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A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes

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Synopsis

The evidence to date regarding corticosteroid exposure in pregnancy and select pregnancy and birth outcomes is limited and inconsistent. Here we provide a narrative review of published literature summarizing the findings for oral clefts, preterm birth, birth weight, preeclampsia and gestational diabetes mellitus. Whenever possible, the results are limited to oral or systemic administration with a further focus on use in autoimmune disease. Although previous studies of corticosteroid exposure in pregnancy reported an increased risk of oral clefts in the offspring, more recent studies have not replicated these findings. Further, most of the literature lacks robust statistical analysis accounting for underlying disease or disease activity. The evidence to date suggests that first trimester corticosteroid use may confer a small increase in the odds of cleft lip with or without cleft palate, although data are conflicting and it is unknown to what extent the underlying maternal disease may contribute. There is little support that systemic corticosteroid use in pregnancy independently causes increases in risks of preterm birth, low birth weight, or preeclampsia. There is not sufficient evidence to determine whether corticosteroids could contribute to gestational diabetes mellitus.

Keywords

Pregnancy; corticosteroids; adverse pregnancy and birth outcomes; review

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Introduction

Corticosteroids are administered in pregnancy for their immunosuppressive and anti-inflammatory effects[1] They are used to treat symptoms of autoimmune conditions, as many standard immunosuppressive drugs and biologic agents are regarded as riskier in pregnancy or as having unknown effects on fetal development.[2] Synthetic corticosteroids are often used to manage patients' disease severity and flares. These corticosteroids were developed to have amplified glucocorticoid activity and reduced mineralocorticoid activity compared to naturally-occurring cortisol and have significantly more potent anti-inflammatory activity.[3] Although it is considered optimal to use prednisone at less than 20mg/day in pregnancy, it is generally accepted that higher doses are allowable for aggressive disease.[4] Inflammation from uncontrolled autoimmune activity is potentially more harmful to maternal and fetal health than high-dose steroids.[4]

Corticosteroids and the placenta

Cortisol, a naturally occurring glucocorticoid in humans, is critical for embryogenesis. However, in most species, maternal glucocorticoid levels are much higher than those in the developing fetus.[5] The passage of natural and synthetic glucocorticoids is regulated primarily by 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2). This enzyme is expressed in aldosterone-selective tissues and the placenta and encoded by the HSD11B2 gene. 11βHSD2 converts active glucocorticoids such as cortisol and prednisolone to their inactive metabolites: cortisone and prednisone.[5,6] Approximately 90% of cortisol is converted into cortisone. However, 11βHSD2 is less efficient at metabolizing synthetic corticosteroids, resulting in greater fetal exposure to active corticosteroids.[6] There remains, however, a significant conversion of synthetic short-acting corticosteroids to inactive metabolites. Clinical studies have reported 8 to 10 fold lower concentrations of fetal prednisolone to maternal prednisolone following maternal intravenous administration.[3] Endogenous fetal glucocorticoid levels are maintained at significantly lower levels than maternal levels; thus, even small transfers of synthetic corticosteroids across the placenta could have adverse developmental effects. It is important to evaluate the potential for adverse pregnancy or birth outcomes during this critical time in human development.

Adverse pregnancy and birth outcomes

Autoimmune conditions are more prevalent in women than men, and often occur during a woman's reproductive years.[7] Generally, autoimmune conditions are not thought to substantially affect fertility,[4] and thus many women and their clinicians are confronted with concerns about how autoimmune disease and the associated treatments may affect pregnancy and birth outcomes. Concerns about the safety of corticosteroids in pregnancy arose in the 1950's following reports of oral clefts in the offspring of pregnant mice treated with corticosteroids.[8] The association between corticosteroids and oral clefts was also observed in epidemiologic studies, although estimates have varied widely and results have been inconsistent.[9] Additional findings suggested that oral corticosteroids (specifically prednisone) were associated with intrauterine growth restriction in humans and mice; these outcomes were reported to be independent of maternal disease.[10] Finally, a parallel body of

literature has noted the increased risks for numerous adverse pregnancy and birth outcomes in women with autoimmune diseases, including preterm birth, preeclampsia, and gestational diabetes mellitus.[4,11-13] These papers generally conclude with an unanswered question: is the increased risk for adverse outcomes associated with the disease or the treatment?

In an effort to address this question, this review focuses on systemic corticosteroids and the associations with oral clefts, low birth weight (<2500 grams), preterm birth (<37 weeks gestation), preeclampsia and gestational diabetes mellitus. This review focuses on systemic corticosteroids, rather than inhaled or topical treatments, given the greater systemic bioavailability and systemic effects of these forms,[14-18] and consequently the potential for greater fetal exposure. Careful consideration is given to study design and statistical analysis, with emphasis on the comparison group and mitigation of confounding by disease indication or severity.

Literature review

Studies for this narrative review were identified from Pubmed, with the search terms 'glucocorticoids' or 'corticosteroids' or 'prednisone' and 'pregnancy outcomes', 'birth outcomes', 'oral clefts', 'preeclampsia', 'preterm birth', 'birth weight', or 'gestational diabetes'. Additional searches were performed for 'pregnancy or birth outcomes' and 'rheumatoid arthritis', 'Crohn's disease', 'inflammatory bowel disease', 'systemic lupus erythematosus', 'autoimmune disease' and 'rheumatic diseases'. Search results were narrowed to focus on oral or systemic corticosteroids, and whenever possible, limited to indications for autoimmune conditions.

Oral clefts

Clefts of the lip and palate affect approximately 1.7 in 1000 live births, with lifelong effects on speech and hearing.[19] Development of the lip and palate require a highly coordinated series of events that are completed by the 5th or 6th week for closure of the lip and the 8th or 9th week for closure of the palate.[20,21] Typically, the causes of disruption in this process are unknown.[19] Oral clefts can be categorized into those that affect the palate only, the lip only, or the lip and the palate.[20,22] Given the low prevalence, researchers often group the latter two into one category (cleft lip with or without cleft palate).[20] Cleft palate alone has a lower prevalence than cleft lip (with or without cleft palate) and the two are thought to have different genetic and etiologic risk factors.[20,22] Following earlier findings that corticosteroids caused cleft palate in mice,[8] several epidemiologic studies have investigated the association in humans (Table 1).

Due to the low prevalence of oral clefts, most studies of systemic corticosteroids have been case-control[9,23-27] although at least two were retrospective cohort studies.[28] All case-control studies relied on recall of medication exposure by parents after the birth,[9,23-27] potentially biasing associations if parents of offspring with clefts report medication use with more or less accuracy than controls. Several case-control studies stratified exposure into oral or systemic corticosteroids[9,23,24,26,27] and a few focused on systemic use[24,26] reported statistically significant associations of approximately 2 to 9-fold greater risk for cleft lip

with or without cleft palate. Others found similar increases in odds with confidence intervals slightly crossing the null (resulting in p>0.05).[9,23,27]

In general, early case-control studies (prior to 2000) reported stronger odds of cleft lip with or without cleft palate following corticosteroid exposure as summarized in a meta-analysis in 2000 (odds ratio (OR) any corticosteroid use during the first trimester: 3.4, 95% CI 2.0,5.7).[29] Of note, although previous studies separately estimated cleft lip and cleft palate, the meta-analysis grouped all outcomes into “oral clefts”. In more recent studies, the strength of the associations of corticosteroids and oral clefts have reduced to non-significant findings. Analyzing data from the National Birth Defect Prevention Study (NBDPS) in the time periods of 1997-2002 and 2003-2009, Skuladottir and colleagues reported weaker associations between systemic corticosteroids and cleft lip and palate in the latter years.[9] The study followed the same protocol and procedures, case ascertainment and recruitment practices during both time periods. The authors note the increased use of corticosteroids among mothers of controls and the decreased use among mothers of cleft lip and palate cases in the latter time period. Overall, it is unclear what is driving the observed reduction in risk, but some possibilities include a temporal trend towards shorter durations or lower doses of systemic corticosteroids in favor of alternative treatments. Additionally, the underlying medical conditions necessitating corticosteroid use may change over time, resulting in different risk estimates.

Two retrospective population-based cohorts have been reported.[28,30] Both studies relied upon medical records of corticosteroid exposure, mitigating risk of recall bias. Unfortunately, in both studies the authors were unable to estimate the risk of oral corticosteroids, specifically, due to no observed exposed cases. In the study by Hviid and colleagues using all live births in Denmark from 1996-2008 (n=832,636), estimates for exposure to any corticosteroids during the first trimester did not correlate with increased risk for cleft lip or cleft palate. Only those exposed to topical corticosteroids had a higher risk of cleft lip with or without cleft palate (OR 1.45 (1.03,2.05)), although it is unclear if the increased risk is due to systemic absorption from the topical treatment, the dermatologic condition for which the topical steroids were used (i.e. eczema or psoriasis) or disease severity.[28] Another study by Bjørn and colleagues relied on live births from primiparous women in northern Denmark from 1999-2009 (n=83,043). The unadjusted odds of oral clefts following exposure to any corticosteroids (inhaled or oral) in the first trimester was also null (OR: 0.4 (0.1, 2.8)).[30] Due to the relatively small sample, cleft lip and cleft palate were analyzed together.

A serious methodologic consideration for all studies in Table 1 is that none adjusted for underlying disease or disease severity. Confounding by disease or disease severity occurs when the underlying disease or severity of the disease is associated with the exposure, is not a result of the exposure, and is associated with the outcome. In the case of corticosteroids, the first two points are undisputable, i.e. corticosteroids are taken as a result of the underlying disease and associated flares.[23] Whether maternal disease or disease activity is associated with oral clefts, directly or through common causes such as smoking, alcohol, inter-pregnancy interval or obesity,[31,32] remains unanswered. Consequently, studies that group any underlying indication for corticosteroids without statistical adjustment for the

disease or severity are difficult to interpret. Furthermore, none of the studies considered systemic corticosteroid dose, which is necessary to evaluate potential teratogenicity.

Another methodologic consideration for the body of evidence is temporality of the corticosteroid exposure relative to the oral cleft. Several studies of oral clefts count exposure from a few weeks prior to estimated conception through the end of the first trimester.[9,24-28,30] However, the critical periods for formation of the lip and palate encompass only specific weeks in the first trimester.[20,21] This could lead to potential exposure misclassification, i.e., for those exposures that took place only outside the biologically relevant time period in early gestation. This bias from misclassification would result in smaller effect estimates. Skuladottir and colleagues attempted to look at any corticosteroid use by small time intervals (1-4 weeks preconception, and 1-4 weeks, 5-8 weeks and 9-12 weeks post-conception).[9] Even with 2,372 cases of clefts, the number of pregnancies exposed to corticosteroids within specific gestational windows were very small. This lead to inconsistent results, demonstrating the difficulty of defining risk periods for corticosteroid use in epidemiologic studies.

In summary, the evidence for cleft palate alone is not sufficient to summarize. The estimated risk of cleft lip with or without cleft palate from corticosteroid exposure has weakened over time, and no study published after 2003 has reported a statistically significant risk estimate. The largest case-control study to date (NBPDS) has estimated a modest (60%) increase in the odds of cleft lip with or without cleft palate, although the confidence interval did slightly cross 1.0.[9] Cohort studies, which are not subject to recall bias, have been limited by insufficient sample sizes to differentiate between routes of administration[28,30] or type of oral cleft.[30] Examining the evidence and methodological limitations in totality, systemic corticosteroids may be associated with small increases in the risk of cleft lip with or without palate. Assuming a causal odds ratio of 1.6 (from the NBPDS), the risk of cleft lip with or without cleft palate among women using corticosteroids in the relevant time frame would increase from 1.7 per 1000 live births to 2.7 per 1000 live births. Ultimately, the sample sizes required to detect a relatively small risk of cleft lip and to address the contribution of specific maternal diseases, dose and timing, are challenging to obtain.

Preterm birth and low birth

Following reports that corticosteroids were teratogenic in mice, researchers reported that prednisone use in pregnancy was associated with low birth weight in the full term offspring of both humans and mice.[10,33] Researchers studying rodent models concluded that corticosteroids, not underlying maternal disease, were the cause of the findings.[10] Many epidemiologic studies of pregnancies complicated by autoimmune diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE) have noted the increased risk of low birth weight and preterm birth.[11-13,34] Although the majority of such studies have not attempted to isolate the effects of corticosteroids from underlying maternal disease, some have as summarized in Table 2.

Low birth weight

A few studies have reported birth weight or intrauterine growth restriction (IUGR) as an outcome. Among women with Crohn's disease in Denmark, corticosteroids (local and/or systemic) were not associated with birth weight after adjusting for gestational age and disease activity (adjusted risk ratio (aRR): 1.1 (0.2, 5.7)). Of note, although neither the crude nor the adjusted effect estimates were statistically significant, the risk ratio was reduced by 21% after adjustment for maternal age and parity.[35] Similarly, in a study of pregnant women with RA,[36] although birth weight was associated with prednisone use, upon adjustment to a standard deviation score accounting for gestational age at delivery and sex of the newborn, the results were no longer statistically significant. A study in a cohort of pregnant women with SLE reported elevated odds of IUGR following prednisone use, although confidence intervals were wide and crossed the null.[37] It was not apparent that the estimates were adjusted for gestational age or disease severity. Finally, although Gur and colleagues found a univariate association between lower birth weight and any corticosteroid use among premature births,[38] the results are difficult to interpret as there was no adjustment for maternal disease.

Preterm birth

Studies have examined the use of prednisone or prednisolone in pregnant women with SLE and the odds of preterm birth.[37,39] Two reports of increased risk in women with SLE appear to be univariate comparisons unadjusted for disease severity or any other maternal characteristics, and are therefore not easy to interpret.[37,39] A third univariate association in a population based study was not adjusted for underlying maternal disease.[38] From the Danish cohort of pregnant women with Crohn's disease, Nørgård and colleagues reported that after adjusting for mothers' age, parity and disease activity, there was no association between prednisolone and preterm birth.[35] Finally, from a separate Danish cohort of pregnant women with IBD, there was an increased risk of preterm delivery following systemic corticosteroid use compared to women without IBD (adjusted hazard ratio (aHR): 6.3 (3.1, 12.7)).[40] The hazard ratio was adjusted for maternal characteristics (including age, smoking and alcohol use) but not underlying disease or disease severity. Of note, among women with IBD without medication use, there was a 50% increase in the risk of preterm birth relative to women without IBD (aHR: 1.5 (1.0, 2.4)).[40] This suggests that IBD itself contributes to the increased risk of preterm birth. Further, the authors note that associations with preterm birth were strongest in the women who used corticosteroid medication, which is both a marker of active disease and also associated with preeclampsia. Thus, they conclude that early delivery may have been necessitated by severe disease activity or preeclampsia as opposed to a direct effect from corticosteroids.[40]

Compared with the previous studies examining the risk of oral clefts, these studies tended to be conducted in women with a specific disease, removing the potential for confounding by indication. However, as noted, only one study[35] adjusted for disease activity, and upon adjustment, estimates for preterm birth were not statistically significant. A few authors noted positive associations between disease[40] or disease severity[36,40] and preterm birth or birth weight. Interestingly, in the cohort of pregnant women with RA, disease severity remained a

significant predictor of birth weight after adjusting for gestational age and prednisone use.[36] These findings, and the attenuation of associations after accounting for disease severity, highlight the great likelihood for confounding by disease severity in this body of research. Although it is difficult to tease apart disease severity and corticosteroid use, measuring disease activity and adjusting for it in multivariate analyses will better inform clinical decision making.

To summarize, it appears that disease severity, not corticosteroids, is responsible for reported associations with preterm birth. Furthermore, one can surmise that any association between corticosteroids and low birth weight is most likely mediated by gestational age, with little evidence of a direct effect on birth weight.

Preeclampsia

Preeclampsia, a pregnancy disorder characterized by high blood pressure and proteinuria, is a serious pregnancy complication associated with both maternal and fetal morbidity and mortality.[41] Preeclampsia is histologically described by restrained trophoblast invasion, vasculitis, thrombosis and ischemia of the placenta.[42] Although specific mechanisms are not understood, it is hypothesized that preeclampsia may have an autoimmune contribution.[42] Indeed, preeclampsia has been associated with both RA and SLE.[13,34]

At least three studies have reported effects of corticosteroids on the risk of preeclampsia (Table 3). One study analyzing perinatal outcomes in patients with SLE was not adjusted for any potential confounders, thus making interpretation difficult.[39] Authors analyzing the Danish National Birth Cohort reported an increased risk of preeclampsia from systemic corticosteroid use when compared to women without IBD (aHR: 3.5 (1.4, 9.1)), which was adjusted for maternal characteristics but not disease or disease severity.[40] Finally, relying on a large healthcare database in British Columbia, Palmsten and colleagues found that women who used corticosteroids for the first time during pregnancy had an elevated (although not statistically significant) risk of preeclampsia relative to those who used corticosteroids in the past year before pregnancy (aRR 1.4 (0.9, 1.9)).[43] Continuous use of corticosteroids in this population was not associated with preeclampsia relative to past users. These results were adjusted for underlying disease and proxy measures for disease severity. The authors noted dissimilarities in factors related to autoimmune characteristics at baseline between first-time users and past users, hypothesizing that residual confounding by disease severity may bias estimates of first-time users.[43]

The only study that adjusted for disease and a proxy of disease severity did not find evidence of an association between corticosteroid use and preeclampsia.[43] Any increased risk associated with autoimmune conditions is most likely confounded by the disease severity. Additionally, previous studies of preeclampsia have not evaluated the dose of corticosteroids, which is important as prednisone at high doses can cause sodium retention and high blood pressure.

Gestational diabetes mellitus

The risk of gestational diabetes mellitus from corticosteroid use has received little attention to date (Table 3). This condition, characterized by high blood glucose levels in pregnancy in women without previously diagnosed diabetes, is associated with adverse outcomes in the developing fetus.[44] The rationale for studying corticosteroids with gestational diabetes mellitus follows reports in humans and animal models of higher plasma cortisol levels in individuals with gestational diabetes mellitus.[45]

In a retrospective cohort study of 25 pregnancies with idiopathic thrombocytopenic purpura (ITP) and 108 pregnancies without ITP, >4 weeks of prednisone use was associated with gestational diabetes mellitus (24% vs. 2.8%, p=0.01).[45] These results were not adjusted for any maternal conditions, and it was suggested that all ITP subjects were exposed to >4 weeks of prednisone, prohibiting disentanglement of underlying disease and medication.[45] The second study was conducted within a retrospective cohort of 116 women with IBD and 381 women without IBD.[46] Leung and colleagues reported an increase odds of gestational diabetes mellitus from oral prednisone or intravenous corticosteroids relative to women without IBD (OR: 4.5 (1.2, 16.8)). These results were only adjusted for age and smoking. When women with IBD without corticosteroid use were compared, there was no longer a statistically significant finding (OR: 2.0 (0.0, 15.3)).[46] Due to the low prevalence of gestational diabetes mellitus, only 15 women experienced the outcome (7 with IBD and 8 without IBD), resulting in very wide confidence intervals and precluding further statistical adjustment.

In summary, neither study is of sufficient methodologic quality to rule out an effect of systemic corticosteroid use on the development of gestational diabetes mellitus. As noted in previous sections, confounding by disease and disease severity must be addressed to support the hypothesized association.

Summary and considerations for further research

As summarized in Tables 1-3, many researchers have investigated the effects of corticosteroids on adverse pregnancy and birth outcomes. This type of research informs clinicians and pregnant women when assessing risk: benefit ratios. Foregoing treatment for an autoimmune condition is not an option for many pregnant women, as active disease can pose threats to both maternal and fetal health.[4] Due to ethical concerns, randomized clinical trials are rarely possible, and investigations must rely on observational data. One of the greatest threats to internal validity in observational studies results from confounding. In pharmacoepidemiology studies, confounding by indication is one of the most difficult to address.[47] Disease and disease severity are often related to pharmacologic exposure and to adverse outcomes. Investigations that do not account for this systematic bias are largely incapable of estimating the independent effects of the pharmacologic agent. Therefore, studies that compare oral corticosteroids with alternative treatments in women with autoimmune disease would reduce confounding by underlying disease and would provide clinically relevant risk information. In addition, the threat of recall bias inherent to case-

control studies can be mitigated by relying on medical or pharmacy dispensing records for exposure assessment.

Another concern when interpreting results for all outcomes is whether timing of exposure or dose was accounted for. This was discussed specifically for oral cleft formation earlier, but also applies to the other outcomes investigated. For example, for preterm birth, corticosteroid use should not be considered after 37 gestational weeks as the outcome is no longer possible. Further, when exposure is dichotomized as use any time during pregnancy vs no use, bias can arise when corticosteroid use occurs after the onset of the outcome (e.g. preeclampsia, gestational diabetes mellitus). Finally, it is particularly useful to examine the daily and cumulative dose of pharmacologic agents, especially in patients with autoimmune conditions in which disease severity alters the course of therapy. Recent work examining the daily and cumulative dose of prednisone in pregnant women with autoimmune disease revealed variability in amount and pattern of use which can be linked with perinatal outcomes.[48]

As a final consideration, it has been shown that placentas from female fetuses born within 72 hours of betamethasone administration had higher 11βHSD2 activity levels compared with placentas from male fetuses, suggesting female offspring may be more protected from corticosteroid exposure.[6] Additionally, maternal psychological factors may downregulate 11βHSD2 activity, resulting in greater corticosteroid exposure to the developing fetus.[49] Future research on the effects of corticosteroids in pregnancy and birth outcomes may benefit from investigation into offspring sex, maternal psychological stress, and other potential modifiers.

In summary, there may be a modest increase in the risk of cleft lip with or without palate from systemic corticosteroid use, but data are conflicting, and it is unknown to what extent maternal disease itself could contribute. There is little evidence that systemic corticosteroid use in pregnancy independently increases risks of preterm birth, low birth weight, or preeclampsia. Currently, there is not enough evidence to determine whether systemic corticosteroids could contribute to gestational diabetes mellitus. Future studies would benefit from more rigorous evaluation of confounding by disease or disease severity. Further inquiry into the impacts of dose and timing of corticosteroid use, as well as potential effect modifiers, could identify subgroups whose pregnancies are adversely effected by corticosteroids.

Despite the lack of direct evidence supporting causal associations between antenatal systemic corticosteroid exposure and adverse pregnancy outcomes, clinicians should follow similar principles when prescribing corticosteroids for the pregnant woman with autoimmune disease as for non-pregnant rheumatic disease patients: to use the minimal dose and duration of corticosteroid to safely treat active disease manifestations. As always, the overall risks of corticosteroid use, which are dose and duration dependent, must be balanced with the necessity of treating active underlying disease.

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Key points

1. Corticosteroids are often necessary to control the symptoms of various medical conditions in pregnancy, including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease.
2. Investigations into adverse pregnancy and birth outcomes following corticosteroid exposure have lacked adequate exploration into confounding by disease or disease severity.
3. There may be a small increased risk of cleft lip with or without cleft palate associated with first trimester corticosteroid use. This review does not find sufficient evidence to support an increased risk of preterm birth, low birth weight, or preeclampsia following systemic corticosteroid use in pregnancy. There is insufficient evidence to determine whether systemic corticosteroids are linked to gestational diabetes mellitus.

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Table 1

Studies of oral or systemic corticosteroids and the risk of oral clefts (organized chronologically)

Author	Year	Study population	Study design	Number of cases	Odds ratio, 95% CI	Corticosteroid Use During 1st Trimester
Czeizel A et al.[23]	1997	Hungarian Case-Control Surveillance of Congenital Abnormalities (Hungary)	Population based case-control	n=1,223 CLP	CLP: 1.3 (0.8, 2.0)	Oral[a]
Rodriguez-Pinilla E et al.[24]	1998	Spanish Collaborative Study of Congenital Malformations (Spain)	Hospital-based case- control	n=631CLP	CLP: 8.9 (2.0, 37.9)	Systemic use
Carmichael SL et al.[25]	1999	California Birth Defects Monitoring Program (United States)	Population based case-control	n=348 CLP n= 141 CP	CLP: 4.3 (1.1, 17.2) CP: 5.3 (1.1, 26.5)	Any use Any use
Pradat P el al.[26]	2003	MADRE project (worldwide)	Case-control	n= 645 CLP	CLP: 1.9 (1.2, 3.0)	Systemic use
Carmichael SL et al.[27]	2007	National Birth Defects Prevention Study (United States)	Population based case-control	n=1,141 CLP n=628 CP	CLP: 2.1 (0.9, 4.7) CP: 0.8 (0.2, 3.6)	Systemic use Systemic use
Hviid A el al.[28]	2011	Danish Medical Birth Registry (Denmark)	Population based retrospective cohort	n= 875 CLP n=357 CP	CLP: 1.1 (0.8, 1.4) CP: 1.2 (0.8, 1.8)	Any use Any use
Skuladottir el al.[9]	2014	National Birth Defects Prevention Study (United States)	Population based case-control	n=2,680 CLP n=1,415 CP	CLP: 1.6 (0.9, 2.8) CP: 0.8 (0.3, 2.1)	Systemic use Systemic use
Bjørn AB et al.[30]	2014	Danish Medical Birth Registry (Denmark)	Population based retrospective cohort	n=147 oral clefts	CLP: 0.4 (0.1, 2.8)	Any use
Park-Wyllie L et al.[29]	2000	Meta-analysis focusing on oral clefts	Meta-analysis of case-control studies* [b]	n=2,551 oral clefts	Summary OR: 3.4 (2.0, 5.7)	Any use

CLP=cleft lip with or without cleft palate; CP=cleft palate; OR=odds ratio; CI=confidence interval.

[a] estimate for corticosteroids at any time in pregnancy

[b] Robert (1994), Czeizel (1997), Rodriguez-Pinilla (1998), Carmichael (1999)

Table 2

Studies of oral or systemic corticosteroids and the risk of preterm birth, low birth weight, or IUGR (organized chronologically)

Author	Year	Study population or location	Study design	Outcome	Measure of association with corticosteroid use	Corticosteroid	Indication for use
Gur C et al.[38]	2003	Israeli Teratogen Information Service	Retrospective cohort of 311 pregnant women exposed to glucocorticoids and 790 unexposed women	Preterm birth	26.9% vs. 10.8% (p=0.001)	Prednisone	Multiple
				Birth weight (amongst PTBs)	2300g vs. 2550 g (p=0.003)	Any corticosteroids	Multiple
Chakravarty et al.[39]	2005	Stanford University (California)	Retrospective cohort of 63 pregnancies in 48 women with SLE between 1991 and 2001	Preterm birth	OR: 1.8 (1.1, 3.0)	Prednisone	SLE
Nørgård B et al. [39]	2007	Danish National Registry of Patients (Denmark)	Retrospective cohort study of 900 children born to CD women between 1996 and 2004)	Low birth weight	RR: 1.1 (0.2, 5.7)	Local or systemic corticosteroids	CD
				Preterm Birth	RR: 1.4 (0.6, 3.3)	Local or systemic corticosteroids	CD
de Man YA et al.[36]	2009	PARA study (Netherlands	Population based cohort study of 152 women with RA	Birth weight SDS	Beta estimate: -0.2 (-0.6, 0.2)	Prednisone	RA
				Gestational age	38.8 weeks vs. 39.9 weeks (p=0.001)	Prednisone	RA
Al Arfaj AS et al.[37]	2010	King Khalid University Hospital (Saudi Arabia)	Retrospective cohort of 383 pregnancies exposed to SLE between 1980-2006	Preterm birth	OR: 5.7 (1.3, 25.1)	Prednisolone	SLE
				IUGR	OR: 2.6 (0.9, 8.0)	Prednisolone	SLE
Boyd HA et al.[40]	2015	Danish National Birth Cohort (Denmark)	86,591 women with livebirths (666 with IBD) enrolled between 1996-2003	Preterm birth	HR: 6.3 (3.1, 12.7)	Systemic corticosteroids	IBD

SLE= systemic lupus erythematosus; CD=Crohn's disease; OR=odds ratio, RR=risk ratio; HR=hazard ratio; RA=rheumatoid arthritis; IUGR=intrauterine growth retardation; IBD=inflammatory bowel disease; SDS=standard deviation score (adjusted for gestational age)

Table 3

Studies of oral or systemic corticosteroids and the risk of gestational diabetes or preeclampsia (organized chronologically)

Author	Year	Study population or location	Study design	Outcome	Measure of association with corticosteroid use	Corticosteroid	Indication for use
Chakravarty EF et al.[39]	2005	Stanford University (California)	Retrospective cohort of 63 pregnancies in 48 women with SLE between 1991 and 2001	Preeclampsia	OR: 1.8 (0.7, 5.0)	Prednisone	SLE
Yildirim Y et al.[45]	2006	Aegean Obstetrics and Gynecology Training and Research Hospital (Turkey)	Retrospective cohort of 25 pregnant women with ITP and 108 pregnant women without ITP	Gestational Diabetes	24.0% vs. 2.8% (p=0.01)	>4 weeks of corticosteroid vs. no use	ITP
Palmsten K et al.[43]	2012	Healthcare database British Columbia (Canada)	306,831 pregnancies with live birth between 1997-2006	Preeclampsia	RR: 0.9 (0.5, 1.6)	Continuous use vs. past use corticosteroid	Multiple
				Preeclampsia	RR: 1.4 (0.9, 1.9)	First use vs. past use corticosteroid	Multiple
Boyd HA et at.[40]	2015	Danish National Birth Cohort (Denmark	86,792 women with livebirths (666 with IBD) enrolled between 1996-2003	Preeclampsia	HR: 3.5 (1.4, 9.1)	Systemic corticosteroids	IBD
Leung YPY et al.[46]	2015	Alberta Health Services (Canada)	Retrospective cohort of 116 live births to women with IBD between 2006-2009; 381 matched women without IBD.	Gestational Diabetes	OR: 4.5 (1.2, 16.8) (IBD on steroids vs. controls)	Oral prednisone or intravenous corticosteroids	IBD
				Gestational Diabetes	OR: 2.0 (0.0, 15.3) (IBD on steroids vs. IBD not on steroids)	Oral prednisone or intravenous corticosteroids	IBD

SLE: systemic lupus erythematosus; IBD=inflammatory bowel disease; ITP=idiopathic thrombocytopenic purpura; OR=odds ratio, RR= risk ratio; HR=hazard ratio;