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SUCCESSFUL PREGNANCY OUTCOME IN PATIENT WITH CONGENITAL ADRENAL HYPERPLASIA

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Abstract

The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both. There are two forms of CAH: classic, devided into salt-waisting and simple virilizing, and non-clasic form. Fertility is relative in CAH, but the incidence of spontaneous miscarriage is higher.

We present a patient with simple virilising form of CAH and pregnancy. Our patient was admitted in the hospital in 2014 when we diagnosed simple virilisng form of CAH. She came with history of two unsuccesfull IVF's, in 2013 and 2014. Dexamethason therapy was introduced. In preparation for conception, the steroid replacement was changed to Prednisolon. There was one more IVF performed, in 2016, again without succes. Our patient concieved naturally in august 2017. The screening conducted at the first visit of 14 weeks of gestation was normal and further tests conducted at gynaecologist were also normal. During pregnancy, she continued to take prednisolone (minimum dose 7.5 mg/day to maximum dose 20 mg/day). Check ups were done each two months. She delivered female, weighs 2.9 kg by elective cesarean section at 38+1 week of gestation. The baby exhibited normal Apgar score. The external genitalia were normal. After the delivery, the patient had taken prednisolone (15 mg/day) consistently for theCAH.

Choosing the appropriate type and dose of steroid replacement is quite challenging in the treatment of women with classical CAH desiring pregnancy.Succesfull management of CAH in pregnancy requires a firm knowledge of endocrine changes that occur during gestation. From a fetal and neonatal standpoint, accurate prenatal diagnosis alows good prenatal treatment in an attept to minimize clinical problems in the neonates.

Key words: CAH, pregnancy, steroid replacement

Introduction

The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, which involves a deficiency of an enzyme needed for the synthesis of cortisol, aldosterone, or both [1-3]. It is one of the most common genetic diseases affecting approximately 1:10,000 to 1:20,000 newborns . It comprises a group of defects in adrenal steroidogenesis with subsequent cortisol deficiency caused by mutations in genes encoding one of the enzymes or cofactors for cortisol biosynthesis. Mutations in the gene CYP21A2, encoding for the enzyme 21-hydroxylase (21-OH), are by far the most common affecting more than 90% of all patients. The lack of cortisol leads to increased ACTH secretion by the pituitary, stimulating adrenal growth and thereby resulting in adrenal hyperplasia. Furthermore, it increases steroid precursor accumulation leading to adrenal androgen excess. Clinically, female patients with classic 21OHD suffer from prenatal virilisation of the external genitalia, and both sexes are at risk for life-threatening adrenal crises during their entire life. Suboptimal treatment in childhood and adolescence causes short stature and disturbance of pubertal development [1, 2, 4-6]. The phenotype of CAH clinical manifestation depends on the degree or type of gene deletion or mutation and the resultant deficiency of the steroidogenic enzyme [7-9] .Two copies of an abnormal gene are required for disease to occur, and not all mutations and partial deletions result in disease [6-9].

It can be defined as classical CAH (C-CAH), or nonclassical or late-onset CAH (NC-CAH). C-CAH can be of either the salt wasting (SW) or simple virilizing (SV) type. NC-CAH 21-OH deficiency is much more common than C-CAH (10), with a reported prevalence of 0.1–0.4% in the general population

[11]. It is also more frequent in ethnicities such as Ashkenazi Jewish, Mediterranean, Middle-Eastern, and Indian populations [12].

Main clinical presentation, especially at C-CAH is genital anomalies, which ranges from complete fusion of the labioscrotal folds and a phallic urethra to clitoromegaly, partial fusion of the labioscrotal folds, or both up to precocious pubic hair, clitoromegaly with shallow vagina, or both, accompanied by accelerated growth and skeletal maturation (Fig.1), [1,2,6,9]. The other important clinical presentation is with oligomenorrhea, hirsutism, and/or infertility[4]. Treatment usually includes supplying enough glucocorticoids to reduce hyperplasia and overproduction of androgens or mineralocorticoids and providing replacement estrogen [4,8]. Females with ambiguous genitalia require surgical evaluation and, if needed, plan for corrective surgery. With adequate medical and surgical therapy, the prognosis is good, however, infertility is common [4,8,13,14].

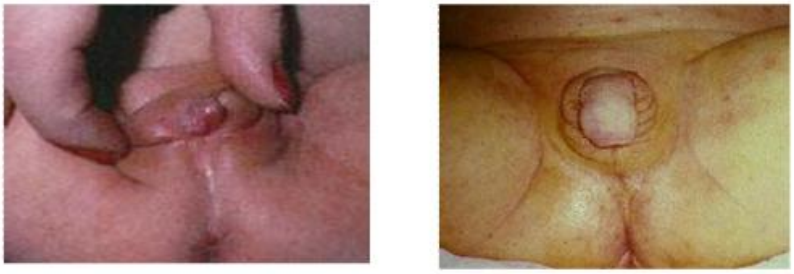

Figure 1. Severe virilization in two female patients with the 46,XX karyotype with congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency

Traditionally, reduced fertility and pregnancy rates have been reported in women with classic CAH. Fertility rates of 60-80% and 7-60% have been reported in women with classic SV and classic SW CAH, respectively [15]. In contrast to reduced fertility in classic CAH, pregnancies are commonly normal and uneventful. Thus, fertility rather than pregnancy rates seem to be reduced compared to the general population[16,17]. Fertility is only mildly reduced in NC CAH, and seems to be mainly due to hormonal imbalance. However, without glucocorticoid treatment, an increased miscarriage rate has been reported [18-20]. More recent reports show significant increase in fertility rates, even among patients with classic CAH, possibly as a result of earlier treatment of CAH, improved compliance with therapy and surgical advances in genital reconstruction[17].

Case report

A 36 years old female patient was admitted in the hospital due to irregular periods, oligomenorrhea, hirsutism, and infertility. Gynaecologist has been consulted for the first time in 2006 and diagnosis, at that time, has been settled : Sterilitas primaria, CAH-late onset. Corticotherapy has been administered for short period of time followed by contraceptive pills. IVF was done in 2013 and 2014 - no success. Noncompliance and deviation from the hydrocortisone dosage was noticed in different periods of adult life and there was a period of 6-8 years when she was lost to follow-up.

At admission in our hospital, in March 2015, physical examination revealed that her body mass index (BMI) was 26 kg/m^2. Clinical investigation showed excessive hair growth (male pattern with significant virilization with male distribution of body hair, a strong beard requesting daily shaving, male bodily features, breast hypoplasia, a prominent Adams' apple and a deep voice. Ferriman-Gallwey score was 22. Laboratory analyses revealed free testosteron 14,21 mmol/l, DHEA-S 8.55 mikromol/l, androstenedion 6,0 ng/ml, cortisol 805 nmol/l, ACTH 45 pg/ml, 17 hydroxiprogesterone 29 ng/ml, insulinemia 24,5 mikroU/ml, glycaemia 6,1 mmol, HOMA-IR 6,64. There was no pathology on pelvic

ultrasonography. A CT scan of abdomen was performed - bilateral hypertrophy and oval focal lesion on left suprarenal gland. Molecular genetic analysis revealed pathologic mutations that contribute to 21-OH deficiency arise as a consequence of unequal crossover – P30L I172N, i.e. she was compound heterozygotes with different mutations on each chromosome (one severe, I172N, and one mild, P30L). Definite diagnosis was: simple virilizing form of C-CAH. Dexamethason therapy was introduced, but there was still no satisfactory complience. After the decision to concieve, the therapy was regularly taken, but with a modest result. In preparation for conception, the steroid replacement was changed to Prednisolon. There was one more IVS performed, in 2016, again without succes. Sufficient folicules were harvested and fertilized, however, the embryos were lost 3-5 days after implantations.

Our patient concieved spontaneously in august 2017,at her almost 40 years of age. The screening conducted at the first visit of 14 weeks of gestation was normal and triple test conducted at 16+3 week of gestation was also normal. Ultra sonography was performed. 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 15 mg/day). She was followed-up in two months interval, titrating prednisolone dose.

Cesarean section was preferred, as she had cephalopelvic disproportion and history of vaginoplasty. She delivered female weighs 2.9 kg by elective cesarean section at 38+1 week of gestation. The baby exhibited normal Apgar score (9/10). 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

Once pregnancy is achieved, new issues regarding management during pregnancy arise. Rationale for 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. Maternal clinical status should be assessed regularly during gestation to determine the need for increased glucocorticoid or mineralocorticoid therapy. Excessive nausea, vomiting, salt craving, and poor weight gain may indicate adrenal insufficiency. In our patient there was mild nausea at the beginning of the pregnancy, without glucocorticoid or electrolte dysbalance. Blood glucose should be monitored because gestational diabetes may be more frequent among pregnant women with CAH [21]. Insulinemia, glycaemia and glicated hemoglobin were followed every two months. Basal insulinemia was increased as the pregnancy went on, but decreased insulin sensitivity is normal in the third trimestar, while glycaemia and glicated hemoglobin were in reference range. Maternal hormone levels should be evaluated in the context of laboratory-specific reference ranges for pregnancy [22]. Free testosterone levels should be targeted to the high normal range for pregnancy. Glucocorticoid replacement should consist of either prednisolone or hydrocortisone because dexamethasone is not inactivated by placental 11 β-hydroxysteroid dehydrogenase type II and therefore can cause fetal adrenal suppression and low birthweight [21]. In our patient swich from dexamethason to prednisolon was made before pregnancy. During labor and delivery, the mother should receive increased doses of hydrocortisone, as in distressing situations [21,23,24,25]. Elective caesarean section should be considered especially for those who have had reconstructive surgery of external genitalia. Women with CAH often have android pelvis characteristics increasing risk for cephalo-pelvic disproportion and dystocia [21,23]. In our patient, Cesarean section was performed, due to vaginoplasty and cephalo-pelvic disproportion, without need of extra glucocorticoid add-on.

Although there have been few reports of masculinization of external genitalia, this problem seems to be very rare, and girls born to women with CAH are generally unaffected. In fact, the placenta serves as a metabolic barrier and reduces fetal exposure to maternal androgens through placental aromatization of maternal testosterone and androstenedione. Other maternal factors that can contribute to fetal protection include a reduction in bioavailable testosterone due to increased sex hormone-binding globulin

levels and the potential anti- androgenic effects of progesterone(21,26). In our case, there was completely normal baby girl born, with normal external genitalia.

Conclusion

Choosing the appropriate type and dose of steroid replacement is quite challenging in the treatment of women with classical CAH desiring pregnancy. Succesfull management of CAH before and during pregnancy requires a firm knowledge of endocrine changes that occur during gestation. From a fetal and neonatal standpoint, accurate prenatal diagnosis alows good prenatal treatment in an attept to minimize clinical problems in the neonates.

References:

1. Al-Agha, A., A. Ocheltree, and M. Al-Tamimi, Association between genotype, clinical presentation, and severity of congenital adrenal hyperplasia: a review. The Turkish Journal of Pediatrics 2012; 54:323-32.
2. Alka, K., et al., A Success Story in Congenital Adrenal Hyperplasia. The Journal of Obstetrics and Gynecology of India 2012; 62(S1):S78-S80.
3. Mula-Abed, W., et al., Congenital Adrenal Hyperplasia due to 17-alpha-hydoxylase/17,20-lyase Deficiency Presenting with Hypertension and Pseudohermaphroditism: First Case Report from Oman. Oman Medical Journal 2013; 29(1):55-9.
4. Mnif, M.F., et al., Reproductive outcomes of female patients with congenital adrenal hyperplasia due to 21-hydroxylase defi ciency. Indian Journal of Endocrinology and Metabolism 2013; 17(5):790-3.
5. Belinda, G., et al., Congenital adrenal hyperplasia - experience from a tertiary centre in South India. Indian Journal of Endocrinology and Metabolism 2012; 16(Suppl 2):S385–S386.
6. Koh, J., et al., Clinical Features of Congenital Adrenal Insufficiency Including Growth Patterns and Significance of ACTH Stimulation Test. Journal of Korean Medical Science 2013; 28: 1650-6.
7. Binay, C., et al., Prevalence of Nonclassic Congenital Adrenal Hyperplasia in Turkish Children Presenting with Premature Pubarche, Hirsutism, or Oligomenorrhoea. International Journal of Endocrinology 2014; 2014:1-7.
8. Mahdi Kamoun, M.M.F., Mohamed Habib Sfar, and Mohamed Abid, Congenital adrenal hyperplasia: Treatment and outcomes. Indian Journal of Endocrinology and Metabolism 2013; 17(Suppl1):S14-S17.
9. Piaggio, L.,et al. Congenital adrenal hyperplasia: review from a surgeon's perspective in the beginning of the twenty-first century. Frontiers in Pediatrics 2014; 1(50):1-7.
10. O. Lekarev and M. I. New Adrenal disease in pregnancy- Best Practice and Research: Clinical Endocrinology and Metabolism 2011;(25)6:959–973.
11. Pinkas, S. Fuchs, Y. Klipper-Aurbach et al., Non-classical 21-hydroxylase deficiency: prevalence in males with unexplained abnormal sperm analysis,"Fertility and Sterility 2010; (93)6:1887–1891.
12. R. C. Wilson, S. Nimkarn, M. Dumic et al., "Ethnic-specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency," Molecular Genetics and Metabolism 2007(90)4:414–421.
13. Seyam, R., et al., Long-term outcome of genital reconstruction of Middle Eastern women with congenital adrenal hyperplasia. Urology Annals 2013:5(4):277-82.
14. Trapp, C. and S. Oberfield, Recommendations for Treatment of Nonclassic Congenital Adrenal Hyperplasia (NCCAH): an Update. Steroids 2012; 77(4):342-6.
15. Mulaikal RM, Migeon CJ, Rock JA. Fertility rates in female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. N Engl J Med 1987;316:178-82.

16. Casteràs A, De Silva P, Rumsby G, Conway GS. Reassessing fecundity in women with classical congenital adrenal hyperplasia (CAH): Normal pregnancy rate but reduced fertility rate. Clin Endocrinol (Oxf) 2009;70:833-7.
17. Reisch N, Arlt W, Krone N. Health problems in congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Horm Res Paediatr 2011;76:73-85.
18. Moran C, Azziz R, Weintrob N, Witchel SF, Rohmer V, Dewailly D, *et al*. Reproductive outcome of women with 21-hydroxylase-deficient nonclassic adrenal hyperplasia. J Clin Endocrinol Metab 2006;91:3451-6.
19. Bidet M, Bellanné-Chantelot C, Galand-Portier MB, Golmard JL, Tardy V, Morel Y, *et al*. Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 2010;95:1182-90.
20. Witchel SF. Nonclassic congenital adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes 2012;19:151-8.
21. Witchel SF. Management of CAH during pregnancy: Optimizing outcomes. Curr Opin Endocrinol Diabetes Obes 2012;19:489-96.
22. Lo JC, Grumbach MM. Pregnancy outcomes in women with congenital virilizing adrenal hyperplasia. Endocrinol Metab Clin North Am 2001;30:207-29.
23. Ogilvie CM, Crouch NS, Rumsby G, Creighton SM, Liao LM, Conway GS. Congenital adrenal hyperplasia in adults: A review of medical, surgical and psychological issues. Clin Endocrinol (Oxf) 2006;64:2-11.
24. Ambroziak U, Bednarczuk T, Ginalska-Malinowska M, Ma³unowicz EM, Grzechociñska B, Kamiñski P, et al. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency-management in adults. Endokrynol Pol 2010;61:142-55.
25. Merke DP. Approach to the adult with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 2008;93:653-60.
26. Johannsen TH, Ripa CP, Mortensen EL, Main KM. Quality of life in 70 women with disorders of sex development. Eur J Endocrinol 2006;155:877-85.