PERSONAL REVIEW

Use of systemic glucocorticosteroids in pregnancy: Be alert but not alarmed

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SUMMARY

Concerns have been raised regarding the use of repeated courses of systemic glucocorticosteroids given to pregnant women with threatened premature labour to improve fetal lung maturity. Most worrying are animal studies showing detrimental effects on the developing brain, though human data to date are conflicting. Additional concerns relate to the fetal origins of adult diseases, particularly vascular diseases such as hypertension and atherosclerosis. It is currently recommended that obstetricians give only a single course of antenatal corticosteroids to pregnant women to enhance lung maturity instead of giving repeated doses, which was previously a common practice. Other clinicians including dermatologists, gastroenterologists and rheumatologists may have reason to provide systemic glucocorticosteroids to pregnant women. Although systemic glucocorticosteroids all cross the placenta to some degree, the extent to which they do so depends on the drug involved. The choice of systemic glucocorticosteroid for the pregnant women in light of this evolving literature is discussed.

Key words: brain, central nervous system, foetus, newborn, prenatal exposure delayed effect.

INTRODUCTION

Systemic glucocorticosteroids have been used for many years in pregnant women and are generally believed to be safe for the unborn child. They are considered Category A medications in pregnancy by the Australian Drug Evaluation Committee. Despite this, emerging evidence drawn predominantly from the paediatric and obstetric literature does raise some concerns regarding the use of SGCS in pregnancy. The author aims to summarize this literature to assist dermatologists to understand the issues.

HISTORICAL OVERVIEW

In 1972, a RCT was published showing that antenatal SGCS given to pregnant women early in premature labour markedly reduced the risk of respiratory distress syndrome in their newborns. Respiratory distress syndrome (also known as hyaline membrane disease) is the major cause directly or indirectly of neonatal morbidity and mortality in premature infants.

During the very same year, Archie Cochrane, a UK physician and the name behind the Cochrane collaboration, published his influential work. In 1979, he wrote ‘It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials’. Despite repeated randomized trials throughout the 1970s and 1980s and a systematic review of randomized trials in 1990 providing incontrovertible evidence in favour of antenatal SGCS therapy, obstetricians all over the world were slow to adopt this treatment. The causes of this tardiness are unclear although a possible explanation mooted in a recent Cochrane review was that the use of antenatal SGCS was not promoted by any pharmaceutical company.

The consequence of the failure of obstetricians to adopt antenatal SGCS was that tens of thousands of premature babies probably suffered and possibly died, and needed more expensive treatment than was necessary along the way. The Cochrane collaboration has long utilized the diagrammatic representation of the RCT of antenatal SGCS as their logo. The diagram summarizes the evidence that would have been revealed had the available RCT of antenatal SGCS been reviewed systematically in 1982.

By the mid-1990s, the message had got through regarding the use of antenatal SGCS, and this was in widespread use
for women in premature labour. Despite a paucity of RCT of multiple courses of antenatal SGCS, it became commonplace for obstetricians to give multiple courses of SGCS to women who remained at risk for preterm birth. A survey of SGCS prescribing practices by Australian obstetricians showed 85% prescribed repeat courses of SGCS for women in which the risk of preterm birth persists or recurs, and similarly high rates were found in the USA and UK.

Evolving Concerns

At the turn of the new millennium, concerns were raised regarding the repeated use of SGCS and fetal brain growth and development. There is considerable evidence from experimental animals that corticosteroids can have an adverse effect on the growth and development of the immature brain. Animal models tell us what can happen, not necessarily what does happen, and while a lot of the literature pertains to small mammals (rodents, rabbits), sheep and monkeys have also been studied. A recent review concluded that the effects of repeated maternal glucocorticoids on fetal development are a concern. For example, in pregnant sheep single and repeated doses of betamethasone resulted in retarded brain growth in the foetuses, with repeated doses having more profound effects, particularly at term. In pregnant sheep, repeated (but not single) doses of betamethasone resulted in reduced myelination in both premature and term foetuses as measured by thickness of the retinae. Some human data support a transiently smaller head circumference, although other studies have not shown this. Postnatal SGCS given to premature infants with chronic lung disease have also been associated with an increased risk of neurological impairment.

Another difficult to resolve concern with use of repeated courses of SGCS relates to their longer-term potential to predispose to adult disease. It is hypothesized that by influencing fetal programming, antenatal SGCS may predispose to adult hypertension, type 2 maturity onset diabetes, coronary artery disease and cerebrovascular accidents.

An Australian study showed that teenage children who received any antenatal SGCS in utero have higher blood pressure (both systolic and diastolic) in comparison with those children who did not.

The current consensus is to give a single course of antenatal SGCS only (as per the published evidence from RCT), and to await further trials of benefits and risks as there is insufficient evidence to support the previously widespread practice of repeated doses of antenatal SGCS. The standard single course for women in threatened premature labour consists of a total of 24 mg of either betamethasone or dexamethasone in divided dosage over 48 hours. This is approximately equivalent to 125 mg of prednisolone.

The Role of the Placenta in Handling Antenatal Systemic Glucocorticosteroids

All exogenously administered SGCS given to pregnant women to some extent cross the placenta. The amount of a given SGCS administered to the mother that ends up in the fetal circulation depends upon a number of variables, including the type of SGCS given, the dose, the route of administration, the binding affinity of carrier proteins and the extent of placental metabolism. These processes are complex. Essentially, the placenta functions to limit maternally derived exogenous or endogenous glucocorticosteroid access to the foetus. Specifically, the placental enzyme 11β hydroxysteroid dehydrogenase converts active hydroxylated corticosteroids to inactive 11 ketone compounds. The degree of conversion depends on the structure of the particular substrate. Designed to deal with endogenous maternal corticosteroids, this enzyme does less well in performing its function as a physiological barrier to some exogenous maternal corticosteroids, particularly dexamethasone and betamethasone. In a study unlikely to be repeated today, pregnant women were given a radio-labelled infusion of prednisolone or prednisone close to the time of elective Caesarean section. Fetal plasma levels of exogenous prednisolone were 8–10-fold less than simultaneous maternal plasma levels, whereas maternal and fetal plasma levels of exogenous prednisone were similar. This suggests that for prednisolone the placenta does function as a relatively effective though incomplete barrier. Methylprednisolone crosses the placenta poorly, while hydrocortisone crosses well.

Little information could be found on the transfer of intralosional or topical glucocorticosteroids across the placenta. Although it is known that topical glucocorticosteroids can be absorbed in amounts large enough to cause systemic adverse effects identical in type to systemically administered glucocorticosteroids, the number of reports of such adverse effects is small and seems to involve gross misuse of a topical glucocorticoid preparation.

Conclusion

Dermatologists may have occasion to use SGCS in several instances in pregnant women, including specific pregnancy dermatoses and other conditions coincident with pregnancy. Dermatologists are unlikely to use multiple courses of SGCS in pregnancy as has been used previously by many obstetricians, but are more likely to use a single long course (e.g. pemphigoid gestationis), or a single short course (e.g. flare of atopic dermatitis). Dermatologists should be aware that:

1. There have been recent changes in the prescribing patterns of SGCS to pregnant women with threatened premature labour by obstetricians as detailed above. The reasons for these recent changes predominantly relate to the absence of RCT showing benefit for multiple courses and the concerns of potential neurological effects on the developing brain (smaller head size, less myelination). Although there is strong evidence for effects on the developing brain from animal studies, human studies to date have shown conflicting results.
2. The placenta functions as a barrier to protect the foetus from maternal corticosteroids, both endogenous and exogenous.

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5. Some glucocorticosteroids are better than others at overcoming the placental barrier, but to some extent all exogenous glucocorticosteroids do cross this barrier. Prednisolone appears to cross the placenta only to a small extent in comparison with prednisone, and may for this reason be preferred. In the pregnant woman who cannot tolerate oral glucocorticosteroids (e.g. hyperemesis gravidarum), a parenteral glucocorticosteroid that crosses the placenta poorly may be preferred. Betamethasone and dexamethasone have been traditionally used by obstetricians because they cross the placenta well, as does hydrocortisone; whereas methylprednisolone crosses the placenta poorly.

4. Any decision by dermatologists regarding SGCS use in pregnancy also needs to consider the possible adverse effects on both mother and foetus of not treating the skin condition.

5. There is little information regarding the transfer of intralesional glucocorticosteroids or topical glucocorticosteroids across the placenta, though it is assumed any amount transferred would likely be small and not clinically significant in the vast majority of cases of reasonable usage.

REFERENCES


