Antenatal treatment of a mother bearing a fetus with congenital adrenal hyperplasia

C G D Brook

The virilisation of a female fetus by overproduction of adrenal androgens secreted by an adrenal gland with 21-hydroxylase deficiency is well known. Although reconstructive genital surgery can greatly improve matters, the long term outlook for reproduction is extremely poor for many reasons, including anatomy.1 2 The idea of prenatal treatment of 21-hydroxylase deficiency by administering glucocorticoids to the mother to prevent virilisation was superficially extremely attractive.3 Where do we stand 15 years later?

Treatment protocol and rationale

The aim of treatment is to suppress the secretion of androgens from the adrenal gland of the affected female fetus because they will masculinise her external genitalia and probably, through conversion to oestrogen by aromatase, defeminise her brain and subsequent behaviour. In principle, the management protocol for a mother suspected of carrying a fetus affected with 21-hydroxylase deficiency, usually because she and her partner have had a previously affected child, is logical and straightforward.

Dexamethasone is started as soon as the pregnancy is confirmed and before virilisation can start. It is important to recognise that male sexual differentiation starts at about six weeks of gestation, and formation of the penis is complete at 14 weeks, so there is no time to lose.

It is necessary before conception to perform molecular studies on the proband and on both parents and also to confirm biochemically the heterozygote state of both parents to determine whether a molecular diagnosis will be possible. If it is, DNA can be isolated from a chorionic villous sample taken at between 10 and 12 weeks of gestation or from an amniotic fluid sample at 15-16 weeks. It should be possible to determine quickly whether the fetus has the same molecular defect as the proband and what is its karyotype.

In the one in eight eventuality that the mother is carrying an affected female fetus, treatment with dexamethasone is continued until term. The aim is to deliver a female baby with normal genitalia, or, at very least, with a degree of virilisation much less than that seen in other affected family members.

Genetic pitfalls

Nothing in genetics is as straightforward as it seems at first sight and this is certainly true of 21-hydroxylase deficiency. The underlying molecular pathology of the system is extremely complex with gene and pseudogene, sometimes in multiple copies, located within the major histocompatibility complex on chromosome 6, along with genes for various components of the complement system.

Mutation analysis is not easy, especially in congenital adrenal hyperplasia, and unaffected parents can appear genotypically identical with their offspring (through the finding of multiple mutations on single alleles5 6 and non-amplification of alleles). Even more puzzling is the observation that patients can have the disease without demonstrable genetic mutations.8

In the face of these mismatches of genotype and phenotype, there is an absolute need for postnatal verification of a diagnosis made antenatally. We need to think carefully about both the mother and the fetus and about the very serious ethical issue of treating seven of eight pregnancies unnecessarily, if only to 12–14 weeks of gestation, because the fetus is unaffected, heterozygote, or male (number needed to treat4 = 8).

Effects on the mother

Doses of dexamethasone have usually been large: 20 µg/kg/24 h (equivalent to 0.7mg/m2) in three divided doses has been recommended in the United States for reasons that are not entirely clear as the dose needed overnight to suppress adrenal function is 0.3 mg/m2 body surface area.9 Consequently rather frightening side effects (weight gain, oedema, hypertension, glucose intolerance, hirsutism, and striae among others) have been reported,10 which have been seen to a much lesser extent in the clinical practice at our centre where we have used 0.25 mg three times daily (about 0.5mg/m2/24 h). As maternal Cushing syndrome has a bad track record for the mother and the baby,11 we need to recognise the dangers of maternal complications at these sorts of doses.

Early amniocentesis (at 10–14 weeks of gestation) is slightly riskier in terms of miscarriage (3% less chance of successful pregnancy...
outcome) than amniocentesis performed at the conventional time (15–16 weeks), when the risk of miscarriage is about 1%. The overall risk of complications with either procedure is about 5%. Amniocentesis performed at the conventional time is not only slightly safer but is also more accurate for fetal karyotyping than chorionic villous sampling because amniotic fluid samples are altered about 10 times less often by inherent chromosomal mosaic problems than villous samples.

Chorionic villous sampling, which increases the risk of pregnancy loss compared with amniocentesis performed at the conventional time by 0.5–4%,\(^1\) comes into its own for the diagnosis of genetic disorders because it yields large amounts of DNA. Ideally the procedure should be performed at 10–12 weeks of gestation, and certainly not before 10 weeks because of the up to 2% risk of associated fetal limb defects.\(^1\)

**Effects of the fetus**

The outcome of this treatment has generally been favourable in terms of improving genital ambiguity, but still about half of the affected treated females have needed surgical attention to their genitalia.\(^1\) This may partly be because dexamethasone has variable effects on fetal adrenal function.\(^1\) There must also be tissue response variability too because not all babies with classical congenital adrenal hyperplasia have ambiguous genitalia at birth.\(^1\) The timing of treatment is particularly relevant: a late onset or an inadequate dose of dexamethasone may prevent clitoral enlargement but may not prevent the formation of a urogenital sinus, which is a serious congenital abnormality with very adverse long term consequences.

Babies in utero are generally protected against exposure to their own and their mother's cortisol, and fetal concentrations of cortisol are much lower than those of their mothers through a number of mechanisms. It is precisely to override this protection that dexamethasone, which is a synthetic fluorinated steroid, is used—for example, for the treatment of fetuses at risk of hyaline membrane disease with steroids to induce lung maturation. It is also used to suppress adrenal androgen secretion in babies with congenital adrenal hyperplasia. We can expect that there will be side effects of such treatment. How serious are they, particularly for the seven of eight fetuses who are treated unnecessarily during the first trimester?

Treatment of rats with low doses of dexamethasone throughout pregnancy reduces birth weight and produces persistently elevated blood pressure when the rats reach adult life.\(^1\) This is probably mediated through changes in the renal vasculature. The studies of Barker et al\(^2\) show how dangerous this could be for humans.

There has been only one good study of the long term effects of antenatal treatment of congenital adrenal hyperplasia: it comes from Sweden and makes scary reading.\(^3\) Fetal and childhood growth were generally satisfactory but adverse events were reported in both children treated just in the first trimester and those treated for the whole of gestation. Of 19 unaffected children, one boy treated for seven weeks had agenesis of the corpus callosum and another had delayed psychomotor development. Failure to thrive was reported in three unaffected girls, and one further girl had unexplained mood swings, so there was something to remark in about one third of the group. In the group of six affected girls treated for the whole of gestation, three were considered to have adverse events, even though only one had serious long term consequences.

**Conclusion**

There is no doubt that antenatal treatment of a mother bearing a fetus with congenital adrenal hyperplasia is effective in reducing genital ambiguity—but at a price. The price includes chorionic villous sampling and/or amniocentesis with their attendant risks, the problems associated with molecular diagnosis, and the unknown long term effects of exposing seven of eight babies to unnecessary treatment.

I find myself sobered by what I have reread during the preparation of this article, even though I know full well the extent of the continuing disaster of genital ambiguity in affected females. Like previous authors,\(^1\) I do not think that we should abandon the idea, but antenatal treatment should, like marriage, not be “enterprised, nor taken in hand, unadvisedly, lightly or wantonly”. It needs the fullest of informed consent; it should only be undertaken by experts; it should be coupled with very long term follow up; it should only be undertaken in the context of large (probably international) collaborative trials.

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Congenital adrenal hyperplasia is a lifelong endocrine disorder, the understanding and management of which involves a complex interplay of factors: genetic mechanisms; steroid production, action, and metabolism; pharmacokinetics of steroid formulations; growth, puberty, and reproduction; surgical reconstructive techniques; psychosexual development.

How beneficial would antenatal treatment be for the immediate and later management of congenital adrenal hyperplasia? There is every expectation that masculinisation of the female external genitalia can be prevented by treatment with judicious doses of dexamethasone given to the mother from early pregnancy (six to seven weeks of gestation). The relief of having a normal appearing girl is incalculable for parents who have gone through the experience of having an infant with ambiguous genitalia who needs complex repeated surgical procedures. The benefit is not only immediate, but should also be evident in later life for other studies that heterosexual activities are influenced by the outcome of corrective surgery of the genitalia. The causes of reduced fertility in women with congenital adrenal hyperplasia are multiple and include low maternalism. Perhaps this latter observation is akin to the defeminised behaviour observed in childhood, phenomena attributed to prenatal androgenic effects on the developing brain. Another feature that probably contributes to low fertility rates in congenital adrenal hyperplasia is the universal presence of polycystic changes in ovaries on ultrasound. Even though such changes are observed in about 20% of normal females, the propensity to develop polycystic ovarian syndrome and all the attendant morbidities must be greater for a woman with congenital adrenal hyperplasia. Thus, treating a female congenital adrenal hyperplasia fetus with antenatal steroids has a number of actual and potential benefits.

What of the potential dangers of antenatal treatment highlighted by Professor Brook in his review and debated in detail in a recent trio of papers in an endocrine journal. There is concern about the need to treat initially all pregnancies at risk until an affected female fetus is identified by prenatal testing. The danger of miscarriage as a result of the test procedures is emphasised, but such warnings are generic to fetal medicine practice. Amniotic fluid steroid analysis using specific chromatographic techniques on mid-trimester samples is the safest invasive test and very reliable. However, this approach does lengthen the time for treatment deemed unnecessary. The molecular genetics of 21-hydroxylase deficiency is complicated by phenomena such as transfer of genetic material from a pseudogene to an active gene by recombination events, gene duplication, uniparental disomy, and gonadal mosaicism. Nevertheless, a limited number of mutations account for most cases of 21-hydroxylase deficiency. A priori, the approach does lengthen the time for treatment deemed unnecessary.
Antenatal treatment for congenital adrenal hyperplasia

Disorders which cause genital ambiguity such as the syndromes of androgen insensitivity. Certain mutations in the CYP21 gene are always associated with salt wasting and hence lead to severe masculinisation. Conversely, a few well defined mutations result in the mild late onset form of congenital adrenal hyperplasia, for which antenatal treatment would not be indicated. Although there will always be rare exceptions to the rule which usually offer fascinating insights into molecular emphasis on genetic curiosities.

Dexamethasone is currently the glucocorticoid of choice for antenatal treatment for several reasons. It circulates unbound and is not readily deactivated when it crosses the placenta by the 11β-hydroxysteroid dehydrogenase type 2 isoenzyme, which normally catalyses the cortisol-cortisone shuttle. Pharmacokinetic studies in patients with congenital adrenal hyperplasia indicate satisfactory oral bioavailability and a half life for dexamethasone of about three to four hours. It is advisable to administer the dose every eight hours. The quoted daily dose of 20 µg/kg was derived from the results of suppressed midtrimester amniotic fluid 17-hydroxyprogesterone concentrations. Maternal side effects can be excessive, and further studies are needed to determine the lowest dexamethasone dose that can adequately suppress excessive adrenal androgen secretion. The combination of changing maternal size and a lowering of the administered dose later in pregnancy should reduce the incidence of side effects.

What is the risk to the fetus from this treatment? In general, infants born to mothers who have received steroids during pregnancy for a variety of reasons are not subject to more congenital malformations or adverse effects on growth and development. There must be concern about the effect of dexamethasone on the early developing fetus, particularly when seven out of eight do not need the treatment. However, there is no evidence currently of measurable ill effects, either at birth or in later childhood. The experimental rat model of dexamethasone induced fetal growth retardation and later hypertension is of scientific interest, but the results cannot be directly related to the human situation, either for the newborn or for morbidity in adult life. The Swedish study of antenatal congenital adrenal hyperplasia treatment certainly contains the most informative outcome data so far reported. The paper describes adverse events in several treated infants, but most are the result of factors or specific disorders unrelated to steroid exposure.

However, it is important not to be complacent just because treatment is successful in preventing abnormal genital development and in maintaining normal growth and development in most infants. Nevertheless, that medical treatment alone produces completely normal genitalia in a female infant with severe congenital adrenal hyperplasia is a major endocrine achievement. Indeed, 11β-hydroxylase deficiency, which is a form of congenital adrenal hyperplasia that causes the most profound masculinisation, has also now been successfully treated antenatally. The initial results of antenatal treatment for congenital adrenal hyperplasia are impressive. However, there must be a mechanism to ensure a coordinated approach on a national scale towards antenatal diagnosis, treatment, and subsequent monitoring long term for all infants exposed to dexamethasone in utero. Such an exercise will soon be underway through the auspices of the British Society for Paediatric Endocrinology and Diabetes, in collaboration with similar studies in other European countries.

IEUAN HUGHES

Department of Paediatrics
University of Cambridge
Addenbrooke’s Hospital
Cambridge CB2 2QQ, UK
email:iah1000@cam.ac.uk

Commentary

There can be few situations more worrying to new parents than ambiguous genitalia in their newborn baby, with the uncertainty of sex and diagnosis until tests have been carried out. The commonest cause is 21-hydroxylase deficiency congenital adrenal hyperplasia in an affected female infant. In this situation, there is the prospect of surgery (perhaps repeatedly) in infancy, and sometimes at adolescence, and concerns about fertility and psychosexual orientation and functioning.

Thus when there has been a previously affected female child, the possibility of prenatal treatment to reduce or prevent significant neonatal virilisation in a second affected female fetus and obviate the need for surgery in infancy and beyond is potentially attractive.

Prenatal treatment with the potent and long acting synthetic glucocorticoid dexamethasone has been available and administered for over 15 years, and an algorithm for the prenatal management of the “at risk” pregnancy has been published. What is an appropriate dose? What is the evidence that it is effective in terms of reducing virilisation significantly? Could there be positive effects on psychosexual orientation or fertility? Is it safe for the mother? What and how significant are potential side effects in the fetus and on the subsequent development of the child or even adult?

Fetuses in whom treatment would be appropriate are affected females, a one in eight possibility with each pregnancy. However, dexamethasone must be started very early in pregnancy, before sexual differentiation starts at six weeks gestation and considerably before antenatal diagnosis is possible. Thus seven out of eight infants will have treatment unnecessarily for a number of weeks. In affected female infants, treatment is continued to term.

Important outcomes have not been comprehensively evaluated in significant numbers of pregnancies, but several large scale studies have now been reported in varying detail. Maternal complications have included increased appetite, weight gain (sometimes extreme), oedema, hypertension, glucose intolerance, mood swings, epigastric pain, facial hirsutism and Cushingoid features (including moon-face, plethora with permanent scarring), and spontaneous miscarriage. The reasons for the differing reported incidence of such problems are as yet unresolved. There is possibly an unexplained/unexpected fetal miscarriage rate of up to 1% at or near term.

All 44 prenatally treated children in Sweden and Norway have been studied at birth and followed up for between one and 10 years. Short term dexamethasone treatment produced no difference in growth (weight and length/height) at birth or subsequently compared with controls. Although six affected girls treated throughout gestation showed appreciably reduced virilisation compared with their older sisters, in the cohort of treated children there was a substantial number of unexpected fetal problems including hydrocephalus, agenesis of the corpus callosum, mental retardation and ataxia, and a mitochondrial disorder. In the matched control group, there was one child with Down syndrome.

A formal systematic review of the relevant literature is currently in progress. However, it is already clear that the data reported so far, worrying as they are, are for relatively small numbers from observational studies, with no randomisation or placebo control groups, and are likely to be considerably biased. Nor do they lend themselves readily to relevant analyses of concern, which must now include blood pressure, cardiovascular risk factors, somatic and brain growth, psychosexual orientation,
and sexual and psychological functioning and fertility.

In this, as in other areas of paediatric endocrinology, there is an urgent need for large well-constructed clinical trials to ensure accurate results with statistical and clinical significance. There must be more collaboration between centres, both nationally and internationally, to design prospective controlled multicentre trials which can recruit sufficient numbers for meaningful efficacy and safety outcomes to be obtained over a long period of time; all perinatal trials should report long-term morbidity.

There still remains insufficient evidence on the appropriate dosage regimen, safety in the mother, and short and long-term safety and efficacy in the fetus from appropriately controlled studies to recommend the use of dexamethasone outside the context of such controlled scientific studies.

CHRISTOPHER J H KELNAR
Consultant Paediatric Endocrinologist and Senior Lecturer
Department of Child Life and Health, University of Edinburgh
email: dkcantavor@gmail.com