Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies


Authors' objectives
To determine the risk, if any, of steroid use on the foetus with respect to major malformations, and, more specifically, oral clefts (cleft lip with or without cleft palate, or cleft palate alone).

Searching
MEDLINE (from 1966 to December 1999), EMBASE (from 1988 to October 1999), and Current Contents (from January to December 1999) were searched using 'glucocorticosteroid' in combination with 'congenital anomalies', 'drug-induced', 'teratogen' or 'birth defect'. Abstracts of meetings published in Teratology and Pediatric Research from 1995 to 1998 were examined for material not yet published. The bibliographies of the identified studies were also reviewed.

Study selection
Study designs of evaluations included in the review
Controlled studies, either case-control or cohort studies, that included at least ten patients were eligible. The included studies had to report rates of major malformations in the corticosteroid and control groups.

Specific interventions included in the review
Studies that examined the effects of systematic exposure to any corticosteroids in the first trimester of pregnancy (any dose, all indications, and any duration) were eligible. Topical and inhaled steroids were excluded. The following types of corticosteroids were included: prednisolone, cortisone, corticotropin, hydrocortisone, prednisone, dexamethasone, betamethasone, methylprednisolone, and triamcinolone. Prednisolone dose equivalents were estimated when possible; these ranged from 2.5 to 100 mg/day. Some studies examined the effects of exposure to corticosteroids and other medications. The specified cointerventions included sulfasalazine.

Participants included in the review
Infants of women who were exposed to corticosteroids in the first trimester of pregnancy were eligible. The women in the included studies received systemic steroids for the following medical conditions: rheumatoid arthritis; systemic lupus erythematosus; ankylosing spondylitis; psoriatic arthropathy; asthma; eczema; inflammatory bowel disease (colitis, ulcerative colitis and Crohn's disease); urticaria; sarcoidosis; hay fever; Addison's disease; and subfertility.

Outcomes assessed in the review
Studies that assessed major malformations in the infants were eligible. Major malformations were defined using the criteria described by Heinonen et al. and Holmes (See Other Publications of Related Interest nos.1-2, respectively). Incidences of oral cleft (cleft lip with or without cleft palate, or cleft palate alone) were also assessed.

How were decisions on the relevance of primary studies made?
Two reviewers, who were blinded to the authors' names, journal and study location, selected the studies for inclusion. Any disagreements were resolved by discussion with a third reviewer. The reasons for exclusion were identified and inter-rater agreement was measured.

Assessment of study quality
Validity was assessed using a quality assessment score for epidemiological studies, as developed by the group (see Other Publications of Related Interest no.3). Inter-rater agreement was measured. Two reviewers, who were blinded to the authors' names, journal and study location, assessed study validity. Any disagreements were resolved by discussion with a third reviewer. Inter-rater agreement was measured.
Data extraction
Two reviewers, who were blinded to the authors' names, journal and study location, extracted the following data:
disease of the mother; the number of neonates; the types and doses of corticosteroids used; and the type of birth defect.
The number of neonates exposed to corticosteroids who did and did not exhibit major malformations, and the number
of neonates not exposed to corticosteroids who did and did not exhibit major malformations, were extracted in the form
of 2x2 tables. Inter-rater agreement was assessed and any disagreements were resolved by discussion with a third
reviewer. In women with multiple pregnancies, each pregnancy was considered as an independent event. Stillbirths and
abortions were excluded unless the study specifically mentioned assessment of malformations. A Mantel-Haenszel odds
ratio (OR) and 95% confidence interval (CI) was calculated for each of the studies.

Methods of synthesis
How were the studies combined?
The studies were grouped according to study the design (cohort or case-control design), and a Mantel-Haenszel
summary OR and 95% CI were calculated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test, prior to pooling the data. The analysis was repeated
after excluding one study that did not differentiate between major and minor malformations. A cumulative OR was also
calculated by combining studies in chronological order. The association between corticosteroids exposure and oral cleft
was determined. An incidence rate of major malformations was calculated using data from the included studies and
from studies rejected due to the absence of a control group. The correlation between the study quality scores and the
OR was examined. The mean, raw mean, and meta-analytic mean were calculated from the incidence rate of major
malformations.

Results of the review
Six cohort studies (51,470 patients) and four case-control studies (71,705 patients) were included.

Major malformations.
Findings from the cohort studies suggested that exposure to corticosteroids in the first trimester of pregnancy may be
associated with a marginally, but not statistically significantly, increased risk of major malformations. The pooled OR
was 1.45 (95% CI: 0.80, 2.60). There was no evidence of heterogeneity (p=0.17). After the removal of one study in
which major and minor malformations were not separated, the increase in major malformations in the exposed group
compared with the non-exposed group reached statistical significance. The OR was 3.03 (95% CI: 1.08, 8.54).

Oral cleft.
Cleft palate was the most commonly reported anomaly in cohort studies: there were 3 cases in the exposed group,
compared with no cases in the controls.

A significant association was found between first-trimester corticosteroids and oral clefts in case-control studies. The
OR was 3.35 (95% CI: 1.97, 5.69). The specific phenotypes of the clefts were: isolated cleft palate (4 cases), isolated
cleft lip (6 cases), cleft lip and palate (5 cases), and cleft lip without palate specified (10 cases).

There was no evidence of an association between the quality of studies and their OR (correlation -0.32). The incidence
rate was 3.5% (meta-analytic mean from 15 studies including studies without a control group) and 3.9% (raw average).

Authors' conclusions
Prednisone does not represent a major teratogenic risk in humans at therapeutic doses, but it does increase the risk of
oral cleft by an order of 3- to 4-fold; this is consistent with existing animal studies.

CRD commentary
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The aims were stated and the inclusion criteria were defined in terms of the study design, intervention, participants, and outcome. Several relevant sources were searched and the methods used to select the studies were described. It was not stated whether any language restrictions were applied. The authors stated that the quality of studies was assessed using a tool developed for epidemiological studies but, although a reference was given, no details either of the criteria used or the results of this quality assessment were presented in the review.

Relevant data were extracted and tabulated, and the methods used to extract the data were described. The authors stated that inter-rater agreement was assessed for the study selection, data extraction and quality assessment processes, but the results of the assessment were not reported. Statistical heterogeneity was evaluated prior to combining data in a meta-analysis, and sensitivity analyses were performed.

There appears to be uncertainty as to whether the exposed and non-exposed control groups differed only in their exposure to corticosteroids. Other than this, the evidence presented appears to support the authors' conclusions.

**Implications of the review for practice and research**

Practice: The authors state that the apparent increased risk of oral clefts has to be balanced against potentially serious implications for the mother, and indirectly to the foetus, if steroid therapy is discontinued or not initiated.

Research: The authors state that more studies will be needed to determine which cleft phenotype is associated with corticosteroids, i.e. whether it is cleft lip with or without palate or cleft palate alone, or both.

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**Other publications of related interest**


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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.