Prenatal treatment of mothers with fetuses at risk for congenital adrenal hyperplasia: How relevant is it to Indian context?

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ABSTRACT

Management of congenital adrenal hyperplasia (CAH) from embryonic stage to adulthood is a critical challenge. We would like to comment on some of the practical difficulties in offering prenatal treatment for CAH-affected fetuses in Indian population. For initiating the prenatal dexamethasone (DEX) treatment, all members of the family need to be informed about the risks and benefits of the treatment to the mother and the fetus as well as about the available invasive diagnostic tests to determine the gender and genotype of the fetus. Prenatal sex disclosure is not routinely practiced in India due to high female feticide rate. The treatment has to be given to both unaffected and affected female fetuses until the determination of prenatal sex. Moreover, most of our populations reside in rural areas where the antenatal care is not adequate. Prenatal DEX treatment in India outruns the risks rather than the benefits, as evident from the literature on the safety of pregnant mothers and fetuses.

Key words: Chorionic villus sampling, dexamethasone, genetic sex, virilization

In patients with congenital adrenal hyperplasia (CAH), the production of cortisol and aldosterone are diminished and adrenal androgen secretion is increased. This hyperandrogenism leads to varying degrees of virilization of external genitalia[1,2] in 46, XX fetuses. In order to prevent this ambiguity, dexamethasone (DEX) treatment in CAH-risk pregnancies was introduced in France and in USA.[3,4] Later, other groups also reported a reduction in the degree of virilization in affected female fetuses with DEX treatment.[5,6] The treatment has been proven to be highly effective for the reduction of genital masculinization in 46, XX fetuses, if begun by the 8th week postconception and used consistently throughout pregnancy.[7,8] However, one study from Italy[9] stated that "to prevent truly the genital virilization, the treatment has to be started <8 weeks of gestational age." In which case, 7 out of 8 pregnancies have to be exposed to DEX treatment unnecessarily, albeit briefly (till the gender and genotype determination by invasive conventional chorionic villus sampling [CVS] at the gestational age between 10 and 11 weeks). Postnatal steroid therapy also improves the appearance of external genitalia during the first years of life.[10] A recent study[1] has captured all positive and negative outcomes of the CAH children on treatment and compared them with the control group. However, the authors summarized that "their studies do not replicate a previously reported adverse effect of short-term prenatal DEX exposure on working memory and on cognitive function in CAH girls with long-term DEX exposure contributing to concerns about potentially adverse cognitive after effects of such exposure."

Some animal studies on prenatal glucocorticoid therapy have raised concerns regarding the possible negative effects on behavioral and somatic development.[11,12] Adult corticosteroid exposed rodent offspring are characterized by hypertension, hyperinsulinemia and hyperglycemia, fatty liver. Hyperactivity of the hypothalamic-pituitary

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adrenal axis and altered affective behavior, reminiscent of anxiety, as well as impaired learning and memory functions were also observed.[13] In the rhesus monkey, prenatal DEX during the last trimester resulted in offspring with elevated basal and stress-stimulated cortisol at the age of 10 months as well as smaller hippocampal volume. In the African vervet monkey, *Chlorocebus aethiops*, high-dose DEX exposure (120-200 g/kg) from midgestation until term resulted in offspring with an exaggerated cortisol response to stress in both prepubertal and in adult stages. These animals exhibited hypertension, impaired glucose tolerance, and hyperinsulinemia.[14]

A long-term follow-up of individuals treated prenatally with betamethasone due to a risk of preterm birth. The authors also noted that 30 years after the exposure, these individuals, particularly women, exhibited insulin resistance and 7% of the adults had elevated basal, morning cortisol levels.[15] Retrospective follow-up studies of mothers and 43 children treated from Sweden and Norway during 1985-1995 reported that some type of maternal discomforts could be attributed to DEX, and severe adverse events were also noted in the treated group compared with the control group.[16-19] As a consequence of these findings, further recruitment of patients were put on hold for the ongoing prospective study of prenatal DEX treatment of CAH in Sweden until larger and more conclusive studies are published.[13] In another report, the authors reviewed the pathophysiology of CAH, the safety and ethical considerations of prenatal DEX treatment, and the views of multiple medical societies. They concluded that this experimental therapy should only be done in prospective trials approved by ethical review boards.[7,20] The recent article on the use of DEX for the antenatal treatment for mothers with affected CAH fetuses stated that neither the FDA nor the EMA have granted a license and also suggested that the usefulness of fetal cells in the maternal circulation to karyotype the fetus should reduce the overall exposure time to DEX, but careful long-term follow-up is required.[21] Prenatal sex determination is prohibited in India due to high female feticide rate. The treatment has to be given to both unaffected as well as to the affected female fetuses until the determination of prenatal sex. For treating the affected female fetuses, both parents have to be informed about the risks, benefits, and uncertainties of the treatment and the gender of the fetus. Moreover, most of our populations reside in rural areas where the antenatal care is not adequate.

This makes the necessary follow-up care, which is essential for the regular monitoring of the patient on prenatal DEX treatment for the known side affects like maternal hypertension and edema. The benefits of DEX treatment outweigh the risks involved to the fetus and to the mother, when the follow-up care and monitoring facilities are inadequate.

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