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Case Report

PREGNANCY AND DELIVERY OF A PATIENT WITH CONGENITAL ADRENAL HYPERPLASIA: CASE REPORT

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ABSTRACT
Congenital adrenal hyperplasia (CAH) during pregnancy is a rare condition. Only a few cases have been reported in the literature. CAH patients has lower pregnancy rate compared to normal women. A 25-year-old G2P0010, diagnosed case of 21-hydroxylase deficient simple virilizing form of classic CAH visited. She got pregnant spontaneously without any trial of assisted reproductive technology. At the age of 5year, she underwent clitoral resection and vaginoplasty. She took prednisolone and fludrocortisone after operation. She delivered healthy singleton female baby by cesarean section. Here, we report a case of successful pregnancy and delivery in a patient with CAH.

***Keywords*:** *Congenital Adrenal Hyperplasia, Delivery, Fertility, Pregnancy*

INTRODUCTION
Congenital adrenal hyperplasia (CAH) is an inherited autosomal recessive disorder of adrenal steroidogenesis and is usually caused by 21-hydroxylase deficiency. Cortisol and less frequently aldosterone production is decreased or absent, resulting in an increased adrenocorticotropic hormone (ACTH) secretion by pituitary and consequently, excessive production of adrenal androgen and progesterone, including 17-OH-progesterone.
The clinical symptoms of CAH due to 21OHD demonstrate a wide spectrum of severity, with the most severe, classical cases diagnosed in the neonatal period due to salt-wasting and prenatal virilization in affected females, including persistence of a urogenital sinus, labioscrotal fusion and clitoromegaly. Surgery of external genitalia is required to restore a female anatomy in these girls, whereas ovaries are functional and mullerian-derived internal genital structures are normal. Thus, with proper management, fertility is possible in these patients.
CAH is a monogenic, autosomal recessive disorder (Lajic *et al.*, 2004). More than 90 percent of CAH is caused by 21-hydroxylase deficiency. The classic form generally presents at childbirth with serious virilization and/or salt wasting, however, a late onset of non-classic form of CAH is generally diagnosed at childhood or after adolescence (Lee and Oh, 1992). In classic form of CAH, glucocorticoid (often with mineral ocorticoid) treatment is required, on the other hand in the milder non-classic form, treatment is given when patients get symptoms due to hyper androgenemia such as hirsutism, oligomenorrhea, and infertility. The diagnosis of non-classic form of CAH (NCCAH) is based on increase of 17-hydroxyprogesterone, the metabolite of progesterone and precursor to cortisol, and dehydroepiandrosterone sulfate. Infertility is comparative in NCCAH, though there is a higher occurrence of spontaneous miscarriage (Moran *et al.*, 2006). NCCAH women with menstrual dysfunction respond well to adrenocortical inhibition with prednisone, and the significant improvement of menstrual regularity is frequently noted (Birnbaum and Rose, 1984). Here, we report a case of successful pregnancy and delivery in a patient with CAH.

CASES
A 25-year-old G2P0010 a diagnosed case of 21-hydroxylase deficient simple virilizing form of classic CAH visited obstetrics and gynecology department PGIMER, Chandigarh at 14 weeks from the endocrinology department for pregnancy maintenance. Her diagnosis had been identified at birth in view

of abnormal external genitalia, with a high testosterone level, raised 17-hydroxyprogesterone level, enlarged clitoris and heterozygous for V281L, 2318X and R356w (mutation test report) of CYP21A2 gene, located on chromosome 6. At the age of 5, she underwent clitoral resection and vaginoplasty at urology department of PGIMER, Chandigarh. She took prednisolone and fludrocortisone after operation. The treatment sustained without any complication. The treatment had continued and urology department referred this case to endocrinology department after surgery. She had no significant family history. She attained menarche at 12 yrs. of age, menstrual cycle were regular of 2-3 days/28 -30 days and she had excessive hair growth on face and arms for which she had to shaves every alternate day, in view of hirsutism, she started on tab novelon at age of 16 years and this was stopped after marriage. She married at age of 23 years and her husband is unaware of her disease and surgical treatment. In February 2014 she had missed abortion at 13 week of gestation, for which D/C was done. H mole was diagnosed on histopathology report for which she was under β HCG F/U till May 2014. After abortion, she again got pregnant spontaneously without any trial of assisted reproductive technology in September 2014. At 14 weeks of gestation, she first visited to our department in PGIMER, Chandigarh. The screening conducted at the first visit of 14weeks of gestation was normal and triple test conducted at 16+3 week of gestation was also normal. Ultra sonography was performed at two to four weeks. The development of foetus was appropriate to the gestational age without any sign of intrauterine growth retardation or large for gestational age. During pregnancy, she continued to take prednisolone (minimum dose 7.5 mg/day to maximum dose 20 mg/day) on demand at endocrinology department. Cesarean section was preferred, as she had cephalopelvic disproportion and history of vaginoplasty. She delivered female weighs 3.2 kg by elective cesarean section at 38+6 week of gestation. The baby exhibited normal Apgar score. The external genitalia were normal and there was normal karyotype (46, XX) in chromosomal study. After the delivery, the patient had taken prednisolone (15 mg/day) consistently for the CAH**.**

DISCUSSION

Since CAH was first described by DeCrecchio in 1865, it has academically confirmed by Wilkins *et al.,* (1951). Due to the genetic deficiency required for biosynthesis of cortisol, the creation of cortisol was decreased and the secretion of ACTH increased as the hypothalamus-pituitary axis reacts to the low level of cortisol. It induces the hyperplasia of adrenal cortex, thus, precursor and testosterone of cortisol was mass-produced and the distinctive clinical symptoms are shown (Miller and Levine, 1987). Therefore, it is cured by supplementary hormone administration (Bongiovanni and Root, 1963). It is known that 21-hydroxylase deficiency is the main cause of CAH in the rate of 90% to 95% (Lin-Su *et al.*, 2008).

CAH is divided into simple virilizing, salt-wasting, and non classical form according to clinical manifestation. Co-occurrence of synthesis disability of cortisol and aldosterone with complete enzyme deficiency is the most severe form. Untreated infants with renal salt-wasting suffer insufficient feeding, body-weight loss and dehydration which can advance to azotemia, vascular collapse, shock and death. Adrenal crises arise in the newborn period as early as one to seven weeks of life (Kuhnle *et al.,* 1986). Therefore, early diagnosis and appropriate cure should be conducted immediately after birth. Non classical CAH, occasionally called late-onset, mild, arises when there is only a mild insufficiency of enzyme 21-hydroxylase. These patients do not waste salt, and females are not virilized at birth (Temeck *et al.*, 1987). In the case of non classical 21-hydroxylase deficiency, there would be no specific abnormality at birth, but it has mild symptoms, such as menstrual irregularity, hirsutism, and infertility, around menarcheand sometimes it shows masculinization of external genitalia (Feuillan *et al.*, 1988, Levine *et al.*, 1980). Endocrine test of 21-hydroxylase deficiency suggests that the high concentration of progesterone and 17-hydroxyprogesterone in blood is significant to decide the effect of treatment because progesterone blocks the conversion to the11-deoxycortisol. The excretion of pregnanetriol and the level of androstenedione and testosterone in urine are elevated caused by the increase of 17-hydroxy progesterone. Early diagnosis and the treatment are important which gets rid of the excessive secretion of adrenocorticotropic hormone (ACTH), replenishes required hormone, and corrects external genitalia. Long-lasting glucocorticoid replacement treatment is the mainstay of therapy for CAH patients. It reduces

17-hydroxyprogesterone and adrenal androgen by normal range as glucocorticoids replacement replenishes cortisol and inhibits the secretion of ACTH**.** Since, Blizzard and Wilkins (1957) administrated cortisone for the first time, cortisol, cortisone and prednisolone have been used; however, it is known that cortisol has the most significant effects by proving stable physiological supplementing comparatively. Getting pregnant of CAH patients requires several conditions, strict keeping of steroid replacement, appropriate vaginal opening for coitus, and sufficient adrenal suppression during the attempts to get pregnant (Mulaikal *et al.,* 1987). CAH patients has lower pregnancy rate compared to normal women, however, cortisol replacement therapy enables the normal pregnancy, and moreover glucocorticoid treatment raises the pregnancy rate of non-classical CAH patients as much as the rate of normal women (Lee *et al.,* 1996). When the fetusis at risk for CAH, dexamethasone (20 μg/kg/day in 3 divided doses) is administered to the pregnant women before the ninth week of gestation, or ideally before the seventh week, blind to the sex or affected state of the fetus. This inhibits fetal hypothalamic-pituitary-adrenal axis, excess adrenal androgen secretion and prevents virilization in affected females (Merke and Bornstein, 2005). Dexamethasone is used because it crosses the placenta, crossing from the maternal to the fetal circulation**.**

Rationale for prenatal treatment idea of prenatal treatment is to treat the foetus with a glucocorticoid via the mother, in order to suppress the foetal adrenal androgen over secretion and prevent the genital malformations. The aim is to avoid or substantially reduce the need for difficult and stressful corrective genital surgery in affected females. Hydrocortisone was tried in the first case treated, but due to incomplete prevention of virilization (hydrocortisone is largely inactivated by the placenta), DEX has subsequently been used. Virilization of external genitalia by androgens occurs from 6 to 8 weeks of gestation. Thus, in order to be effective in preventing female genital virilization, treatment must begin in the early first trimester. The dose is typically 20μ/kg per day, based on pre-pregnancy maternal weight, to a maximum of 1.5 mg daily in three divided doses, beginning before the seventh week of gestation. This regimen has been shown to normalize amniotic fluid 17-hydroxy progesterone levels in CAH-affected foetuses. Prenatal diagnosis is subsequently performed and treatment is discontinued if the foetus is male or an unaffected female, whereas CAH-affected female foetuses are treated until term. Treatment is offered to women who have previously given birth to a child with severe CAH. Since CAH is an autosomal recessive disease, the risk of an affected child in these families is one in four in each pregnancy. Since only affected females will suffer from virilizing malformations, only one out of eight foetuses will benefit from the treatment. Thus, in seven out of eight cases the foetus will be treated with DEX for a few weeks in early development without any benefit of the treatment.

Conclusion

In pregnancies with an unaffected fetus, the placenta serves as a metabolic barrier to reduce fetal exposure to circulating maternal androgens. Dexamethasone has been used to reduce fetal androgen production in an affected fetus. However, as the outcome of prenatal treatment with dexamethasone is not clear it is not recommended as a routine approach. The complexity of care in women with CAH highlights the need for multidisciplinary team comprising a pediatrician, geneticist, endocrinologist, gynecologist and psychologist.

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