Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review

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CRD summary
The review found that intrauterine exposure to synthetic glucocorticoids reduced basal hypothalamus-pituitary-adrenal activity among foetuses and (in some cases) among neonates and infants. The effects were more consistent after pain-related stress. In view of several limitations in the review, which included a suboptimal search and failure to report detailed statistical data, the authors’ conclusions require cautious interpretation.

Authors’ objectives
To evaluate the effect of intrauterine exposure to synthetic glucocorticoids on foetal, newborn and infant hypothalamus-pituitary-adrenal (hpa) axis function.

Searching
PubMed was searched from 1965 to 2007 without language restrictions. Search terms were reported. Reference lists of retrieved articles were checked and several authors were contacted for additional studies.

Study selection
Controlled and uncontrolled studies of the effects of intrauterine synthetic glucocorticoids on the hpa function of offspring (foetal, neonatal, infant or adult) were eligible for inclusion. Control conditions could include placebo, no intervention, a differing dose of glucocorticoid or a differing time interval between treatment and sample collection. Outcomes of interest were indicators of hpa axis activity (specific hormones listed in the review) in amniotic fluid, cord blood, saliva or placental tissue.

Studies differed widely in their indication for use of glucocorticoids; the most common indication was lung maturation in foetuses at risk of preterm delivery. Mean gestational age at birth (where stated) varied across and within studies from 23 to 41 weeks. The most commonly used glucocorticoids were betamethasone and dexamethasone, usually given intramuscularly. Most of the experimental studies in the review were placebo controlled. The review reported basal hpa function (foetal, neonatal, infant and adult) and hpa reactivity to pharmacological, physiological or psychological stimulation. Outcome measures and sample collection methods differed widely across studies. Few studies included more than two months’ post partum follow-up.

Two reviewers independently selected the studies. Disagreements were resolved by consensus.

Assessment of study quality
Up to two points were allocated for each of the following components of study quality: randomisation; comparability of groups for treatment indication, gestational age at birth and birth weight (either by design or by statistical adjustment); within-study homogeneity of treatment type and treatment indication; and sample size.

It appeared that two reviewers independently conducted the assessment and disagreements were resolved by consensus.

Data extraction
Descriptive data were extracted on changes in hormones of interest and presented in an online table. Statistically significant increases or decreases were denoted in the tables.

Two reviewers independently extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Studies were combined in a narrative synthesis organised by outcomes. Three separate sensitivity analyses were conducted on components of study quality: better design (as indicated by at least partial randomisation and/or comparable groups), within-study homogeneity and large sample size. Subgroup analyses investigated the effect of glucocorticoid dose/regimen and time interval between treatment and sample collection.

**Results of the review**

Forty-nine studies were included in the review (n=5,157, range one to 710): five experimental (included three randomised controlled trials (RCTs), two of which were double-blinded), 42 quasi-experimental and two case reports. Eight studies were randomised or partially randomised, 18 were comparable or controlled for at least two out of three variables of interest, 39 were homogeneous for treatment type and/or indication and 28 had sample sizes of at least 25.

**Findings in better-designed studies with at least partial randomisation and/or comparable groups (10 studies):**

All five studies of foetuses found that basal hpa function was significantly reduced by glucocorticoid exposure. One of three studies of neonates and infants found significantly reduced concentrations of cortisol in the first two postpartum days and weeks in the exposed group, but two did not. A single study of adults found no statistically significant difference between the groups in cortisol concentration after adjusting for potentially confounding variables.

In one of three studies that assessed the effect of dose on hpa function, higher doses of glucocorticoids were associated with a reduction in basal hpa activity and endocrine stress reactivity. Four studies that reported the effect of different time spans between exposure and assessment had inconsistent findings.

No statistically significant association was found between the intervention and hpa reactivity to pharmacological stimulation (three studies). Two studies evaluated the effect of physiological stressors; one found no statistically significant association between glucocorticoid exposure and hpa reactivity to respiratory stress and the other found significantly increased hpa reactivity to pain in the exposed group.

**Findings overall:** When all 49 studies were considered, their findings agreed in most respects with those of the higher-quality studies. The review reported other findings and sensitivity analyses.

**Authors' conclusions**

Intrauterine exposure to synthetic glucocorticoids reduced basal hpa activity among foetuses and (in some cases) neonates and infants. The effects were more consistent after pain-related stress.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Only one database was searched, so some studies may have been missed. The search was not restricted by language. Attempts to retrieve unpublished studies were very limited, so the review may have been prone to publication bias. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer select studies, assess validity and extract data. The decision to combine the studies by narrative synthesis was appropriate (in view of study heterogeneity). Study quality was taken into consideration in the interpretation of findings. However, no effect estimates or measures of statistical variability were reported for study findings, statistical significance was not quantified and some important aspects of study quality (such as follow-up rate) were unclear. These factors made it difficult to determine the reliability or clinical relevance of the review findings. Very few of the included studies were randomised and, as the authors noted, the observational studies were at high risk of selection bias. In view of several limitations in the review, which included a suboptimal search and failure to report detailed statistical data, the authors’ conclusions require cautious interpretation.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that large RCTs with long-term follow-up were needed on the effect on hpa function of intrauterine exposure to synthetic glucocorticosteroids. Studies needed to address potential sex differences, diurnal variability of hpa function, physiological mechanisms, clinical outcomes and associations with maternal stress. Comparison of human and animal literature in this area was needed.
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