

Reproductive outcomes of female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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ABSTRACT

Fertility in women with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) appears to be reduced, especially in women with the classic salt-wasting type. Several factors have been suggested to contribute to this subfertility such as androgen excess, adrenal progesterone hypersecretion, consequences of genital reconstructive surgery, secondary polycystic ovaries syndrome, and psychosexual factors. In contrast to this subfertility, pregnancies are commonly normal and uneventful. Adequate glucocorticoid therapy and improvement of surgical and psychological management could contribute to optimize fertility in CAH female patients, even among women with the classic variant. This review provides current information regarding the reproductive outcomes of women with CAH due to 21-OHD and the fertility and pregnancy issues in this population.

Key words: Congenital adrenal hyperplasia, fertility, 21-hydroxylase deficiency, pregnancy

INTRODUCTION

Congenital adrenal hyperplasia (CAH) refers to a group of inherited autosomal recessive disorders that cause a deficiency in an adrenal enzyme resulting in altered cortisol and aldosterone synthesis. The loss of negative feedback inhibition by cortisol leads to increased hypothalamic-pituitary-adrenal axis activity, and subsequent hyperplasia of the adrenal gland. The most frequent CAH variant, accounting for 95% of all affected patients, is 21-hydroxylase deficiency (21-OHD) and due to mutations in the CYP21A2 gene.^[1]

Different forms are recognized in CAH due to 21-OHD:

Classic CAH, the most severe form comprises both salt-wasting (SW) and simple virilizing (SV) forms, and the non-classic (NC) form which may be asymptomatic or associated with signs of postnatal or even adult onset androgen excess. The classic form has a frequency of about one in 10.000 to one in 15.000 in the general population, whereas the NC form is more common with an estimated incidence of about one in 1.000.^[1]

With the availability of glucocorticoid replacement allowing patients to reach adulthood, recent attention has been paid towards long-term health problems such as fertility. Several lines of evidence indicate that fertility rate in women with CAH is reduced, especially in the SW variant of classic CAH. Several factors have been suggested to contribute to this low fertility.^[2-5]

This review provides current information regarding the reproductive outcomes of women with CAH due to 21-OHD and the fertility and pregnancy issues in this population.

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REPORTED FERTILITY AND PREGNANCY RATES IN CONGENITAL ADRENAL HYPERPLASIA FEMALES

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.^[6] 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.^[7,8]

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.^[9-11]

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.^[8]

CAUSES OF SUBFERTILITY IN WOMEN WITH CONGENITAL ADRENAL HYPERPLASIA

Subfertility in females with classic CAH is due to several contributing factors, including androgen excess, adrenal progesterone hypersecretion, consequences of genital reconstructive surgery, secondary polycystic ovaries syndrome, ovarian adrenal rest tumors, and psychosexual factors.^[2,3,8,12]

ANDROGEN EXCESS

Androgen excess is believed to be one of the major factors responsible for poor fertility outcomes in females with CAH. Tonic oversecretion of androgens (partly aromatized to estrogens) results in continuous steroidal feedback and thus, loss of gonadotropin cyclicality, leading to anovulation or dysovulation. Adrenal androgens may also directly inhibit folliculogenesis by a negative effect on aromatase activity in granulosa cells.^[10] Maintaining adequate adrenal androgen suppression can restore regular menstrual cycles in nearly all women with NC 21-OHD, but this is not the case for women with classic variant.^[10,13]

ADRENAL PROGESTERONE HYPERSECRETION

The elevated concentrations of progesterone in the follicular phase may have a minipill-like effect on the endometrium leading to anovulatory cycles. Several deleterious effects of progesterone hypersecretion were suggested. It could affect the quality of cervical mucus

and sperm penetration, accelerate endometrial maturation, decrease endometrial receptivity, impair implantation and also could have adverse effects on oocyte quality.^[14] Even good suppression of 17 α -hydroxyprogesterone does not always affect progesterone elevation.^[15] Adrenalectomy has been successfully used in single cases to normalize progesterone concentrations and resulted in spontaneous conception.^[7] However, this procedure bears a number of risks, including surgical and anesthetic complications and leaves the patient completely adrenal insufficient.^[16]

SECONDARY POLYCYSTIC OVARIES SYNDROME

Because of the virilizing effects of androgens overproduction, affected girls may present with hirsutism, androgenic alopecia, oligomenorrhoea or amenorrhoea.^[17] Ultrasonic features of polycystic ovaries are a common finding in mild and classic CAH.^[18] Polycystic ovaries syndrome, as defined by the Rotterdam criteria is common in CAH patients and could contribute to infertility.^[17-19]

Several factors appear to promote the development of this syndrome. Androgen excess impairs hypothalamic sensitivity to progesterone, resulting in a persistently rapid gonadotropin releasing hormone pulse frequency and subsequent luteinizing hormone (LH) hypersecretion. In addition, prenatal excess androgen exposure could program the hypothalamic pituitary axis for hypersecretion of LH contributing thus to ovarian hyperandrogenism.^[18,20]

CONSEQUENCES OF GENITAL RECONSTRUCTIVE SURGERY

Genital surgery may result in sexual dissatisfaction. In the CAH adult study executive follow-up, 46% of the women reported being unhappy about their sex life.^[21] A cross-sectional study of 24 adult women with classic CAH who had undergone genital surgery showed that there was significant impairment to clitoral sensation compared to unaffected controls and CAH women who had not undergone genital surgery.^[22] Vaginal stenosis, poor cosmesis, anorgasmia, and painful intercourse were also reported.^[22] Diminution or loss of erotic sensitivity and orgasmic capacity due to clitoroplasty are thought to be more severe after clitorectomy than after new techniques which preserve innervation and clitoral sensation. Long-term results from patients who have undergone new operative methods are lacking to date, as few of these patients have reached sexual maturity. However, short-term results are promising both cosmetically and functionally.^[23]

OVARIAN ADRENAL REST TUMORS

In males with CAH, testicular adrenal rests are relatively common, and are thought to be associated with impaired fertility. In CAH females, ovarian adrenal rest tissue (OART) is extremely rare, with only three cases reported until now.^[24-26] OART is difficult to identify with commonly used imaging modalities. It is therefore unknown if presence of OART actually attributes to negative fertility outcomes in CAH females.

PSYCHOSEXUAL FACTORS

Psychosexual factors may also play a role in the overall reduction in childbirth rates in classic 21-OHD.^[27] In childhood, girls with CAH have more masculine and less feminine interests regarding toys, sports and playmates, and are more likely to use physical aggression in conflict situations.^[27,28] This masculinized behavior, being most pronounced in SW CAH, has been attributed to the effects of the prenatal exposure to high androgen levels leading to masculinization of the female fetal brain.^[29] In adulthood, females with 21-OHD have often a disturbed body image, less favorable sexual self-image, less partnership and marriage and reduced heterosexual activity.^[30] Adult women with CAH have also been demonstrated to have higher anxiety and depression scores compared to control groups.^[31]

For the majority of the adult women with CAH, gender identity was clearly female, and gender dysphoria seems to be very rare. Thus, prenatal androgenization affects typically gender-related behavior and not gender identity.^[32] In addition, most of these patients report a heterosexual orientation, but there is an increased rate of homosexual and bisexual orientation compared with unaffected women. An increased rate of non-heterosexual orientation, compared with controls, was also seen among women with the NC variant of CAH.^[33]

PREGNANCY OUTCOME IN WOMEN WITH CONGENITAL ADRENAL HYPERPLASIA

Once pregnancy is achieved, new issues regarding management during pregnancy arise.^[18] 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.^[18] Blood glucose should be monitored because gestational diabetes may be more frequent among pregnant women with CAH.^[18] Maternal hormone levels should be evaluated in the context of laboratory-specific reference ranges for pregnancy.^[34]

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.^[18] During labor and delivery, the mother should receive increased doses of hydrocortisone, as in distressing situations.^[2,3,13,18]

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.^[2,18]

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.^[2,31]

FERTILITY PRESERVATION IN WOMEN WITH CONGENITAL ADRENAL HYPERPLASIA

Prevention of subfertility requires a multidisciplinary approach. Subfertility in CAH women can have its origin already in the peripubertal years and is therefore of interest to the pediatric endocrinologist. Continued monitoring of hormone balance and careful readjustment of glucocorticoid dose are necessary to obtain regular ovulatory cycles and optimize fertility.^[35,36] Furthermore, ovulation induction and assisted reproductive techniques are now available to women who remain infertile despite effective adrenal androgen suppression.^[34]

CONCLUSION

The reasons for reduced fertility in women with CAH are various and include biological, social and psychosexual factors. Prevention of subfertility requires a multidisciplinary approach from infancy through adulthood. Adequate glucocorticoid therapy and improvement of surgical and psychological management could contribute to improve fertility rates in women patients with CAH, even among those with the classic variant. With careful individualized management, women with CAH can become pregnant.

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