Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Endocrinology

Preventing Female Virilisation: Role of Antenatal Dexamethasone

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DOI: 10.36347/sjams.2023.v11i01.025 | **Received:** 03.12.2022 | **Accepted:** 09.01.2023 | **Published:** 25.01.2023

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Abstract **Original Research Article**

Antenatal treatment with dexamethasone in pregnancies affected by congenital adrenal hyperplasias (CAH) therefore suppresses fetal androgen production and prevents virilisation of female infants. Antenatal DXM is reported to be efficacious, preventing or ameliorating virilisation in 80–85% of cases. ***Materials and methods****:* In this study, we report a case of patient pregnant at 6 weeks; with a history of 2 children followed up for a classic form of HCS, she is admitted to our department for the administration of dexamethasone to prevent fetal virilization. ***Case Report*****:** 23-year-old patient pregnant at 6 weeks, not known of having congenital adrenal hyperplasia (CAH), concept of consanguineous marriage 1 degree; she had a history of 2 children followed up for a classic form of HCS, the first died at the age of 1 and 10 months and the 2 child died on D26 of life. After having made a prenatal diagnosis where an analysis of the SRY gene on fetal circulating DNA showed the absence of this gene, which confirms the female sex of the fetus. An obstetrical ultrasound was done which objectified a pregnancy estimated at 6 weeks with suspicion of clitoral hypertrophy (At 16 weeks), in view of this observation the patient was referred to us for additional care and possible dexametasone. On questioning, the patient did not report any signs of hyperandrogenism. All evolving in a context of unquantified moderate weight loss and asthenia without signs of adrenal insufficiency. The clinical examination showed no melanoderma or slate spots, BP= 105/71mmHg, RR = 19 cycles/min. CF=81bpm? BMI = 28.68 kg/m2. Tanner: S5P5. the patient was put on 1.5 mg/d of dexamethasone divided into 3 doses.a monthly measurement of DHEAS and cortisol was requested. The Decrease of plasma concentrations of cortisol and DHEAS in the mother testifies to good fetal adrenal suppression. A low-calorie diet and monitoring of blood pressure and blood sugar to detect signs of under or overdose of corticosteroid therapy. Ultrasound monitoring of the fetus done each month, the first ultrasound done 1 month after Dexamethasone treatment shows the disappearance of the clitoral hypertrophy seen on the initial ultrasound. Patient gave birth at 38 weeks of amenorrhea by caesarean section, the newborn is female, the birth weight is 2Kg 600, the external genitalia are normal. The newborn was hospitalized in the neonatology department for monitoring and screening of The congenital adrenal hyperplasia. ***Conclusion:*** CAH is an uncommon but important and ethically complex condition where there are significant maternal and fetal risks both with and without antenatal treatment. It is time for the historical recommendation of administering prenatal DXM to all pregnancies of high-risk families for CAH to be reevaluated. Given the potential maternal and fetal effects, a multidisciplinary national strategy is required to optimize diagnosis and prenatal treatment and facilitate follow-up. Only then, can families be fully informed of the natural history of treated and untreated fetal CAH.

Keywords: Antenatal treatment, congenital adrenal hyperplasias (CAH), Antenatal DXM, hyperandrogenism.

INTRODUCTION

The congenital adrenal hyperplasias (CAHs) are autosomal recessive disorders, resulting in deficient adrenal cortisol production with excessive adrenal androgen production. They affect 1 in 14,000–15,000 newborns [1]. The most common form creates a deficiency in the enzyme 21-hydroxylase, diverting steroid precursors away from cortisol (glucocorticoid) and aldosterone (mineralocorticoid) production and increasing adrenal androgen biosynthesis. There are two clinical subtypes of CAH: nonclassical and classical. In classical CAH, 46 XX female fetuses are virilised in utero due to their increased exposure to androgens. This results in the development of clitoromegaly, fusion of the labioscrotal folds and formation of a common

urogenital sinus in place of a separate urethra and vagina. Classical CAH can be further classified as simple virilising, or salt-wasting, where there is also deficient adrenal aldosterone production. Adequate replacement of glucocorticoid to the affected individual results in normalisation of adrenal androgen production.

Dexamethasone (DXM) crosses the placenta and when administered to a pregnant woman becomes bioavailable to the fetus. Antenatal treatment with dexamethasone in pregnancies affected by CAH therefore suppresses fetal androgen production and prevents virilisation of female infants. Antenatal DXM is reported to be efficacious, preventing or ameliorating virilisation in 80–85% of cases [2].

While antenatal treatment effectively prevents fetal virilisation, it does not remove the need for lifelong monitoring and treatment with glucocorticoids and mineralocorticoids [2]. To effectively prevent virilisation, treatment is institutedin early pregnancy, ideally at six weeks and certainly prior to nine weeks gestation, when the fetal adrenal cortex begins to secrete androgens. Consequently, treatment is often commenced before a confirmed diagnosis of gender and/or a CAH-affected fetus. This means that, of high-risk pregnancies known to be at 25% risk of CAH, seven of eight fetuses (all male fetuses and three of four female fetuses) are treated unnecessarily. Antenatal DXM is still considered by some experts as the most appropriate treatment to offer for fetal CAH as it reduces female virilisation, helps avoid the need for postnatal genital reconstructive surgery and prevents the emotional distress experienced by parents having a child with ambiguous genitalia. However, concerns have been raised by some follow-up studies, international professional bodies and an Australian Senate Inquiry regarding the adverse effects of prenatal DXM on both the mother and the child [3, 4]. These potential adverse effects include those associated with high-dose dexamethasone use on the mother, and longterm neurocognitive and metabolic effects on the fetus.

MATERIALS AND METHODS

In this study, we report a case of patient pregnant at 6 weeks; with a history of 2 children followed up for a classic form of HCS, she is admitted to our department for the administration of dexamethasone to prevent fetal virilization.

CASE REPORT

23-year-old patient pregnant at 6 weeks, not known of having congenital adrenal hyperplasia (CAH), concept of consanguineous marriage 1 degree; she had a history of 2 children followed up for a classic form of HCS, the first died at the age of 1 and 10 months and the 2 child died on D26 of life.

After having made a prenatal diagnosis where an analysis of the SRY gene on fetal circulating DNA showed the absence of this gene, which confirms the female sex of the fetus.

An obstetrical ultrasound was done which objectified a pregnancy estimated at 6 weeks with suspicion of clitoral hypertrophy (At 16 weeks), in view of this observation the patient was referred to us for additional care and possible dexametasone.

On questioning, the patient did not report any signs of hyperandrogenism. All evolving in a context of unquantified moderate weight loss and asthenia without signs of adrenal insufficiency.

The clinical examination showed no melanoderma or slate spots, BP= 105/71mmHg, RR = 19 cycles/min. CF=81bpm? BMI = 28.68 kg/m2. Tanner: S5P5 the patient was put on 1.5 mg/d of dexamethasone divided into 3 doses.a monthly measurement of DHEAS and cortisol was requested. The Decrease of plasma concentrations of cortisol and DHEAS in the mother testifies to good fetal adrenal suppression; – a low-calorie diet and monitoring of blood pressure and blood sugar to detect signs of under or overdose of corticosteroid therapy.

Ultrasound monitoring of the fetus done each month, the first ultrasound done 1 month after Dexamethasone treatment shows the disappearance of the clitoral hypertrophy seen on the initial ultrasound patient gave birth at 38 weeks of amenorrhea by caesarean section, the newborn is female, the birth weight is 2Kg 600, the external genitalia are normal with a Prader score of 0 (Fig 1).

The newborn was hospitalized in the neonatology department for monitoring and screening of The congenital adrenal hyperplasia.

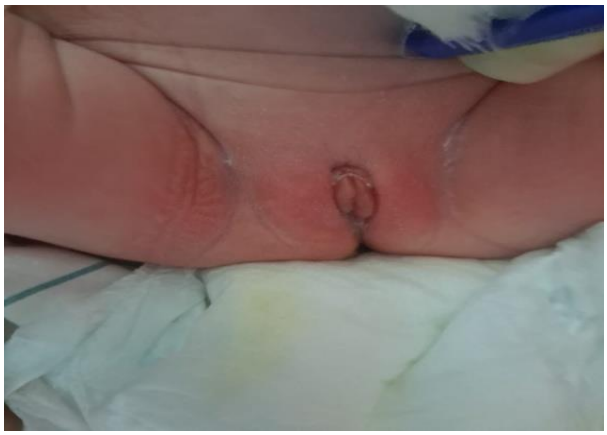

Fig 1: Normal external genitalia in newborns

DISCUSSION

Antenatal DXM Treatment for Pregnancies at Risk of CAH-Affected Females

The fetus develops an adrenal cortex by the 4th week of gestation, and by the 6th–7th week, it begins to secretesteroid hormones [5]. The majority of CAH-affected fetuses have a defect in the CYP21A2 gene, affecting the enzyme 21-hydroxylase which is involved in the pathway of both cortisol and aldosterone synthesis [2]. The deficit in 21- hydroxylase results in diversion of cortisol and aldosterone precursors to adrenal androgen synthesis. Low levels of cortisol and aldosterone activate a negative feedback pathway, resulting in increased ACTH, more steroid precursor and increased adrenal androgen production. The resulting abnormally high androgen levels cause virilisation in female fetuses.

A high-risk pregnancy is most commonly identified through an affected proband in the family, or occasionally through carrier testing of the partner if one parent is known to be affected or a carrier. Antenatal treatment has previously consisted of 20 lg/kg/day of DXM (based on prepregnancy weight), up to a maximum of 1.5 mg/day, taken over three daily doses and commenced around the seventh week of gestation [6, 7]. DXM is the chosen glucocorticoid for prenatal treatment because it has a longer half-life, is able to cross the placenta (as it is not inactivated by placental 11-beta-hydroxysteroid dehydrogenase) and successfully suppresses fetal ACTH secretion [5, 6]. Using this approach, treatment is continued until invasive testing – most commonly with CVS – determines whether the fetus is male or an unaffected female, in which case treatment is ceased, a so-called short course treatment. If the fetus is a CAH-affected female, then DXM treatment is continued to term, a 'long-course' treatment. As seven of eight at-risk pregnancies receive an unnecessary short-term course of DXM in early pregnancy, the risks of antenatal DXM need to be weighed against the benefit for the one of eight affected female fetuses where early administration of antenatal steroids is highly effective in reducing virilisation.

Antenatal DXM for Affected Fetuses: the Benefits

Among affected fetuses, antenatal DXM is highly efficacious in reducing virilisation. Postnatal assessment of virilisation is carried out by assigning a Prader score; 0 represents normal female genitalia, and 5 represents normal male genitalia. In a study of 532 pregnancies which included 61 classical CAH-affected females, New *et al*., [6]. reported an average Prader score of 0.96 among infants treated with prenatal DXM, compared with an average score of 3.75 in those that were untreated. Suboptimal response has been associated with non compliance, incorrect dosing, intolerance of maternal side effects and delayed implementation [8]. In 2000, the American Academy of Pediatrics recommended commencing treatment with 20–25 lg/kg of DXM in two or three divided doses per day for informed mothers with a high-risk pregnancy by five-week gestation [9]. More recently, accumulating data on the maternal–fetal effects of prenatal corticosteroids has prompted a revision in practice.

Maternal and Fetal Effects of Antenatal DXM Maternal side effects

Prenatal treatment with DXM is associated with significant maternal side effects, including weight gain, oedema, mood change, sleep disturbance, acne and striae development [5, 6, 10]. One study reported that the maternal side effect profile was sufficiently severe that one-third of women said they would not choose to use DXM in a future pregnancy [11]. There has not been a confirmed association with major pregnancy complications such as hypertension, gestational diabetes, stillbirth or spontaneous abortions [5, 10].

The fetal impact of antenatal DXM exposure

Most concern regarding antenatal treatment of CAH relates to potential long-term sequelae of glucocorticoid exposure in utero, including effects on growth, metabolism, cognitive function and disturbance of the hypothalamic–pituitary–adrenal (HPA) axis. Assessing the impact of fetal exposure to exogenous glucocorticoids has largely been informed by extensive animal research, and follow-up of those infants exposed to short-term glucocorticoids to reduce morbidity and mortality from preterm birth. Glucocorticoids used to enhance fetal lung maturation such as DXM and betamethasone are resistant to the effects of placental 11-b hydroxysteroid, resulting in high bioactivity at the level of the fetal tissues. The resultant increase in alveolar stability and improved pulmonary maturity is responsible for the dramatic reduction in neonatal morbidity and mortality among infants born below 34-week gestation following short-term administration of glucocorticoids. The benefits of short-term treatment in a population at high risk of adverse outcome due to prematurity are undisputed, but outside of this setting, the potential adverse effects of extended exposure to glucocorticoids warrant careful consideration.

Modified treatment regimens If treatment is to be offered to affected females throughout pregnancy, the dose used should be as low as possible to minimise potential long-term health risks, yet sufficient to minimise virilisation. Physiological glucocorticoid replacement would lead to suppression of adrenal androgen production while avoiding long-term side effects of supraphysiological exposure to glucocorticoid during fetal development. While the current dosing of 20 lg/kg/day of DXM has been shown to suppress levels of fetal 17-hydroxyprogesterone and hence adrenal androgen production, this does not adjust for fluctuating fetal cortisol production across gestation, and physiological glucocorticoid replacement could be

achieved at a lower dose [4, 7]. While a case study has reported that lower doses of DXM have been successfully used without virilisation occurring [12], this regime has not been subjected to an interventional placebo-controlled trial study [12]. In addition, as genital reconstructive surgery is considered only in infants with more severe virilisation (at Prader ≥ 3), lower doses of antenatal dexamethasone which do not entirely suppress virilisation, but which reduce the Prader stage to one where infant surgery is not indicated would be of benefit.

Further research is required to determine the optimal dose and length of treatment with the aim of preventing virilisation, while minimising maternal and fetal side effects [4]. The future of fetal therapy in this field may also include novel models of transplacental drug delivery. DXMloaded polymeric nanoparticles have been found to efficiently cross the placenta, thus avoiding systemic dosing and overcoming problems with compliance due to unwanted maternal side effects [13].

Current recommendations on antenatal treatment of CAH from expert advisory groups The current management of CAH-affected families is controversial. The 2010 Endocrine Society guidelines recommend that treatment of pregnancies at high risk of CAH with prenatal DXM be 'considered experimental' [4]. Given that DXM treatment (i) benefits only one in eight high-risk pregnancies, (ii) is not necessary to preserve life or protect intellectual capacity and (iii) is largely used to reduce parental stress and prevent surgery, they have concluded that such treatment should only be implemented by specialist centres involved in ethically approved studies with standardised registries [4]. The task force summarised their position as having 'placed a higher value on preventing unnecessary exposure of mother and fetus to DXM and avoiding potential associated harms and a relatively lower value on minimising the emotional toll of ambiguous genitalia on parents and patients', a sentiment echoed by some experts [2, 14]. Others have taken a more neutral position, highlighting the importance of prioritising the autonomy, values and preferences of fully informed and consenting parents [10]. Locally, a 2013 Australian Senate Inquiry was tasked with examining current practices affecting the sexual health and reproduction of individuals affected by disorders of sex development, including congenital adrenal hyperplasia. Two of the final recommendations directly.

CONCLUSION

CAH is an uncommon but important and ethically complex condition where there are significant maternal and fetal risks both with and without antenatal treatment. It is time for the historical recommendation of administering prenatal DXM to all pregnancies of high-risk families for CAH to be reevaluated. Given the potential maternal and fetal effects, a multidisciplinary national strategy is required to optimize diagnosis and prenatal treatment and facilitate follow-up. Only then, can families be fully informed of the natural history of treated and untreated fetal CAH.

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