European Dermatology Forum

Updated evidence-based (S3) European Dermatology Forum guideline on the use of topical corticosteroids in pregnancy

Developed by the Guideline Subcommittee "Topical Corticosteriods" of the
European Dermatology Forum

Subcommittee Members:
Prof. Dr. Ching Chi-Chi, Taoyuan (Taiwan)
Prof. Dr. Werner Aberer, Graz (Austria)
Prof. Dr. Jasna Lipozenčić, Zagreb (Croatia)
Prof. Dr. Uwe-Frithjof Haustein, Leipzig (Germany)
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Dr. Gudula Kirtschig, Tübingen (Germany
Prof. Dr. Jean-Paul Gabbud, Bern (Switzerland)
Prof. Dr. Sarolta Kápáti, Budapest (Hungary)
Prof. Dr. Fenella Wojnarowska, Oxford (United Kingdom)

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Prof. Dr. Christos Zouboulis, Dessau (Germany)
Prof. Dr. Dr. Torsten Zuberbier, Berlin (Germany)

Chairman of EDF Guideline Committee:
PD Dr. Alexander Nast, Berlin (Germany)

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EDF Guidelines Secretariat to PD Dr. Nast:
Bettina Schulze, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte,
Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
phone: ++49 30 450 518 062, fax: ++49 30 450 518 911, e-mail: bettina.schulze@charite.de

Croatian Academy of Medical Sciences, Zagreb, Croatia

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C-C. Chi,*† G. Kirtschig,‡ W. Aberer,§ J.-P. Gabbud,¶ J. Lipozenčić, S.** Kárpáti,†† U-F. Haustein,‡‡ F. Wojnarowska,§§ and T. Zuberbier¶¶

*Department of Dermatology and Centre for Evidence-Based Medicine, Chang Gung Memorial Hospital, Chiayi, Chiayi, Taiwan

†College of Medicine, Chang Gung University, Taoyuan, Taiwan

‡Department of General Medicine and Interdisciplinary Care, University of Tübingen, Tübingen, Germany

§Department of Dermatology, University of Graz, Graz, Austria

¶Dermatology and Venereology, Bern, Switzerland

** Croatian Academy of Medical Sciences, Zagreb, Croatia

††Department of Dermatology, Venereology and Dermato-oncology, Semmelweis University, Budapest, Hungary

‡‡Department of Clinical and Experimental Dermatology, University of Leipzig, Leipzig, Germany

§§Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

¶¶Allergy-Centre-Charité, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Berlin, Germany

Corresponding author

Prof Dr med Dr h c Torsten Zuberbier

Department of Dermatology and Allergy

Charité - Universitätsmedizin Berlin

Charitéplatz 1

D-10117 Berlin

Tel. +49 30 450 518 135

Fax +49 30 450 518 919

E-mail: Torsten.Zuberbier@charite.de

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What's already known about this topic?

- Only limited data on the fetal effects of topical corticosteroids are available.

What does this study add?

- Mild/moderate topical corticosteroids are preferred to potent/very potent ones for use in pregnant women. Use of potent/very potent topical corticosteroids, especially when the applied amounts are large, is associated with an increased risk of low birth weight.
- The current evidence does not support associations of maternal use of topical corticosteroids with birth defect, preterm birth, and fetal death.
- In the choice of the topical corticosteroids, also the risk benefit needs to be assessed regarding cutaneous side effects for the mother with a higher risk of older topical corticosteroids in comparison to more modern ones with a better therapeutic index.

Summary

Topical corticosteroids may be needed for treating skin conditions in pregnancy. Nevertheless, only limited data on the fetal effects of topical corticosteroids are available. A guideline subcommittee of the European Dermatology Forum was organised to update an evidence-based guideline on the safe use of topical corticosteroids in pregnancy. The current best evidence is from an updated Cochrane Review which included 14 observational studies with 1,601,515 study subjects and found no significant associations between maternal use of topical corticosteroids of any potency and some adverse pregnancy outcomes including mode of delivery, birth defect, preterm delivery, and fetal death. However, maternal use of potent/very potent topical corticosteroids, especially in large amounts, is associated with an increased risk of low birth weight. We conclude that mild/moderate topical corticosteroids should be preferred to potent/very potent ones in pregnancy and that the well-known topical side effects of corticosteroids on the mother's side need to be in the focus of the choice.

Introduction

Topical corticosteroids are frequently prescribed for treating various dermatoses including eczema,[1] psoriasis,[2] discoid lupus erythematosus,[3] and bullous pemphigoid.[4] Women with these dermatoses may need topical corticosteroid treatment during pregnancy. Pregnant women with specific dermatoses of pregnancy, for example atopic eruption of pregnancy, need topical corticosteroid treatment as well.[5] Nevertheless, the effects of topical corticosteroids on the fetus are largely unclear. Drug references for example the British National Formulary do not provide explicit instructions on prescribing topical corticosteroids in pregnancy.[6] A typical labelling for use of topical corticosteroids in pregnancy is: "should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."[7]

Clinical decisions are usually a trade-off between conceivable benefit and harm. The lack of knowledge on the safety of topical corticosteroids in pregnancy may result in physicians' hesitancy and non- or under-prescribing. Pregnant women's over-concern of fetal risk may lead to underuse of topical corticosteroids and decreased therapeutic effects.[8] A previous survey of 250 directors of departments of dermatology across Europe found 30% were concerned about prescribing topical corticosteroids to pregnancy women and 91% restrained their prescribing.[9]

For making an informed clinical decision on the use of topical corticosteroids in pregnancy, an evidence-based guideline is warranted. We organised a guideline subcommittee of the European Dermatology Forum and have developed an evidence-based (S3) guideline on the use of topical corticosteroids in pregnancy in 2011.[10] Herein we present an updated guideline in which we added and appraised new evidence

Disclaimer

This guideline was developed by the European Dermatology Forum (available at http://www.euroderm.org/edf/index.php/edf-guidelines/category/5-guidelines-miscellaneous). The recommendations reflect the best data available at the time when this guideline 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.

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 defined by the Oxford Centre for Evidence-Based Medicine (Table 1)[11] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group's approach to rate the quality of evidence (Table 2).[12] The quality of evidence from randomised trials is initially rated as high and observational studies as low. Further evaluation may upgrade the quality of evidence for large magnitude effect, dose response, and confounders likely minimise the effect, and may downgrade due to study limitations, imprecision, inconsistency of results, indirectness of evidence and publication bias.[12]

Evidence for harm from animal studies

Animal experiments showed corticosteroids have fetotoxic effects and are teratogenic. Administration of systemic corticosteroids resulted in cleft palate in rabbits, mice, rats, and hamsters.[13-16] The occurrence of genital organ anomalies in mice correlated with the amounts of corticosteroids applied to the eyes.[17] Administration of dexamethasone in juvenile rhesus monkeys resulted in permanent loss of hippocampal neurons, elevated plasma cortisol levels at the circadian baseline and post-stress concentrations.[18] The birth weight of fetal lambs reduced after prenatal administration of betamethasone in a dose-response relationship.[19]

One animal experiment illustrated that after application on the mothers' skin, appreciable levels of betamethasone 17, 21-dipropionate were detected in the fetal blood of mice and rabbits.[20] Animal studies have found topical corticosteroids are also teratogenic. Diflorasone diacetate cream caused cleft palate after applied to pregnant rats' skin at a dose of 0.001 mg/kg/day, which was just one-third of the equivalent human topical dose. The treated rats had a higher rate of fetal death than untreated controls when the dose was increased to 0.5 mg/kg/day.[21] After topical application of diflorasone diacetate 0.016 mg/kg/day to pregnant rabbits, depressed fetal growth, external anomalies (31.9%), cleft palate (22.2%), and visceral defects (45.5%) were found.[22]

To sum up, animal experiments demonstrated that topical application of topical corticosteroids to pregnant rodents resulted in teratogenic effects, low birth weight, and increased fetal death, but these experiments cannot be extrapolated to humans as the

stratum corneum of the animals is much thinner and the percutaneous absorption is much higher than in humans.

Pharmacology and pharmacokinetics in the mother

The systemic effects of topical corticosteroids rely on the degree of percutaneous absorption and the pharmacokinetic pathways for systemically absorbed corticosteroids. Corticosteroids are bound to plasma proteins, metabolised mainly in the liver, excreted in the kidney, and cross the placenta in pregnant women.

Skin absorption and bioavailability of topical corticosteroids in pregnancy

The 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[23,24] and also on systemic bioavailability (see Figure 1). The degree of percutaneous absorption, and hence the potential for systemic exposure, depends upon the following factors:[25]

- the nature of the corticosteroid chemical compound;
- the nature of the vehicle;
- the integrity of the skin barrier;
- the use of occlusion;
- the surface area and regional anatomic variation of the treated skin;
- the frequency and duration of application ;
- the metabolism of corticosteroids;
- inflammation and/or other diseases in the skin;

- pregnancy (there may be variation in different trimesters).

Hydrocortisone and other corticosteroids have various systemic bioavailability following topical application due to different lipophilicity, degradability, and other pharmacokinetic properties. Hydrocortisone, the least potent corticosteroid, is able to suppress the adrenals following long-term use in children with dermatitis.[26] Clobetasol propionate ointment, the most potent topical corticosteroid, may cause adrenal insufficiency at a very low dose of 2 g per day for 1 week.[23] Adrenal suppression after application of newer topical lipophilic corticosteroids (i.e. mometasone furoate, fluticasone propionate, and methylprednisolone aceponate) under extreme conditions have been documented,[27,28] but was not found for mometasone furoate under more moderate conditions (10 g/day)[29] or in psoriatic patients (15 g/day).[30]

Previous studies found no significant differences in treatment response with once or twice daily application of very potent corticosteroids. Likewise, there was no difference or only a slight difference with once or twice daily application of potent or moderately potent corticosteroids.[31]

The vehicle may enhance penetration and promote systemic absorption.[25] The use of occlusive dressings, hydration of skin, application over large surface areas, and prolonged use can enhance systemic absorption.[25] Percutaneous penetration is increased over thin skin including the face, intertriginous areas, and genital area.[25]

Inflammation and other conditions of the skin may enhance percutaneous absorption of topical corticosteroids. The percutaneous absorption of 1% hydrocortisone cream during flares of eczema increased to 11 to 31 times that in remission.[32] While only

< 0.5% of applied methylprednisolone aceponate was absorbed through intact skin, removal of the skin barrier by stripping increased the absorption to 15.4 ± 7.7%.[24]

The change in the hydration and blood flow of the skin in pregnancy may alter the systemic bioavailability of topical corticosteroids.[33] Nevertheless, there have been no studies on the systemic bioavailability of topical corticosteroids in pregnant women for ethical concerns.

The data from nasal and inhaled corticosteroids may not be directly applicable to the skin. The systemic bioavailability of fluticasone propionate and mometasone furoate through these routes is very low;[34-36] however, the data could not be directly extrapolated to cutaneous application. The newer lipophilic corticosteroids including fluticasone propionate, mometasone furoate, and methylprednisolone aceponate, should perhaps be preferred based on fewer local and systemic side effects,[37,38] but direct evidence from pregnant women is lacking. However, these newer corticosteroids do have a better risk-benefit profile regarding cutaneous side effects (Figure 1)[39] and are maybe preferable due to this benefit. In addition, they have been marketed for over 20 years and used worldwide in a very high number of patients, giving further indirect evidence for safety by the lack of reported side effects.

Metabolism of corticosteroids

Over 90% of absorbed corticosteroids in the plasma reversibly combine with two plasma proteins: corticosteroid-binding globulin (CBG) and albumin. Only unbound corticosteroids can enter cells to exert actions. Most of circulating corticosteroids are bound at normal or low plasma levels. At higher plasma levels of corticosteroids, the

binding capacity of proteins is overwhelmed, and a greater proportion of the corticosteroids are in the free form.[40] A specific circumstance of physiological hypercorticism happens in pregnancy. The high circulating oestrogen levels promote the production of CBG, resulting in elevated total plasma cortisone levels. The physiological significance of these changes during pregnancy on exogenous corticosteroids is unclear.[41]

Corticosteroids are metabolised in the liver to water-soluble compounds which are excreted by the kidneys.[40]

Placental metabolism

The fetal effects of corticosteroids reply on their extent of transplacental passage (Table 3). The key metabolising enzyme of corticosteroids in the placenta is 11β-hydroxysteroid dehydrogenase (11βHSD) that transforms biologically active cortisol (hydrocortisone) into biologically inactive cortisone. Therefore, 11βHSD is the gatekeeper in limiting the quantities of maternal cortisol that pass through the placenta to enter the fetus and in protecting the fetus from unwanted harm.[42] Hydrocortisone is assumed safe for use in pregnancy because of the weak potency and high metabolism in the placenta. However, one study using the fetal-placental unit before abortion found 15% of ^{3}H-cortisol passed through the placenta without being metabolised[43] and another study illustrated a linear relationship between maternal and fetal serum cortisol levels.[44,45] Only 10-12% of prednisolone passed through the placenta.[46] In the meanwhile, dexamethasone, methylprednisolone, and betamethasone are less metabolised by the placenta, and 67%, 45%, and 30% reached the fetus, respectively.[47] Fluticasone propionate and budesonide are unmetabolised,[48] and thus high amounts of them pass through the placenta. To the

best of our knowledge, there is a lack of relevant studies on other corticosteroids. However, the newer corticosteroids like mometasone, which shows a first-pass effect in the liver, are most unlikely to pass the placenta in significant levels, if - like in other corticosteroids - a linear relationship between the maternal and the fetal serum may be assumed. In addition, mometasone is strongly bound to plasma proteins and the free fraction is approximately 10-20 times lower compared to other corticosteroids[49] which should lead to lower transition into the placenta.

Evidence from human studies

The data available as to possible fetal harm from the use of topical corticosteroids in pregnancy were limited. The current best evidence is from a recently updated Cochrane review published in 2015.[50] The review authors systematically searched 10 databases including the Cochrane Skin Group Specialised Register, the Cochrane Pregnancy and Childbirth Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, LILACS, and five trial registers. They identified 14 relevant studies, including 5 cohort and 9 case-control studies which covered a total of 1,601,515 subjects (Table 4).[51-63] A pregnant woman coauthor has been invovled in preparing this review.

Most of the available data were related to orofacial cleft (level of evidence: 3). The majority of the included studies found no significant associations between maternal use of topical corticosteroids and adverse pregnancy outcomes including mode of delivery, birth defect, preterm delivery, and fetal death, although these studies all had certain limitations.[51-60,62] A significant association between topical corticosteroids and

orofacial cleft was found in one small case-control study,[61] while none of other included studies showed a similar effect. Two cohort studies showed a significant association between maternal use of potent/very potent topical corticosteroids and low birth weight.[59,63] One further study identified an increased risk of low birth weight when the dispensed amounts of potent/very potent topical corticosteroids were more than 300 g during pregnancy.[60]

Conclusions

The available data on the safety of topical corticosteroids in pregnancy suggest a lack of associations of their use by the mother with birth defect, preterm birth, fetal death, and mode of delivery. Limited evidence does suggest a significant association of maternal use of potent/very potent topical corticosteroids, especially in large amounts, with low birth weight.[59,60,63] However, the finding was from only two research groups. Further studies are warranted for reproducing this finding.

Recommendations

1. Mild/moderate topical corticosteroids should be used in preference to more potent corticosteroids in pregnancy (low-quality evidence).
2. Potent/very potent topical corticosteroids should be used as second-line therapy for as short a time as possible. Once daily application of potent/very potent topical corticosteroids is recommended. Appropriate obstetric care should be provided as they increase the risk of low birth weight (low-quality evidence).

3. The association between maternal exposure to potent/very potent topical corticosteroids and fetal growth restriction needs to be considered when applying them during pregnancy. However, systemic corticosteroids have a greater bioavailability than that of topical corticosteroids, and thus have a greater potential for fetotoxicity than topical corticosteroids (systemic corticosteroids are associated with a reduction in fetal birth weight and an increase in preterm delivery[64,65]), and should not be used in preference (low-quality evidence).
4. On theoretical grounds the danger of adverse events is increased when areas with high absorption (e.g. genitals, eyelids, flexures) are treated (very low-quality evidence).
5. There are no data available to determine if newer lipophilic topical corticosteroids (mometasone furoate, fluticasone propionate, and methylprednisolone aceponate,) with a good therapeutic index (Figure 1) are associated with a smaller risk of low birth weight. On theoretical grounds a favourable side effect profile for the use in pregnancy is suggested, furthermore they have the practical advantage of once daily application compared to older preparations (very low-quality evidence).

Advice to women about using topical corticosteroids in pregnancy

1. Women can be reassured that there is no significantly increased risk of birth defect, preterm delivery, and fetal death while using topical corticosteroids for medical indications in pregnancy. There is also no increased risk of low birth weight when using mild/moderate topical corticosteroids in pregnancy.
2. Women should be informed that there is a small risk for low birth weight when

using large amounts of potent/very potent topical corticosteroids in pregnancy, but this risk is less than that of systemic corticosteroids, for an additional risk for miscarriage and preterm delivery associated with use of systemic corticosteroids.[65]

3. Depending on the severity of their skin conditions, pregnant women should use topical corticosteroids of the least potency required and limit the use amounts, preferably once daily. Pregnant women should be cautious on sites of high percutaneous absorption for example the skin folds, armpits, and vulva.

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Table 1 Levels of evidence defined by the Oxford Centre for Evidence-Based Medicine

Level 1	Systematic review of randomised trials or n-of-1 trial
Level 2	Randomised trial or (exceptionally) observational study with dramatic effect
Level 3	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**
Level 4	Case-series, case-control, or historically controlled studies**
Level 5	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

Table 2 Grades of recommendation defined by the GRADE Working Group

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The quality of evidence from randomised trials is initially rated as high and observational studies as low. Further evaluation may upgrade the quality of evidence for large magnitude effect, dose response, and confounders likely minimise the effect, and may downgrade due to study limitations, imprecision, inconsistency of results, indirectness of evidence and publication bias.

Table 3 Placental metabolism and transfer of various corticosteroids

	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 never been conducted.

Table 4 Studies on the safety of topical corticosteroids in pregnancy

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 study Population-based, using the dataset Hungarian Case-Control Surveillance of Congenital Abnormalities	20,830 cases of congenital abnormalities, 35,727 controls Prenatal log book, questionnaire and interview	Adjusted OR with 95% CI of maternal ointment corticosteroid treatment in 14 congenital abnormalities 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 congenital abnormalities (but the OR statistic was not reported). Also, no significant association between maternal corticosteroid ointment use and other major or mild congenital abnormalities 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 Pharmaco-epidemiological prescription database	Crude and adjusted OR with 95% CI for low birth weight, malformations, preterm delivery, and stillbirth	No increased risk of low birth weight, malformations, preterm delivery and stillbirth among the exposure group. The adjusted OR (95% CI) for low birth weight, 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 study 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	149,932 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 association 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 study Multi-centric database, Malformation Drug Exposure Surveillance	11,150 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 correlations of first-trimester exposure to topical corticosteroids with cleft palate or lip [OR 0.52 (95% CI 0.16-1.64)], cleft palate [OR 0 (95% CI 0-3.41)], and cleft lip ± palate [OR 0.73 (95% CI 0.23-2.37)].
Mahé; 2007; Senegal; not reported	Cohort study Single maternity hospital	34 of 99 women with exposure to potent topical corticosteroids (28 clobetasol propionate, 60 g/month). Compared to non users of very potent topical corticosteroids 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. χ^2 and Fischer's two tailed exact test, Kruskall-Wallis H test.	Increased frequency of mild vaginal bleeding (p = 0.031), decreased birth weight (P = 0.046), decreased placental weight (P = 0.043), decreased placental cortisol (P = 0.07).
Carmichael; 2007; US; Center for Disease Control and Prevention	Case-control study 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	OR with 95% CI of maternal use of topical corticosteroids 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 centre met standard eligibility criteria.	No significant association 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)]
Carmichael; 2009; US; Center for Disease Control and Prevention	Case-control study Multistate, part of the National Birth Defects Prevention Study	1165 cases of second- or third-degree hypospadias and 3000 non-malformed controls Maternal interviews were conducted using 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	OR with 95% CI of maternal use of topical corticosteroids confirmed by clinical description or operative report. Each case received an additional review by 1 clinical geneticist to ensure that cases from each study centre met standard eligibility criteria.	No significant association between hypospadias and maternal use of topical corticosteroids from 4 weeks before through 18 weeks after conception [OR 0.37 (95% CI 0.12, 1.17)]
Chi; 2011; UK; British Skin Foundation and University of Oxford	Retrospective cohort study Population-based	35,503 pregnant women prescribed topical corticosteroids during the period from 85 days before last menstrual period to delivery or fetal death and 48,630 unexposed women Prescription records	Adjusted RR for orofacial cleft (and its two categories, cleft lip ± palate and isolated cleft palate), fetal growth restriction, preterm delivery, and fetal death	A significant association of maternal exposure to potent/very potent topical corticosteroids with fetal growth restriction [adjusted RR 2.08 (95% CI 1.40-3.10)]. No significant association of topical corticosteroids of any potency with other pregnancy outcomes.

Hviid; 2011; Denmark; Danish Medical Research Council and Lundbeck Foundation	Retrospective cohort study Nationwide	22,480 pregnant women filled prescriptions for topical corticosteroids during the first trimester and 810,156 controls receiving no prescriptions for topical corticosteroids Danish Prescription Drug Register	Adjusted OR with 95% CI of cleft lip ± palate and isolated cleft palate	A significant association of topical corticosteroid use during first trimester and cleft lip ± palate [adjusted OR 1.45 (95% CI 1.03-2.05)]. However, exploratory analyses of the dose-response and potency-response relations did not support a causal association. The observed association may arise from multiple comparisons.
Chi; 2013; UK; Wellbeing of Women and Chang Gung Memorial Hospital, Chiayi	Retrospective cohort study Population-based	2658 pregnant women exposed to topical corticosteroid and 7246 unexposed pregnant women.	Adjusted RR with 95% CI for orofacial cleft, low birth weight, preterm delivery, fetal death, and low Apgar score as well as mode of delivery	A significantly increased risk of low birth weight when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy [adjusted RR, 7.74 (95%CI, 1.49-40.11)]. No associations of maternal topical corticosteroid exposure with orofacial cleft, preterm delivery, fetal death, low Apgar score, and mode of delivery.
Skuladottir; 2014; US; Centers for Disease Control and Prevention	Case-control study Population-based	2372 cleft cases (1577 infants with cleft lip ± palate and 795 infants with cleft palate alone) and 5922 controls without major congenital malformations randomly selected from birth certificates or birth hospitals	Adjusted OR with 95% CI of maternal use of topical corticosteroids during the periconceptional period	The overall association of corticosteroids and cleft lip and palate was 1.0 (95% CI, 0.7–1.4).
Skuladottir; 2014; US; Centers for Disease Control and Prevention	Case-control study Population-based	123 cases with cleft lip ± palate and 61 with cleft palate alone identified through the Medical Birth Registry of Norway, and 551 control mothers randomly selected from the Norwegian Mother and Child Cohort Study	Adjusted OR with 95% CI of maternal use of topical corticosteroids during the periconceptional period	No associations for any cleft type [adjusted OR, 1.0 (95% CI 0.5–2.2), cleft lip ± palate [adjusted OR 1.2 (95% CI 0.5–2.9) nor for cleft palate alone [adjusted OR 0.6 (95% CI 0.1–2.6).
Skuladottir; 2014; Norway; Western Norwegian Health Authorities	Case-control study 2 specialised surgical centres for oral cleft in Norway	573 cleft cases (377 infants with cleft lip ± palate and 196 infants with cleft palate alone) and 763 controls without major congenital malformations randomly selected from the Medical Birth Registry of Norway	Adjusted OR with 95% CI of maternal first-trimester exposure to corticosteroids	No significant associations of first-trimester use of topical corticosteroids with both cleft lip ± palate (adjusted OR 2.3 (95% CI 0.71–7.7) and cleft palate alone (adjusted OR, 3.4; CI 0.87–13)

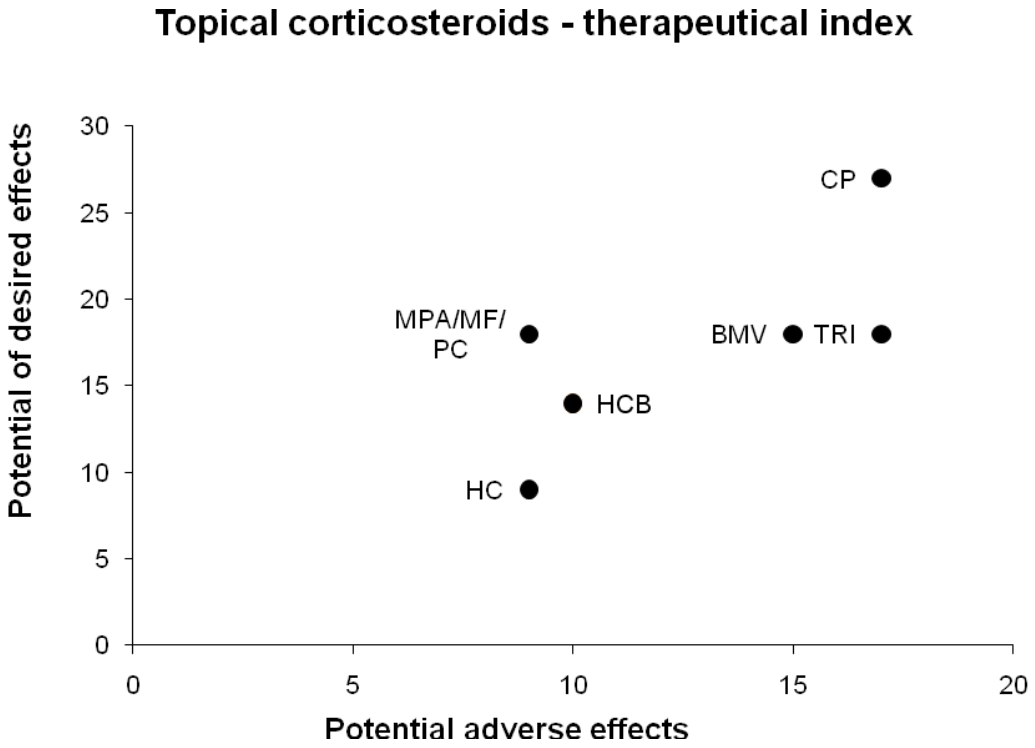
CI, confidence interval; OR, odds ratio; RR, risk ratio.

Table 5 Potency of topical corticosteroids (adapted from the British National Formulary [66] and Chi's thesis[9])

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 fewer adverse effects[37,39] (see Figure 1).

Figure 1 Therapeutic index of topical corticosteroids (modified from Luger TA et al 2004[39]). BMV, betamethasone valerate; CP, clobetasol propionate; HC, hydrocortisone; HCB, hydrocortisone butyrate; MF, mometasone furoate; MPA, methylprednisolone acetate; PC, prednicarbate; TRI, triamcinolone acetonide.



Conflicts of interests

The Work Under Consideration for Publication					
		Aberer	**Chi**	**Gabbud**	**Haustein**
1	Grant	None	None	None	None
2	Consulting fee or honorarium	None	None	None	None
3	Support for travel to meetings for the study or other purposes	None	None	None	None
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	None	None	None
5	Payment for writing or reviewing the manuscript	None	None	None	None
6	Provision of writing assistance, medicines, equipment, or administrative support	None	None	None	None
7	Other	None	None	None	None

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
		Aberer	**Chi**	**Gabbud**	**Haustein**
1	Board membership	None	None	None	None
2	Consultancy	None	Received fees for speaking from Johnson & Johnson Taiwan Ltd, and Pfizer Inc	None	None
3	Employment	None	None	Retired from private practice	None
4	Expert testimony	None	None	None	None
5	Grants/grants pending	None	None	None	None
6	Payment for lectures including service on speakers bureaus	None	Received fees for speaking from Eisai Taiwan Inc, Johnson & Johnson Taiwan Ltd, and Pfizer Taiwan Inc	None	None
7	Payment for manuscript preparation	None	None	None	None
8	Patents (planned, pending or issued)	None	None	None	None

9	Royalties	None	None	None	None
10	Payment for development of educational presentations	None	None	None	None
11	Stock/stock options	None	None	None	None
12	Travel/accommodations/meeting expenses unrelated to activities listed**	None	None	None	None
13	Other (err on the side of full disclosure)	None	None	None	None

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
		Aberer	**Chi**	**Gabbud**	**Haustein**
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	None	None	None	None

Conflicts of interests

	The Work Under Consideration for Publication					
		Karpati	**Kirtschig**	**Lipozencic**	**Wojnarowska**	**Zuberbier**
1	Grant	None	None	None	None	None
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3	Support for travel to meetings for the study or other purposes	None	None	None	None	None
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	None	None	None	None
5	Payment for writing or reviewing the manuscript	None	None	None	None	None
6	Provision of writing assistance, medicines, equipment, or administrative support	None	None	None	None	None
7	Other	None	None	None	None	None

* This means money that your institution received for your efforts on this study.

	Relevant financial activities outside the submitted work					
		Karpati	**Kirtschig**	**Lipozencic**	**Wojnarowska**	**Zuberbier**
1	Board membership	None	None	None	None	None
2	Consultancy	None	None	None	None	s. list attached
3	Employment	None	None	None	None	None
4	Expert testimony	None	None	None	None	None
5	Grants/grants pending	None	None	None	None	s. list attached
6	Payment for lectures including service on speakers bureaus	None	None	None	None	s. list attached
7	Payment for manuscript preparation	None	None	None	None	None
8	Patents (planned, pending or issued)	None	None	None	None	None
9	Royalties	None	None	None	None	None
10	Payment for development of educational presentations	None	None	None	None	None
11	Stock/stock options	None	None	None	None	None

12	Travel/accommodations/meeting expenses unrelated to activities listed**	None	None	None	None	None
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	Other relationships					
		Karpati	**Kirtschig**	**Lipozencic**	**Wojnarowska**	**Zuberbier**
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	None	None	None	None	None

Torsten Zuberbier, MD

Contact details/affiliation:

Department of Dermatology and Allergy
Allergy Centre Charité
Charité -Universitätsmedizin Berlin
Charitéplatz 1 / 10117 Berlin, Germany
Phone +4930450518 135/ Fax 49 30 450518919
Email: torsten.zuberbier@charite.de

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Organizational Affiliations:

Committee member, WHO-Initiative “Allergic Rhinitis and its Impact on Asthma” (ARIA)
Member of the Board, German Society for Allergy and Clinical Immunology (DGAKI)
Head, European Centre for Allergy Research Foundation (ECARF)
Secretary General , Global Allergy and Asthma European Network (GA²LEN)
Member, Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organisation (WAO)

Prof. Dr. med. Dr. h. c. Torsten Zuberbier