Original Investigation

# Pregnancy Outcomes After Maternal Exposure to Topical Corticosteroids
## A UK Population-Based Cohort Study

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**IMPORTANCE** Topical corticosteroids are indicated for pregnant women with skin conditions, but their safety in pregnancy is not fully understood.

**OBJECTIVE** To investigate whether maternal exposure to topical corticosteroids results in adverse pregnancy outcomes.

**DESIGN** Retrospective cohort study.

**SETTING** United Kingdom National Health Service.

**PARTICIPANTS** A total of 2658 pregnant women exposed to topical corticosteroid and 7246 unexposed pregnant women.

**EXPOSURE** Topical corticosteroids dispensed during pregnancy.

**MAIN OUTCOMES AND MEASURES** Orofacial cleft, low birth weight, preterm delivery, fetal death, low Apgar score, and mode of delivery.

**RESULTS** No associations of maternal topical corticosteroid exposure with orofacial cleft, low birth weight, preterm delivery, fetal death, low Apgar score, and mode of delivery were found in the primary analysis (adjusted risk ratio [RR], 1.85 [95% CI, 0.22-15.20] [$P$ = .57]; 0.97 [95% CI, 0.78-1.19] [$P$ = .75]; 1.20 [95% CI, 0.73-1.96] [$P$ = .48]; 1.07 [95% CI, 0.56-2.05] [$P$ = .84]; 0.84 [95% CI, 0.54-1.31] [$P$ = .45]; and $P$ = .76, respectively). Stratified analyses based on potency did not reveal any significant associations in most of these categories either, but an exploratory analysis showed 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]; $P$ = .02).

**CONCLUSIONS AND RELEVANCE** This study reassuringly showed no associations of maternal topical corticosteroid exposure with orofacial cleft, preterm delivery, fetal death, low Apgar score, and mode of delivery. With this study and all available evidence taken together, the risk of low birth weight seems to correlate with the quantity of topical corticosteroid exposure.

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Topical corticosteroids are the most frequently used drugs for treating skin conditions and are prescribed to more than 6% of pregnant women,[1(p130)] but their safety in pregnancy is not fully understood. Topical corticosteroids are teratogenic and result in fetal growth restriction in animals.[2,3] However, pharmacology references do not offer explicit instructions on prescribing topical corticosteroids in pregnancy.[4] The prescribing information of topical corticosteroids states that they should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The US Food and Drug Administration (FDA) labels topical corticosteroids as pregnancy risk category C, meaning that animal studies have shown adverse fetal effects, but there are no adequate and well-controlled studies in pregnant women.[5(ppxiii-xxiv)]

The current available evidence on the safety of topical corticosteroid use in human pregnancy is limited.[6,7] Many of the previous studies only investigated the relation between topical corticosteroid use in early pregnancy and orofacial cleft.[8-12] The results were inconsistent: 1 small case-control study showed a link between maternal first-trimester use of topical corticosteroids and orofacial cleft,[11] but other studies found no such association.[9,10,12-14] A recent Cochrane review[6,7] has highlighted potential problems with low birth weight (LBW). A hospital-based cohort study showed significant associations of use of very potent topical corticosteroids with lower plasma cortisol levels, decreased placental weight, and LBW infants.[15] Our previous population-based cohort study also found a significant association between maternal exposure to potent or very potent topical corticosteroids and fetal growth restriction.[14] However, no similar associations were found in an earlier study.[16] Therefore, the available data on the effects of topical corticosteroid use on pregnancy outcomes are inconclusive. The objective of this study was to investigate whether maternal exposure to topical corticosteroids has adverse effects on pregnancy by examining a comprehensive set of outcomes.

## Methods

### Data Source

We used the Health Informatics Centre (HIC) data sets from 1989 to 2006 to conduct this retrospective cohort study. The HIC manages a database of anonymized longitudinal medical records from National Health Service (NHS) Tayside in Scotland. Everyone registered with the NHS Tayside is allocated a unique identifying number, the Community Health Index number, which is the key to linking each person's health records from general practices, pharmacies, biochemistry laboratories, and hospitals to improve quality and promote research while preserving confidentiality.[17]

### Study Population

The exposed group were pregnant women aged 15 to 44 years who received 1 or more dispensed prescriptions for topical corticosteroids during pregnancy. Women who had received 1 or more dispensed prescriptions for any other form (systemic, injection, inhalation, or nasal) of corticosteroids during pregnancy and women with multiple pregnancy or pregnancy following assisted reproduction were excluded. An early exposed group limited to women receiving 1 or more dispensed prescriptions for topical corticosteroids during the first 12 gestational weeks was used for the analysis of orofacial cleft.

The unexposed group consisted of pregnant women aged 15 to 44 years who did not receive any dispensed prescription for any form of corticosteroids during pregnancy. For each exposed woman, we selected up to 3 unexposed pregnant women by matching for maternal age (5-year bands), as well as the calendar year of pregnancy.

### Ascertainment of Exposure

In the UK NHS, all community prescriptions are written by general practitioners, sometimes on the basis of the advice of referred hospital dermatologists. Hospital outpatients also receive drugs from community pharmacies. The HIC collects data on dispensed prescriptions from community pharmacies and links them to the Community Health Index number.[17] We used the pharmacy records to identify the timing, potency, and dosage of topical corticosteroids dispensed.

### Outcomes

We examined orofacial cleft, LBW (birth weight <2500 g), preterm delivery (delivery prior to 37 completed weeks' gestation), fetal death, mode of delivery (normal vaginal delivery, assisted delivery, and cesarean delivery), and low Apgar score (<7 at 5 minutes[18]).

Preterm delivery, LBW, and low Apgar score are often correlated. It is likely that the fetuses that did not survive to birth would have experienced 1 of these outcomes if they had survived. We therefore did an additional analysis considering preterm delivery, fetal death, LBW, and low Apgar scores as a composite adverse outcome.

### Data Analysis

The $\chi^2$ test was used to compare the potential confounders and mode of delivery between the exposed and unexposed groups. Univariate logistic regression was used to estimate the crude risk ratios (RRs) and 95% confidence intervals (CIs) for the other outcomes in relation to maternal exposure to topical corticosteroids. Multivariate logistic regression with adjustment for confounders including previous exposure to topical corticosteroids within 1 year before pregnancy, lupus erythematosus, antiphospholipid syndrome, hypertension, diabetes mellitus, renal disease, thyroid disorder, thrombophilia, cholestasis of pregnancy, human immunodeficiency virus infection, asthma, and exposure to other medications that may affect pregnancy outcomes (drugs classified as US FDA pregnancy risk category D or X) was used to estimate the adjusted RRs and 95% CIs.[19-25] When analyzing orofacial cleft, LBW, preterm delivery, and low Apgar score, we excluded cases in which the fetus did not survive to birth.

A stratified analysis was performed to calculate the adjusted RRs and 95% CIs in relation to the potency of the topical corticosteroids (mild, moderate, potent, and very potent

Table 1. Potential Confounders and Mode of Delivery in Study Subjects

| Confounder | No. (%) | | P Value (Exposed vs Unexposed)[b] | Early Exposed Group,[c] No. (%) (n = 757) | P Value (Early Exposed vs Unexposed)[b] |
|---|---|---|---|---|---|
| | Unexposed Group (n = 7246) | Exposed Group[a] (n = 2658) | | | |
| Lupus erythematosus | 1 (0.01) | 1 (0.04) | .46 | 1 (0.1) | .05 |
| Antiphospholipid syndrome | 0 | 1 (0.04) | .10 | 1 (0.1) | .002 |
| Hypertension | 0 | 0 | NA | 0 | NA |
| Diabetes mellitus | 46 (0.63) | 13 (0.49) | .40 | 6 (0.8) | .61 |
| Renal disease | 1 (0.01) | 0 | .54 | 0 | .75 |
| Thyroid disease | 58 (0.80) | 23 (0.87) | .75 | 7 (0.9) | .72 |
| Cholestasis of pregnancy | 2 (0.03) | 0 | .39 | 0 | .65 |
| HIV infection | 1 (0.01) | 0 | .54 | 0 | .75 |
| Asthma | 111 (1.53) | 63 (2.37) | .005 | 27 (3.6) | <.001 |
| Receiving US FDA pregnancy risk category D or X drugs | 3368 (46.48) | 1597 (60.08) | <.001 | 491 (64.9) | <.001 |
| Smoking during pregnancy (known for 7228 women) | | | | | |
| Yes | 1596 (24.27) | 588 (24.72) | .67 | 172 (26.3) | .24 |
| No | 4979 (75.73) | 1791 (75.28) | | 481 (73.7) | |
| Scottish index of multiple deprivation rank, quintile (known for 4784 women) | | | | | |
| 1 | 536 (15.04) | 151 (12.62) | .12 | 47 (12.5) | .44 |
| 2 | 1015 (28.48) | 327 (26.80) | | 98 (26.1) | |
| 3 | 634 (17.79) | 234 (19.18) | | 70 (18.7) | |
| 4 | 649 (18.21) | 234 (19.18) | | 73 (19.5) | |
| 5 | 730 (20.48) | 271 (22.21) | | 87 (23.2) | |
| Mode of delivery | | | | | |
| Normal vaginal | 5571 (81.71) | 2048 (81.11) | .76 | ... | |
| Assisted | 364 (5.34) | 143 (5.66) | | ... | |
| Cesarean | 883 (12.95) | 334 (13.23) | | ... | |

Abbreviations: FDA, Food and Drug Administration; HIV, human immunodeficiency virus; NA, not available.

[a] From last menstrual period to delivery or fetal death.

[b] The $\chi^2$ test.

[c] From last menstrual period to 12th gestational week.

categories according to the British National Formulary).[4] When a category of topical corticosteroid was significantly associated with an outcome, we examined the dose-response relationship by means of a multivariate logistic regression model using dosage as a continuous variable. We conducted exploratory analyses on the associations of the dispensed amount of potent or very potent topical corticosteroids with orofacial cleft and LBW. We did sensitivity analyses by adding maternal smoking during pregnancy and socioeconomic status based on the Scottish Index of Multiple Deprivation in the multivariate logistic regression model.

### Ethics Approval

The HIC data sets have gained ethical approval from the Fife, Forth Valley and Tayside Research Ethics Service to provide anonymized data for observational studies. This study was also approved by the Chang Gung Medical Foundation Institutional Review Board (100-1997B).

## Results

This study enrolled 2658 exposed women (including 757 exposed to topical corticosteroids during the first 12 gestational weeks) and 7246 unexposed women. The potential confounders in the exposed and unexposed groups are summarized in **Table 1**. A higher proportion of the exposed women had asthma and received FDA pregnancy risk category D or X medicines during pregnancy than the unexposed women ($P$ = .005 and <.001, respectively).

### Orofacial Cleft

We found no significant association between orofacial cleft and early maternal exposure to topical corticosteroids (crude RR, 1.37 [95% CI, 0.17-11.17]; $P$ = .77; adjusted RR, 1.85 [95% CI, 0.22-15.20]; $P$ = .57) (**Table 2**). Because there were only 8 orofacial clefts, a stratified analysis based on corticosteroid potency was not performed.

### Low Birth Weight

As shown in Table 2, no significant association between LBW and maternal exposure to topical corticosteroids was found (crude RR, 0.97 [95% CI, 0.78-1.19]; $P$ = .76; adjusted RR, 0.97 [95% CI, 0.78-1.19]; $P$ = .75). Stratified analyses according to corticosteroid potency found no significant associations of LBW with maternal exposure to topical corticosteroids of any potency. Sensitivity analyses after adjustment for maternal smoking during pregnancy and socioeconomic levels also found no

Table 2. Analyses on Orofacial Cleft, Low Birth Weight, Preterm Delivery, Fetal Death, and Low Apgar Score

| Outcome | Incidence, Proportion (%) | Adjusted RR (95% CI) | Stratified Analysis, Adjusted RR (95% CI) | | | |
|---|---|---|---|---|---|---|
| | | | Mild Steroid | Moderate Steroid | Potent Steroid | Very Potent Steroid |
| Orofacial cleft | | | | | | |
| Primary analysis | | | | | | |
| Unexposed | 7/7212 (0.10) | 1 [Ref] | ... | ... | ... | ... |
| Early exposed[a] | 1/751 (0.13) | 1.85 (0.22-15.20) | ... | ... | ... | ... |
| Sensitivity analysis[b] | | | | | | |
| Unexposed | 7/7212 (0.10) | 1 [Ref] | ... | ... | ... | ... |
| Early exposed[a] | 0/333 | NA | ... | ... | ... | ... |
| Low birth weight | | | | | | |
| Primary analysis | | | | | | |
| Unexposed | 346/7212 (4.80) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 123/2645 (4.65) | 0.97 (0.78-1.19) | 0.95 (0.73-1.23) | 0.95 (0.65-1.41) | 1.04 (0.72-1.49) | 0.92 (0.29-2.94) |
| Sensitivity analysis 1[c] | | | | | | |
| Unexposed | 308/7157 (4.30) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 106/2622 (4.04) | 0.93 (0.74-1.17) | 0.98 (0.75-1.28) | 0.88 (0.57-1.35) | 0.95 (0.64-1.42) | 1.02 (0.32-3.27) |
| Sensitivity analysis 2[b] | | | | | | |
| Unexposed | 157/3313 (4.74) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 49/1112 (4.41) | 0.91 (0.65-1.27) | 0.84 (0.55-1.27) | 0.69 (0.33-1.43) | 1.06 (0.61-1.85) | 0.73 (0.10-5.50) |
| Preterm delivery | | | | | | |
| Primary analysis | | | | | | |
| Unexposed | 55/7212 (0.76) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 23/2645 (0.87) | 1.20 (0.73-1.96) | 0.91 (0.47-1.74) | 1.07 (0.42-2.69) | 1.42 (0.64-3.15) | NA |
| Sensitivity analysis[b] | | | | | | |
| Unexposed | 47/3313 (1.42) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 22/1112 (1.98) | 1.42 (0.84-2.38) | 1.04 (0.52-2.08) | 1.46 (0.57-3.73) | 1.73 (0.77-3.90) | NA |
| Fetal death | | | | | | |
| Primary analysis | | | | | | |
| Unexposed | 34/7246 (0.47) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 13/2658 (0.49) | 1.07 (0.56-2.05) | 0.79 (0.33-1.88) | 1.41 (0.50-4.02) | 1.62 (0.63-4.18) | 3.43 (0.46-25.59) |
| Sensitivity analysis[b] | | | | | | |
| Unexposed | 12/3325 (0.36) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 4/1116 (0.36) | 1.07 (0.34-3.37) | 0.85 (0.19-3.83) | 1.22 (0.16-9.52) | 1.03 (0.13-8.11) | NA |
| Low Apgar score | | | | | | |
| Primary analysis | | | | | | |
| Unexposed | 88/6763 (1.30) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 26/2457 (1.06) | 0.84 (0.54-1.31) | 0.77 (0.44-1.33) | 0.72 (0.29-1.78) | 1.02 (0.49-2.12) | 1.41 (0.19-10.35) |
| Sensitivity analysis[b] | | | | | | |
| Unexposed | 31/2971 (1.04) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 7/987 (0.71) | 0.72 (0.31-1.66) | 0.65 (0.23-1.86) | 3.42 (0.45-26.19) | 1.66 (0.57-4.79) | NA |
| Composite adverse outcome[d] | | | | | | |
| Primary analysis | | | | | | |
| Unexposed | 454/7246 (6.27) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 165/2658 (6.21) | 1.00 (0.83-1.20) | 0.95 (0.76-1.19) | 0.94 (0.66-1.32) | 1.13 (0.83-1.55) | 1.20 (0.48-2.99) |
| Sensitivity analysis[b] | | | | | | |
| Unexposed | 205/3325 (6.17) | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Exposed | 66/1116 (5.91) | 0.96 (0.72-1.28) | 0.91 (0.64-1.30) | 0.59 (0.30-1.18) | 1.18 (0.74-1.89) | 0.56 (0.08-4.23) |

Abbreviations: NA, not available; Ref, referent; RR, risk ratio.

[a] From last menstrual period to 12th gestational week.

[b] After adjustment for maternal smoking during pregnancy and socioeconomic levels.

[c] After excluding preterm deliveries.

[d] Low birth weight, preterm delivery, low Apgar score, or fetal death.

Table 3. Exploratory Analysis on the Amounts of Strong Topical Corticosteroids and Risk of Low Birth Weight

| Dispensed Amounts of Potent or Very Potent Topical Corticosteroids During the Whole Pregnancy, g | Risk Ratio (95% CI) of Low Birth Weight | P Value |
|---|---|---|
| 1-100 | 1.01 (0.69-1.47) | .96 |
| 101-200 | 1.03 (0.32-3.32) | .96 |
| 201-300 | NA | NA |
| >300 | 7.74 (1.49-40.11) | .02 |

Abbreviation: NA, not available.

such associations. Sensitivity analyses performed by excluding preterm deliveries did not change the results.

However, an exploratory analysis on the association between LBW and the dispensed amount of potent or very potent topical corticosteroids during the whole pregnancy found a significantly increased risk of LBW when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the whole pregnancy (adjusted RR, 7.74 [95% CI, 1.49-40.11]; $P = .02$) (**Table 3**).

### Preterm Delivery

We found no significant associations of preterm delivery and maternal exposure to topical corticosteroids (crude RR, 1.14 [95% CI, 0.70-1.86]; $P = .60$; adjusted RR, 1.20 [95% CI, 0.73-1.96]; $P = .48$). Stratified analyses found no significant associations of preterm delivery with maternal exposure to topical corticosteroids of any potency. Sensitivity analyses performed after adjustment for maternal smoking and socioeconomic levels did not change the results (Table 2).

### Fetal Death

No significant association was found between fetal death and maternal exposure to topical corticosteroids (crude RR, 1.04 [95% CI, 0.55-1.98]; $P = .90$; adjusted RR, 1.07 [95% CI, 0.56-2.05]; $P = .84$). Also, stratified analyses based on corticosteroid potency and sensitivity analyses performed after adjustment for maternal smoking and socioeconomic levels found no such associations (Table 2).

### Mode of Delivery

No significant differences in the mode of delivery were found between the exposed and unexposed groups ($P = .76$) (Table 1).

### Low Apgar Score

We found no significant association of low Apgar score with maternal exposure to topical corticosteroids (crude RR, 0.81 [95% CI, 0.52-1.26]; $P = .35$; adjusted RR, 0.84 [95% CI, 0.54-1.31]; $P = .45$). Stratified analyses did not find significant associations of low Apgar score with maternal exposure to topical corticosteroids of any potency, nor did sensitivity analyses performed after adjustment for maternal smoking during pregnancy and socioeconomic levels (Table 2).

### Composite Adverse Outcome

The analysis using preterm delivery, fetal death, LBW, and low Apgar scores as a composite adverse outcome found no

Table 4. Amounts of Strong Topical Corticosteroids and Risk of Low Birth Weight

| Study | Potent or Very Potent Topical Corticosteroids Prescribed During the Whole Pregnancy, Mean (Range), g | Risk Ratio (95% CI) of Low Birth Weight |
|---|---|---|
| Mygind et al,[16] 2002 | Not reported | 1.23 (0.45-3.37) |
| Mahé et al,[15] 2007 | 600 (120-1700) (of clobetasol propionate) | 2.84 (1.07-7.54) |
| Chi et al,[14] 2011 | 83.5 (10-2800) | 2.08 (1.40-3.10) |
| Chi et al (present study) | 64 (15-490) | 1.04 (0.72-1.49) for potent corticosteroids; 0.92 (0.29-2.94) for very potent corticosteroids |

associations with maternal exposure to topical corticosteroids (crude RR, 0.99 [95% CI, 0.82-1.19]; $P = .92$; adjusted RR, 1.00 [95% CI, 0.83-1.20]; $P = .97$). Also, stratified analyses based on corticosteroid potency and sensitivity analyses performed after adjustment for maternal smoking and socioeconomic levels found no such associations (Table 2).

## Discussion

This study found no association between orofacial cleft and maternal exposure to topical corticosteroids, which is congruent with most of the previous studies.[8-10,13,14] One case-control study identified an association between orofacial cleft and first-trimester use of topical corticosteroids, but the sample size was small and the response rate was low.[11] Another retrospective cohort study found a significant association between first-trimester use of topical corticosteroids and cleft lip with or without cleft palate, but exploratory analyses of the dose-response and potency-response relationship failed to support a causal association. The finding may arise from multiple comparisons.[12] The critical period for the fusion of the lip and palate is from the 5th to the 12th gestational week.[24] Our study used an early exposed group composed of women who received a dispensed prescription for topical corticosteroids during the first 12 gestational weeks and thus had a better estimate of the association with orofacial cleft. However, there were only 8 orofacial clefts; the statistical power regarding this outcome was thus limited.

In the present study (**Table 4**), the mean (range) dispensed quantity of potent or very potent topical corticosteroid during the whole pregnancy was 64 (15-490) g. Similar to a previous study,[16] the present study found no associations between LBW and maternal exposure to topical corticosteroids of any potency. However, our exploratory analysis (Table 3) found the risk of LBW significantly increased when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g (95% CI, 1.49-40.11; $P = .02$). By contrast, the use of less than 200 g of topical corticosteroids did not confer an increased risk of LBW. Two previous cohort studies showed a significant association between fetal growth restriction and maternal exposure to potent or

very potent topical corticosteroids (Table 4).[14,15] In 1 study,[15] the exposed women used a very potent topical corticosteroid, clobetasol propionate, at a very high mean (range) quantity of 60 (12-170) g per month (ie, 600 [120-1700] g during the whole pregnancy). Not only LBW but also lower plasma cortisol levels and a reduced placental weight were noted. In our previous study,[14] the mean (range) prescribed quantity of potent or very potent topical corticosteroids during the whole pregnancy was 83.5 (10-2800) g. Our previous study found not only a significant association of maternal exposure to potent or very potent topical corticosteroids with fetal growth restriction (adjusted RR, 2.08 [95% CI, 1.40-3.10]) but also a significant dose-response relationship ($P = .02$).[14] However, the number needed to harm was 168, ie, 1 additional fetal growth restriction would occur for every 168 pregnant women prescribed potent or very potent topical corticosteroids.[14] Therefore, the absolute risk of LBW may be small when the quantity of topical corticosteroid used is limited and may not have been detected by the present study of a smaller dispensed quantity of stronger topical corticosteroids and of a smaller sample size.

Consistent with previous studies,[14-16] the present study found no associations of maternal exposure to topical corticosteroids with preterm delivery and fetal death. To our knowledge, only 1 previous study has investigated mode of delivery and low Apgar score, and it found no associations between the 2 outcomes and maternal exposure to topical corticosteroids.[15] The present study also found no such associations.

The present study used records of dispensed prescriptions from pharmacies, which include prescriptions given by general practitioners and hospital dermatologists, and thus had better exposure data than a previous study that used prescription records from general practitioners.[14] The present study minimized known confounding by adjusting for maternal comorbidities and exposure to other drugs that may have affected the outcomes (US FDA pregnancy risk category D or X medicines, such as antihypertensive medications). Because maternal smoking during pregnancy and socioeconomic levels were not known for every woman, we conducted sensitivity analyses by adding the 2 confounders in the multivariate logistic regression model. The results from our primary analyses and sensitivity analyses were congruent and thus robust. To the best of our knowledge, this study is the first to consider the confounding from socioeconomic levels.

We obtained detailed data on pregnancy outcomes from the records of maternity admissions (Scottish Morbidity Record 2) and thus could examine pregnancy outcomes that were rarely investigated previously, ie, mode of delivery and low Apgar score. Most previous studies only investigated the association between topical corticosteroid use and orofacial cleft and were limited in scope.[6,8-12] The present study provides a comprehensive set of outcome data that can be a useful reference for physicians and their patients in making decisions regarding use of topical corticosteroids in pregnancy.

Similar to previous studies using data from prescription databases,[12,14,16] maternal adherence to topical corticosteroids was unknown in the present study. However, if pregnant women did not apply topical corticosteroids or applied smaller amounts than prescribed, the risk of adverse pregnancy outcomes might have been underestimated. The HIC data sets did not have data on topical corticosteroids dispensed in hospitals. However, if some women in the unexposed group received topical corticosteroids from hospitals, the adverse effects of topical corticosteroid use would have been underestimated.

In the United Kingdom, there are only 2 available over-the-counter topical corticosteroids, hydrocortisone (a weak corticosteroid) and clobetasone butyrate (a moderate corticosteroid). The HIC data sets do not have data on pregnant women's use of over-the-counter topical corticosteroids. Lack of these data may lead to misclassification and resultant underestimation of the risk. However, to the best of our knowledge, there have been no associations of weak and moderate topical corticosteroids with adverse pregnancy outcomes.[14,16]

Strong topical corticosteroids are frequently prescribed for treating inflammatory dermatoses (eg, psoriasis and atopic dermatitis). A previous study found no significant associations between adverse pregnancy outcomes and inflammatory dermatoses.[26] Another study reported that women with severe psoriasis had an increased risk of LBW infants but did not consider the confounding from pharmacological treatments.[27] Pemphigoid gestationis is associated with LBW and preterm birth.[28] The HIC data sets did not have data on which skin conditions were being treated with topical corticosteroids. In the present study, we adjusted for previous exposure to topical corticosteroids within 1 year before pregnancy in the multivariate analyses to mitigate the confounding from chronic dermatoses, although we could not control the confounding from acute skin conditions such as pemphigoid gestationis because we lacked relevant data.

## Conclusions

This population-based study reassuringly showed no associations of maternal exposure to topical corticosteroids with orofacial cleft, preterm delivery, fetal death, low Apgar score, and mode of delivery. The results provide additional evidence to support the previously published guidelines.[29]

With this study and all available evidence taken together,[14,15] the risk of LBW seems to correlate with the quantity of strong topical corticosteroid exposure (Table 4). The absolute risk for LBW from limited use of strong topical corticosteroids is small, but the risk increases with heavy maternal use of strong topical corticosteroids.[14,15] Therefore, for pregnant women with a skin condition, mild or moderate topical corticosteroids are the preferred treatments if indicated. When potent or very potent topical corticosteroids are needed, the amounts used should be kept to a minimum, and fetal growth should be monitored.

## ARTICLE INFORMATION

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**Author Contributions:** Drs Chi and Wang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Chi, Wojnarowska.
*Acquisition of data:* Chi, Wang.
*Analysis and interpretation of data:* Chi, Wang, Mayon-White.
*Drafting of the manuscript:* Chi.
*Critical revision of the manuscript for important intellectual content:* Wang, Mayon-White, Wojnarowska.
*Statistical analysis:* Chi, Mayon-White.
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*Administrative, technical, or material support:* Wang.
*Study supervision:* Mayon-White, Wojnarowska.

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## REFERENCES

1. Chi CC. *Evidence-Based Assessment of the Safety of Topical Corticosteroids in Pregnancy* [thesis]. Oxford, England: Nuffield Department of Clinical Medicine, University of Oxford; 2009.

2. Diflorasone diacetate cream [package insert]. Hawthorne, NY: Taro Pharmaceuticals; 1999.

3. Narama I. Reproduction studies of diflorasone diacetate (DDA). IV. teratogenicity study in rabbits by percutaneous administration. *Pharmacometrics*. 1984;28(2):241-250.

4. Mehta DK, ed. *British National Formulary*. 53rd ed. London, England: BMJ Publishing Group Ltd and RPS Publishing; 2007.

5. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

6. Chi CC, Wang SH, Kirtschig G, Wojnarowska F. Systematic review of the safety of topical corticosteroids in pregnancy. *J Am Acad Dermatol*. 2010;62(4):694-705.

7. Chi CC, Lee CW, Wojnarowska F, Kirtschig G. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev*. 2009;(3):CD007346.

8. Källén B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac J*. 2003;40(6):624-628.

9. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P; Contributors to the MADRE database. First trimester exposure to corticosteroids and oral clefts. *Birth Defects Res A Clin Mol Teratol*. 2003;67(12):968-970.

10. Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ; National Birth Defects Prevention Study. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol*. 2007;197(6):e1-e7; 683-684.

11. Edwards MJ, Agho K, Attia J, et al. Case-control study of cleft lip or palate after maternal use of topical corticosteroids during pregnancy. *Am J Med Genet A*. 2003;120A(4):459-463.

12. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ*. 2011;183(7):796-804.

13. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology*. 1997;56(5):335-340.

14. Chi CC, Mayon-White RT, Wojnarowska FT. Safety of topical corticosteroids in pregnancy: a population-based cohort study. *J Invest Dermatol*. 2011;131(4):884-891.

15. Mahé A, Perret JL, Ly F, Fall F, Rault JP, Dumont A. The cosmetic use of skin-lightening products during pregnancy in Dakar, Senegal: a common and potentially hazardous practice. *Trans R Soc Trop Med Hyg*. 2007;101(2):183-187.

16. Mygind H, Thulstrup AM, Pedersen L, Larsen H. Risk of intrauterine growth retardation, malformations and other birth outcomes in children after topical use of corticosteroid in pregnancy. *Acta Obstet Gynecol Scand*. 2002;81(3):234-239.

17. Stergachis A, Saunders KW, Davis RL, et al. Examples of automated databases. In: Strom BL, Kimmel SE, eds. *Textbook of Pharmacoepidemiology*. Chichester, England: John Wiley & Sons, Ltd; 2006:198-204.

18. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. *N Engl J Med*. 2001;344(7):467-471.

19. Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. *Plast Reconstr Surg*. 2000;105(2):485-491.

20. Spilson SV, Kim HJ, Chung KC. Association between maternal diabetes mellitus and newborn oral cleft. *Ann Plast Surg*. 2001;47(5):477-481.

21. Brodsky D, Christou H. Current concepts in intrauterine growth restriction. *J Intensive Care Med*. 2004;19(6):307-319.

22. Steer P. The epidemiology of preterm labour. *BJOG*. 2005;112(suppl 1):1-3.

23. Smith GC. Predicting antepartum stillbirth. *Curr Opin Obstet Gynecol*. 2006;18(6):625-630.

24. Arosarena OA. Cleft lip and palate. *Otolaryngol Clin North Am*. 2007;40(1):27-60; vi.

25. Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a meta-analysis. *Cleft Palate Craniofac J*. 1997;34(3):206-210.

26. Seeger JD, Lanza LL, West WA, Fernandez C, Rivero E. Pregnancy and pregnancy outcome among women with inflammatory skin diseases. *Dermatology*. 2007;214(1):32-39.

27. Yang YW, Chen CS, Chen YH, Lin HC. Psoriasis and pregnancy outcomes: a nationwide population-based study. *J Am Acad Dermatol*. 2011;64(1):71-77.

28. Chi CC, Wang SH, Charles-Holmes R, et al. Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. *Br J Dermatol*. 2009;160(6):1222-1228.

29. Chi CC, Kirtschig G, Aberer W, et al. Evidence-based (S3) guideline on topical corticosteroids in pregnancy. *Br J Dermatol*. 2011;165(5):943-952.