosteroids during pregnancy. Moreover, women with specific dermatoses of pregnancy, e.g. polymorphic eruption of pregnancy and pemphigoid gestationis and atopic eruption of pregnancy, also require topical corticosteroid treatment [5]. However, little is known about the effects of topical corticosteroids on the foetus. Pharmacology references such as the British National Formulary do not give specific advice on prescribing topical corticosteroids in pregnancy. Topical corticosteroids are often only labelled in the prescribing information as: **"should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus"**

This lack of knowledge may lead to adverse effects on the mother and foetus. Treatment decisions are almost always a trade-off between potential benefits and harms. Lack of information and clarity regarding the risks of topical corticosteroids leads to physicians' uncertainty and often results in non-prescribing; and causes pregnant women excessive concerns of possible foetal harm, followed by weakened adherence to the regimen compromising therapeutic effectiveness. Conversely there may be over-prescribing of topical steroids with adverse effects on the foetus. A general assumption is that low-potency topical corticosteroids, like hydrocortisone acetate, are safe to be used during pregnancy; however, this might be wrong. Despite the lack of sufficient safety information, many women still use topical corticosteroids during pregnancy; and surveys from Australia, Denmark, Finland, the Netherlands, UK and US show usage of topical corticosteroids by 2-8.6% of pregnant women [6-13]

A survey of 250 heads of dermatology departments throughout Europe showed that 30% had concerns concerning the prescribing of topical steroids and 91% limited their prescribing [13].

Thus guidelines for the safe use of topical corticosteroid use during pregnancy are required for a more informed clinical decision.

Development process of recommendations

Two workshop meetings (2008, Interlaken and Paris) were held to establish a consensus for the development and implementation of European guidelines for the safe use of topical steroids in pregnancy.

At the first meeting it was established that no 'best practices' from national groups exists.

Levels of evidence and grades of recommendation

Much has been written in recent years on the need for clinical guidelines and the criteria they should meet for development and application, as well as evidence and recommendations to be used in their support. We used the levels of evidence described by the Oxford Centre for Evidence-Based Medicine [14] (Table 1) and the Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument [15] (Table 2).

Table 1 Oxford Centre for Evidence-Based Medicine: levels of evidence [14]

1a	Evidence obtained from systematic reviews of multiple randomised controlled trials (RCTs) with homogeneity
1b	Evidence from individual RCT with a narrow confidence interval
1c	All patients died prior to introduction of drug but some now survive or Some patients died prior to introduction of drug but all now survive
2a	Evidence obtained from systematic reviews of multiple cohort studies, with homogeneity
2b	Evidence from individual cohort study or poor-quality RCT (<80% follow-up)
2c	Evidence obtained from outcomes research
3a	Evidence obtained from systematic reviews of multiple case-control studies with homogeneity
3b	Evidence from individual case-control study
4	Evidence from a case series, or poor-quality cohort study, or poor-quality case-control studies
5	Evidence based on expert opinion without critical appraisal, or laboratory research, physiology, or 'first principles'

Table 2 Grades of recommendation [15]

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies, or extrapolations from level 2 or 3 studies
D	Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level

Evidence for harm from animal studies

Corticosteroids have been shown to be teratogenic in animals and have other foetotoxic effects. Systemic corticosteroids have induced cleft palate in rabbits, mice, rats, and hamsters [16-19]. The incidence of sex organ anomalies in mice was found to correlate with the dose of corticosteroids topically applied to the eyes [20]. Prenatal administration of dexamethasone caused an irreversible deficiency of hippocampal neurons, high plasma cortisol at the circadian baseline, and post-stress concentrations in juvenile rhesus monkeys [21]. After prenatal administration of one to four doses of betamethasone 0.5 mg/kg at 7 day intervals, starting from 3 weeks before delivery, the birth weight of foetal lambs was found to be reduced (by 15% after one dose, 19% after two doses, and 27% after three and four doses) [22].

It is noteworthy that considerable amounts of betamethasone 17, 21-dipropionate appeared in the foetal blood of mice and rabbits after topical application to the mothers' skin [23]. Topical corticosteroids were found to be teratogenic in animal studies. Diflorasone diacetate cream induced cleft palate when applied topically to the chest skin of pregnant rats at a dose of 0.001 mg/kg/day, which is only one-third of the comparable human topical dose. When the application dose was increased to 0.5 mg/kg/day, the treated rats had a higher stillbirth rate than the controls [24]. Rabbits given a topical dose of diflorasone diacetate 0.016 mg/kg/day had depressed foetal growth, external anomalies (31.9%), cleft palate (22.2%), and visceral defects (45.5%) [25].

In summary, the animal data show partially dose dependent teratogenic effects in rodents depending on absorption and systemic levels. In addition there is evidence of foetal growth restriction and an increased rate of foetal death.

Pharmacology and pharmacokinetics in the mother

Systemic effects of topical corticosteroids largely depend on the extent of percutaneous absorption, and subsequently on pharmacokinetic pathways for systemically administered corticosteroids. They bind to plasma proteins in varying degrees, are metabolized primarily in the liver and excreted in the kidney and they cross the placenta in pregnant women.

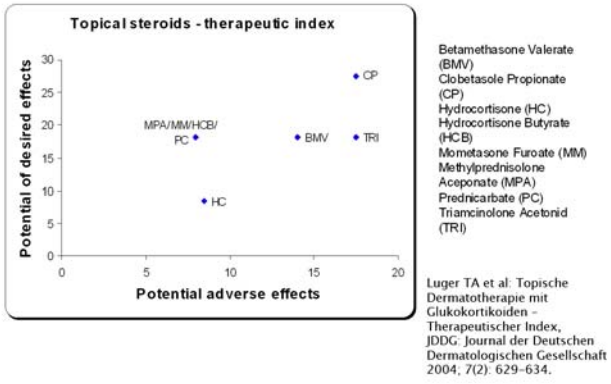
- **Skin absorption and bioavailability of topical steroids in pregnancy**

The extent of percutaneous absorption, and thus the potential for systemic exposure, is determined by many factors including [26]:

- the chemical compound itself
- the vehicle
- the integrity of the epidermal barrier
- the use of occlusive dressings
- the surface area and regional anatomic variation treated
- application frequency and prolonged use
- the metabolism
- pregnancy (there may be variation in different trimesters)

Systemic effects of topical corticosteroids largely depend on the extent of percutaneous absorption, which varies from <0.5 to 7% when applied to intact skin [27, 28] and also on systemic bioavailability see Figure 1.

Figure 1 Therapeutic index of topical steroids (modified from Luger TA et al 2004 [29])



Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Whereas less than 0.5% of the applied methylprednisolone aceponate is percutaneously absorbed through intact skin removal of the epidermal barrier by stripping increased the absorption to 15.4 ± 7.7% [28]. And the percutaneous absorption of 1% hydrocortisone cream during exacerbation of atopic dermatitis can be 11 to 31 times that in remission [30].

Hydrocortisone and other topical corticosteroids have different systemic bioavailability, depending on lipophilicity, degradability and other pharmacokinetic properties. Even hydrocortisone, the least potent corticosteroid, can suppress the adrenals after percutaneous absorption in patients with severe skin disease [31]. Clobetasol propionate ointment, a very potent topical corticosteroid, can result in adrenal insufficiency at doses as low as 2 g per day for 1 week [27]. This has also been described with newer topical lipophilic corticosteroids, mometasone, fluticasone, and methylprednisolone aceponate, under extreme conditions [32, 33], but was not verified for mometasone under more moderate conditions (10 g/day) [34] nor in a study in psoriatic patients (15g/day) [35].

The vehicle may help to enhance penetration and promote systemic absorption. The use of occlusive dressings, well hydrated skin, use over large surface areas, and prolonged use are conditions which augment systemic absorption. Drug penetration is higher on the face, in intertriginous areas, and especially the perineum.

During pregnancy, alterations in the skin hydration and blood flow may change the systemic availability of topical corticosteroids [36]. However, for ethical reasons, no specific investigations regarding topically applied corticosteroids in pregnant women have been performed.

Data from nasal and inhaled steroids may not be directly applicable. The data on mometasone and fluticasone used by these routes are reassuring [37-39], but direct extrapolation to cutaneous application is not possible. On theoretical grounds the newer more lipophilic corticosteroids (mometasone, fluticasone and methylprednisolone aceponate), which have reduced local and systemic side effect profiles should perhaps be preferred [40, 41], but direct data to support this are still awaited.

Metabolism of steroids

After absorption of corticosteroids, 90% or more of cortisol in plasma is reversibly bound to two plasma proteins: corticosteroid-binding globulin (CBG or transcortin), and albumin. Only the unbound fraction can enter cells to mediate corticosteroid effects. CBG is an α-globulin secreted by the liver with high affinity for steroids but relatively low total binding capacity, whereas albumin has low affinity but relatively large binding capacity. At normal or low concentrations of corticosteroids, most of the hormone is bound. At higher steroid concentrations, the capacity of protein binding is exceeded, and a greater fraction of the steroid exists in the free state. A special state of physiological hypercorticism occurs during pregnancy. The elevated circulating oestrogen levels induce CBG production and CBG, and this leads to increased total plasma cortisone. The physiological significance of these changes with regard to exogenous steroids remains to be established.

Biologically active adrenocortical steroids and their synthetic congeners are metabolised in the liver and elsewhere to water soluble compounds that are excreted via the kidneys.

Placental metabolism

The effects of corticosteroids on the foetus depend on their efficiency of penetration through the placenta (see table 3). The key enzyme metabolising corticosteroids in the placenta is the highly expressed 11β-hydroxysteroid dehydrogenase which converts cortisol (hydrocortisone, the active form) to cortisone (biologically inactive). Therefore 11β-hydroxysteroid dehydrogenase is important in regulating the amount of maternal cortisol that crosses the placenta to reach the foetal compartment and in protecting the baby from potential harms [42]. It is assumed that hydrocortisone is safe for use in pregnancy because of its low potency and high metabolism in the placenta, but a study of the maternal-foetal cortisol transfer in the foetal-placental unit before abortion showed that 15% of ^{3}H-cortisol crossed the placenta un-metabolised [43] and another study found a linear relation between maternal and foetal serum cortisol concentrations [44, 45]. Only one-eighth to one-tenth of prednisolone crosses the placenta to reach the foetus [46]. By contrast, dexamethasone, methylprednisolone, and betamethasone are metabolised less extensively by 11β-hydroxysteroid dehydrogenase as about 67%, 45%, and 30% respectively cross the placental barrier [47]. Fluticasone and

budesonide are not metabolised by placental 11β-hydroxysteroid dehydrogenase [48], and therefore high amounts of them may cross the placenta. There are no studies available on the other corticosteroids.

Table 3 Placental metabolism and transfer of various corticosteroids (adapted from Chi's thesis [13])

	Metabolised by placental 11β-hydroxysteroid dehydrogenase	Placental transfer
Prednisolone		10-12%
Hydrocortisone	85%	15%
Betamethasone		28-33%
Methylprednisolone		44.6%
Dexamethasone		67%
Fluticasone	0%	

In summary, it is difficult to predict the effects of topically applied corticosteroid used by the mother on the unborn child, as there are so many independent factors. Clinical trials are unethical and therefore have not been conducted.

Review of evidence from human studies

The literature and data available as to possible harms to the foetus from maternal usage of topical corticosteroids are limited.

A recent Cochrane review [49] identified 7 relevant studies, including 5 case-control and 2 cohort studies which covered a total of almost 660,000 participants (Table 4). The available data were inconclusive (level of evidence: 2a). Most of the studies did not find significant associations between maternal use of topical corticosteroids and adverse pregnancy outcomes including mode of delivery, congenital abnormality, preterm delivery, and stillbirth, but these studies all had drawbacks [50-54]. On the other hand, a significant association between topical corticosteroids and orofacial cleft was found in one small case-control study [55]. A significant association between maternal use of very potent topical corticosteroids and low birth weight was found in one small cohort study [56].

Table 4 Studies included for the Cochrane review

First author; publication year; country; funding source	Study design Setting	Number of participants Ascertainment of exposure	Outcome measures	Results
Czeizel; 1997; Hungary; not reported	Case-control Population-based, using the dataset Hungarian Case-Control Surveillance of Congenital Abnormalities	20830 cases of congenital abnormalities (CAs), 35727 controls Prenatal log book, questionnaire and interview	Adjusted odds ratio (OR) with 95% confidence interval (CI) of maternal ointment corticosteroid treatment in 14 CAs group	An association between cleft lip ± palate and maternal corticosteroid ointment treatment in the whole pregnancy [adjusted OR 2.21 (95% CI 1.11-4.39)] and in the 1st month of gestation [OR 4.19 (95% CI 1.47-11.97)] was revealed. However, the adjusted OR was not significant in the 2nd and 3rd months of gestation, which are the critical period for CAs (but the OR statistic was not reported). Also, no significant association between maternal corticosteroid ointment use and other major or mild CAs was found.
Mygind; 2002; Denmark; Western Danish Research Forum for Health Sciences, Danish Medical Research Council, and Foundation of Hørslev	Retrospective cohort study Based on local population in North Jutland, using Danish Medical Birth registry	363 primiparous, singleton pregnant women exposed to topical corticosteroids within 30 days before conception and/or during pregnancy, 9263 controls receiving no prescriptions Population-Based Prescription Database	Crude and adjusted OR with 95% CI for low birth weight (LBW), malformations, preterm delivery and stillbirth	No increased risk of LBW, malformations, preterm delivery and stillbirth among the exposure group. The adjusted OR (95% CI) for LBW, malformations and preterm delivery among women receiving weak/medium strong corticosteroids were 0.7 (0.17–2.85), 0.93 (0.23–3.80) and 1.04 (0.56–1.92), respectively, and those of strong/very strong corticosteroids were 1.23 (0.45–3.37), 0.56 (0.14–2.28) and 0.99 (0.54–1.84), respectively. The crude OR for stillbirth among women receiving prescription of topical corticosteroid during pregnancy was 2.6 (95% CI 0.83-8.05).
Edwards; 2003; Australia; not reported	Case-control Single teaching hospital	48 cases with nonsyndromic cleft lip or palate, 58 controls Retrospective interview	OR with 95% CI of topical corticosteroid use in the first trimester of pregnancy for cleft lip or palate, using univariate and multiple regression analysis	A significant increase in the prevalence of maternal first-trimester use of topical corticosteroid among cases with syndromic cleft [adjusted OR 18.6 (95% CI 1.29–270), p = 0.032]

Källén; 2003; Sweden; KA Wallenberg Foundation.	Register analysis Population-based, Swedish Medical Birth Registry	149932 women with first-trimester drug exposure, containing 1094 exposed to topical corticosteroid Prospective interview at the first antenatal care visit (usually week 10 to 12)	Expected number of cases with orofacial cleft, compared with observed number as risk ratio (RR; observed/expected) with 95% CI based on exact Poisson distribution	No significant relationship was found between topical corticosteroid use in the first trimester of pregnancy and orofacial clefts [RR 2.01 (95% CI 0.55-5.15)].
Pradat; 2003; multi-national; not reported	Case-control Multicentric database, Malformation Drug Exposure Surveillance (MADRE)	11150 cases with congenital malformations, containing 982 cases of cleft palate or lip Reported by participating researchers	Mantel-Haenszel OR with 95% CI after stratification by registry	No correlation was found between first-trimester exposure to topical corticosteroids and cleft palate or lip [OR 0.52 (95% CI 0.16-1.64)], cleft palate [OR 0 (95% CI 0-3.41)], cleft lip ± palate [OR 0.73 (95% CI 0.23-2.37)].
Mahe, 2007	Cohort Single maternity hospital	34 of 99 women with exposure to potent topical steroids (28 clobetasol propionate, 60 g/month). Compared to non users of very potent topical steroids Interviewed at 6-9 months pregnancy, local area only	Plasma cortisol, Pregnancy outcome: mode of delivery, gestational age, birth weight, placental weight, status of newborn and mother. $_{x}2$ and Fischer's two tailed exact test, Kruskall-Wallis H test.	Increased frequency of mild vaginal bleeding (p = 0.031), decreased birthweight (p = 0.046), decreased placental weight (p = 0.043), decreased placental cortisol (p = 0.07).
Carmichael 2007	Case-control Multistate, part of the National Birth Defects Prevention Study	1110 infants with cleft lip ± cleft palate and 4079 control infants Maternal interviews were conducted with a standardized, computer-based telephone questionnaire in English or Spanish, no earlier than 6 weeks and no later than 24 months after the infant's estimated date of delivery	Confirmed by clinical description or surgical or autopsy report. Each case received an additional review by 1 clinical geneticist to ensure that cases from each study center met standard eligibility criteria.	No significant association was found between cleft lip ± cleft palate and maternal use of topical corticosteroids from 4 weeks before through 12 weeks after conception [OR 0.9 (95% CI 0.2-4.3)]

The World Health Organisation (WHO) International Database of Adverse Drug Reactions (ADRs) was set up by the WHO Collaborating Centre for International Drug Monitoring and collects spontaneous reports of suspected ADRs from national centres in over 90 participating countries and has over 4 million reports being the largest spontaneous report system in the world [57]. A data mining study of the WHO International Database of ADRs was conducted to examine if there were signals for adverse foetal effects from spontaneous reports.

Topical corticosteroids were implicated in 36,612 reports, with mild/moderate topical corticosteroids in 18,520 and potent/very potent topical corticosteroids in 18,092. There were small positive signals for possible associations between maternal use of topical corticosteroids and adverse pregnancy outcomes including orofacial cleft, foetal growth restriction, and preterm delivery, but not for foetal death (level of evidence: 4). Among the reports of combinations of topical corticosteroids and adverse pregnancy outcomes, potent/very potent topical corticosteroids were implicated in a high proportion of reports on orofacial cleft (79%) [13].

The analyses of the available data from the Cochrane Review and the WHO International Database of ADRs highlighted the need for large scale studies, and a large population-based cohort study has been performed using two datasets from the UK General Practice Research Database (GPRD) [58]. The GPRD has full records for over 3.5 million currently registered patients and over 10 million patients in total. These data are collected from over 460 practices and cover 5.5% of the UK population [59].

The GPRD Mother-Baby Link from 2000 to 2006 inclusive, containing 171,650 mothers and 210,112 children, was used as the data source. Over 6% of pregnant women used topical steroids. Pregnant women (13,365) using topical corticosteroids during the period from 85 days before last menstrual period (LMP) to delivery, were compared with those that did not use them (26,492) and the topical steroids used were stratified for potency as shown in Table 5 [13].

Table 5 Potency of topical corticosteroids (adapted from the British National Formulary [60] and Chi's thesis [13])

Potency	Topical corticosteroids
Mild to moderate	Alclometasone dipropionate 0.05%
	Betamethasone valerate 0.025%
	Clobetasone butyrate 0.05%
	Fludroxycortide (flurandrenolone) 0.0125%
	Fluocinolone acetonide 0.00625%
	Fluocortolone 0.25%
	Hydrocortisone 0.1–2.5%
Potent to very potent	Betamethasone dipropionate 0.05-0.064%
	Betamethasone valerate 0.1-0.12%
	Clobetasol propionate 0.05%
	Diflucortolone valerate 0.1-0.3%
	Fluocinolone acetonide 0.025%
	Fluocinonide 0.05%
	***Fluticasone propionate 0.005-0.05%**
	***Hydrocortisone butyrate 0.1%**
	***Mometasone furoate 0.1%**
	***Methylprednisolone aceponate 0.1%**
	Triamcinolone acetonide 0.1%

*The drugs have high potency based on efficacy but lower adverse effects [40] (see Figure 1).

No significant associations of maternal exposure to topical corticosteroids with orofacial cleft and its two categories, cleft lip and palate and cleft palate, were found. Maternal exposure to potent/very potent topical corticosteroids was found to be significantly associated with foetal growth restriction [adjusted risk ratio 2.08 (95% confidence interval 1.40-3.10); number needed to harm (NNH) 168] (level of evidence: 2b). There was a 3% increase in the relative risk for foetal growth restriction associated with every 30 gm (a regular tube) increase of potent to very potent topical corticosteroids prescribed during pregnancy. In contrast, no similar association between maternal exposure to mild/moderate topical corticosteroids and foetal growth restriction was found. No association between maternal exposure to topical corticosteroids of any potency and preterm delivery was found [58].

In a separate dataset from the GPRD, women who had had at least one prescription for topical corticosteroids during the period from 85 days before last menstrual period (LMP) to delivery or foetal death were studied. This study found maternal exposure to topical corticosteroids did not increase the risk for foetal death, both miscarriage and stillbirth [58]. However, maternal exposure to multi-constituent preparations containing certain corticosteroids and antibiotics (including fusidic acid, tetracycline, and neomycin) was independently associated with either miscarriage or stillbirth [13].

Conclusions

Current available data on the safety of topical corticosteroids during pregnancy are limited but suggest a lack of association between their use by the mother and oral clefts in the child. The evidence available does suggest that use of potent/very potent topical corticosteroids with high bioavailability during pregnancy may be associated with placental insufficiency and low birth weight.

However, the findings are from a single dataset [58] and a small cohort study [56]. Further clinical studies are required to confirm this finding.

Recommendations

1. Mild/moderate topical corticosteroids should be used in preference to more potent corticosteroids in pregnancy (Grade of recommendation: B).
2. Potent/very potent topical corticosteroids should be used as second-line therapy for as short a time as possible, and appropriate obstetric care

should be provided as they increase the risk of foetal growth restriction (Grade of recommendation: B).

3. The association between maternal exposure to potent/very potent topical corticosteroids and foetal growth restriction requires caution to be used in the prescribing of these potent/very potent topical treatments. However, systemic corticosteroids have a greater bioavailability than that of topical corticosteroids, and thus have a higher potential for foetotoxicity than topical corticosteroids (systemic corticosteroids are associated with a reduction in fetal birth weight and an increase in preterm delivery [61, 62]), and should not be used in preference (Grade of recommendation: B).
4. On theoretical grounds the danger of adverse events is increased when areas with high absorption (e.g. genitals, eyelids, flexures) are treated (Grade of recommendation: B)
5. The data are not available to determine if newer more lipophilic topical corticosteroids (mometasone, fluticasone and methylprednisolone aceponate,) with a good therapeutic index are associated with less foetal growth restriction despite theoretical grounds to suggest this and the practical advantage of once daily application (Grade of recommendation: C).
6. Antibiotic-containing topical corticosteroid preparations should be avoided in pregnancy (until more robust evidence is available) because of concern for increased risk for foetal growth restriction and foetal death. (Grade of recommendation: C).

Advice to women about using topical corticosteroids in pregnancy

1. Women can be reassured that there is no significantly increased risk for orofacial cleft, preterm delivery and foetal death when using topical corticosteroids in pregnancy. There is also no increased risk for foetal growth restriction when using mild/moderate topical corticosteroids in pregnancy.
2. Women should be informed that there is a small risk for foetal growth restriction when using potent/very potent topical corticosteroids in pregnancy, but this risk is less than that of systemic corticosteroids, as an additional risk for preterm delivery has been found in women using systemic corticosteroids.
3. Depending on the severity of their skin conditions, women should use

topical corticosteroids of the least potency required and limit the amount of use.

Summary and conclusion

The evidence from a Cochrane Review and a data mining study of the WHO International Database of ADRs suggested that the major possible adverse effects on the foetus of topical corticosteroids were orofacial clefts when used preconceptionally and in the first trimester of pregnancy, and foetal growth restriction and preterm delivery especially when potent/very potent topical corticosteroids were used during pregnancy. A large population-based cohort study (84,133 pregnant women from the GPRD) found a significant association of foetal growth restriction with maternal exposure to potent/very potent topical corticosteroids, but not with mild/moderate topical steroids. No significant associations of maternal exposure to topical corticosteroids of any potency with orofacial cleft, preterm delivery, and foetal death were found. However, antibiotic-containing topical corticosteroid preparations were associated with an increased risk for foetal growth restriction and foetal death, but further studies are required to determine if the topical antibiotic was the culprit.

The current evidence is sufficient for doctors and pregnant women to a well-informed decision as to whether to use topical corticosteroids in pregnancy. The evidence suggests that mild/moderate topical corticosteroids are preferred to potent/very potent ones in pregnancy, because of the risk of foetal growth restriction.

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