Inhaled corticosteroids during pregnancy: a review of methodologic issues
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CRD summary
The authors concluded that there was some evidence supporting the safety of inhaled corticosteroids (ICS) for asthma during pregnancy, but most studies were too small to detect differences between ICS and control groups. The authors’ conclusions appeared to reflect the evidence, but unclear reporting of review methods and reliance upon observational studies of uncertain quality meant their reliability was uncertain.

Authors' objectives
To evaluate the safety of inhaled corticosteroids (ICS) for the treatment of asthma during pregnancy.

Searching
PubMed and the Cochrane Library were searched for studies published in English or French before September 2007. Search terms were reported. Reference lists of studies were screened.

Study selection
Studies with a control group that evaluated the effect of ICS use during pregnancy on specified maternal and/or perinatal outcomes were eligible for inclusion. Studies had to report sufficient information to permit calculation of a measure of effect. Maternal outcomes included pregnancy-induced hypertension, pre-eclampsia, caesarean section, haemorrhage, gestational diabetes and asthma exacerbations. Perinatal outcomes included congenital malformation, mean birth weight, low birth weight, preterm delivery and still birth and perinatal mortality.

Included studies were predominantly cohort studies; other designs included case-control and randomised controlled trials (RCTs). Studies used different control groups including pregnant women without asthma, women with asthma not using ICS during pregnancy and women with asthma using theophylline during pregnancy. Where specified most studies evaluated budesonide; no study focused solely on any other ICS. Many studies evaluated any ICS.

The authors stated that three authors independently reviewed all published studies, but it was not clear if this referred to study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated that three authors independently reviewed all published studies, but it was not clear if this referred to data extraction. For each study, proportions or means and standard deviations were extracted for each treatment group together with crude or adjusted effect measures and 95% confidence intervals (CI) or p-values. Where measures of effect were not reported and sufficient data were reported, a crude relative risk (RR) or mean difference was calculated. The power of studies to detect reported effects and the power of non-statistically significant studies to detect a relative risk (RR) of 1.5 or mean difference in birth weight of 500 g were calculated; adequate power was indicated when the power was at least 80 per cent.

Methods of synthesis
The studies were grouped by outcome and combined in a narrative synthesis in which the number of studies reporting a statistically significant association between ICS use and the outcome were discussed. Ranges of crude and adjusted RR or mean differences were also reported.

Results of the review
Twenty-three studies were included. Where reported, the size of experimental groups ranged from 43 to 12,478 and control groups ranged from 65 to 577,730.
Only a few studies adjusted RRs for asthma severity and control, concomitant treatment and other potential confounders. Of the studies reporting nonsignificant associations, only two studies of maternal outcomes and seven studies of perinatal outcomes had a power of 80 per cent or more to detect a RR of 1.5 or mean difference in birth weight of 500 g.

Six studies reported a statistically significant association between ICS use and maternal outcomes. Five reported a significant association between ICS use and perinatal outcomes.

Maternal outcomes (13 studies)
No significant associations were found between ICS use and outcome in all of the six studies of pregnancy-induced hypertension, all four studies of pre-eclampsia, four of six studies of caesarean section, one of two studies of haemorrhage, all three studies of gestational diabetes and three of six studies of asthma exacerbations.

Perinatal outcomes (19 studies)
No significant associations were found between ICS use and outcome in 13 of the 15 studies of congenital malformation, six of eight studies of mean birth weight, all six studies of low birth weight, seven of eight of preterm delivery and the two studies of still birth and perinatal mortality.

Authors' conclusions
There was some evidence supporting the safety of inhaled corticosteroids use during pregnancy, but several studies were underpowered.

CRD commentary
The review question was clearly stated and inclusion criteria were specified. Limiting the search to studies published in either of two languages and listed in only two databases may have resulted in the omission of other relevant studies and raised the potential for publication and language bias. It was not clear if appropriate methods were used to minimise reviewer error and bias during the review process. Although the power of nonsignificant studies to detect a difference was estimated, other aspects of validity were not formally assessed and so results from these studies and any synthesis may not be reliable. In view of the diversity among studies, a narrative synthesis was appropriate. However, other than statistical power, attention was not drawn to higher quality evidence. The authors’ cautious conclusions appeared to reflect the evidence, but lack of clear reporting of review methods and reliance upon observational studies of uncertain quality meant that the reliability of the authors’ conclusions was unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that before it can be concluded that ICS are safe during pregnancy further evaluation is required of the effect of ICS on pregnancy-induced hypertension, pre-eclampsia, caesarean section, haemorrhage, gestational diabetes, stillbirth and perinatal and neonatal death. Future studies should be adequately powered and avoid the limitations of studies included in this review.

Funding
No funding for the review. Individual authors receive salary support or funding from the Fonds de la Recherche en Sante du Quebec, Canadian Institutes for Health Research doctoral research scholarship, and du Conseil du Medicament du Quebec.

Bibliographic details

PubMedID
18342498
DOI
10.1016/j.rmed.2008.01.008

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Anti-Asthmatic Agents /adverse effects /therapeutic use; Asthma /drug therapy; Evidence-Based Medicine; Female; Glucocorticoids /adverse effects /therapeutic use; Humans; Infant, Newborn; Pregnancy; Pregnancy Complications /drug therapy; Pregnancy Outcome

AccessionNumber
12008105529

Date bibliographic record published
03/02/2009

Date abstract record published
10/06/2009

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.