Fertility in Patients with Congenital Adrenal Hyperplasia

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is generally regarded as a paediatric endocrine disease, but nowadays nearly all patients reach adulthood as a result of improved diagnosis and treatment. It is now increasingly recognised that treatment goals shift during life: one of the major treatment goals in childhood and puberty, i.e. normal growth and development, is no longer relevant after childhood, whereas other aspects, such as fertility and side effects of long-term glucocorticoid treatment, become more important in adulthood. This paper focuses on fertility in male and female adult patients with CAH. In males with CAH the fertility rate is reduced compared with the normal population, the most frequent cause being testicular adrenal rest tumours. Development and growth of these tumours is assumed to be ACTH dependent and undertreatment may play an important role. If intensifying glucocorticoid treatment does not lead to tumour decrease, surgical intervention may be considered, but the effect on fertility is not yet known. In females with CAH the degree of fertility depends on the phenotype of the CAH. Most fertility problems are seen in the classic salt-wasting type. Age of menarche and regularity of the menstrual cycle depends on the degree of adrenal suppression. Not only adrenal androgens have to be normalised but also the levels of adrenal progestins (progesterone and 17-OH-progesterone) that interfere with normal ovulatory cycles. The regularity of menstrual cycles can be considered as an important measure of therapeutic control in adolescent females with CAH and therefore as a therapeutic goal from (peri)pubertal years on. Other factors that contribute to impaired fertility in females with CAH are ovarian hyperandrogenism (polycystic ovary syndrome), ovarian adrenal rest tumours, genital surgery and psychological factors. Subfertility in CAH can have its origin already in the peripubertal years and is therefore of interest to the paediatric endocrinologist.

KEY WORDS
congenital adrenal hyperplasia, fertility

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a disorder of adrenal steroid synthesis. In 95\% of cases, it is caused by 21-hydroxylase deficiency, leading to cortisol deficiency and (in most cases) aldosterone deficiency. The compensatory increase in adrenocorticotropic (ACTH) secretion by the pituitary gland leads to stimulation of the adrenals and, consequently, overproduction of androgens. The phenotype of 21-hydroxylase deficiency depends on the degree of enzyme deficiency. Complete 21-hydroxylase deficiency leads to the classic salt-wasting form with congenital virilization in females. Less severe 21-hydroxylase deficiency results in the classic simple virilizing form without aldosterone deficiency. Patients with the mildest form, the late onset form of CAH, present with symptoms caused by androgen excess only: pseudoprecocious puberty, hirsutism, menstrual irregularities and infertility\textsuperscript{1}. 

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Treatment of 21-hydroxylase deficiency consists of glucocorticoid supplementation and in case of aldosterone deficiency also mineralocorticoid supplementation.

In the past, CAH was generally regarded as a paediatric endocrine disease, but nowadays nearly all patients reach adulthood as a result of improved diagnosis and treatment. Thus, the spectrum of CAH as a lifelong chronic disease becomes gradually clear, and it is increasingly recognised that treatment goals shift during life: the major treatment goals in childhood and puberty, i.e. normal growth and development, are no longer relevant after childhood, whereas other aspects, such as fertility and the side effects of long-term glucocorticoid treatment, become more important in adulthood. In this paper we focus on fertility in adult male and female patients with CAH.

**FERTILITY IN MALE PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA**

There is evidence that fertility is impaired in males with CAH. Jääskeläinen *et al.* found a significantly lower child rate (0.07) in 16 male patients with CAH compared with an age matched Finnish male control group (0.34). Other studies report child rate only as additional information in selected patient populations. An alternative method to investigate fertility in men is semen analysis. Wuesthof *et al.* reported normal semen analysis in only 34% of 53 males with CAH. Cabrera *et al.* reported abnormal semen analysis in 46% of 16 investigated patients. In our own series, only four of 11 men with CAH had a normal sperm count. However, not all patients are willing to collect semen for analysis. Measurement of serum follicle stimulating hormone (FSH) and inhibin B levels is also used to assess fertility in men with CAH. Several studies report abnormal FSH levels, indicating Sertoli cell damage. However, it should be noted that in CAH patients with primary testicular damage, serum gonadotropin levels might be suppressed due to high levels of adrenal androgens. Most of these patients also have serum testosterone levels within the normal range, which is the result of conversion of adrenal androgens to testosterone. In this situation a more reliable predictor of testicular damage is the serum inhibin B level, which reflects Sertoli cell function.

The most important cause of infertility in men with CAH is the presence of testicular tumours resulting in primary gonadal failure. Another important factor contributing to infertility is the suppression of the hypothalamic-pituitary-gonadal axis due to high circulating levels of androgens resulting in secondary gonadal failure.

**Testicular adrenal rest tumours**

Testicular tumours in male patients with CAH are thought to arise from aberrant adrenal cells in the testes that are stimulated by ACTH. Therefore they are called testicular adrenal rest tumours. Testicular adrenal rest tumours have also been described in other conditions with high plasma ACTH levels, such as Nelson's syndrome or Addison's disease. However, testicular tumours are also found in well-controlled patients with CAH, with normal or suppressed ACTH. The reported prevalence of testicular adrenal rest tumours in males varies between 0% and 94%, depending on the selection of the patients and the method of detection. In our own series, one or more testicular tumours were found in 16 of 17 patients (age 16-40 years). Ultrasound seems to be the best method for detection and follow up, especially in the case of small non-palpable tumours. Testicular tumours have also been reported in patients under the age of 16 years. We now routinely follow our male children with CAH (n = 25; age 6-19 years) with ultrasound and detected seven boys with small, mostly non-palpable tumours, the youngest patient being 7 years old (unpublished data). The testicular tumours, which are always located in the mediastinum testis, can lead to obstruction of the vascular supply and compression and atrophy of the seminiferous tubules. In addition to these mechanical effects, steroids produced by the tumours could be toxic to testicular tissue (paracrine effect) therefore contributing to testicular failure. These two factors result in primary gonadal failure with elevated gonadotropin levels and low inhibin B levels. Therefore treatment or prevention of the development of testicular tumours is an important goal.
Poor hormonal control with inadequate suppression of ACTH may be a main factor in the aetiology of testicular tumours. By increasing the glucocorticoid dose, ACTH secretion is suppressed and the adrenal rest tissue is no longer stimulated, which may lead to testicular tumour shrinkage. The need for tumour shrinkage and the side effects of increasing glucocorticoid therapy must be carefully balanced, especially in asymptomatic patients. The effect of medical treatment is described mostly in case reports or in small patient groups and the results vary dependent on patient selection, type of CAH and treatment choice. Rutgers et al. reported tumour shrinkage in 75% of 16 patients after increasing the glucocorticoid dose. Walker et al. reviewed 75 cases of testicular tumours in CAH and stated that the majority of the masses regressed with an increase in glucocorticoid dose. Rich et al. reported testicular tumours in three young patients (5, 15 and 17 years old). Intensifying the glucocorticoid therapy resulted in normalising the elevated steroid levels in all patients. However, in no case were the tumours resolved, and there was partial regression in only one patient. In our own study population we also found unpredictable results: tumour decrease was found in six of the 15 male patients with CAH after intensifying glucocorticoid therapy, but tumour decrease was also seen in one patient with undertreatment. Tumour increase was also seen in patients with adequate treatment. Use of dexamethasone instead of hydrocortisone in the night resulted in better adrenal suppression in only one of our patients. Therefore general guidelines for glucocorticoid strategies cannot be given, and the decision for dose and timing of glucocorticoid treatment has to be made individually in all patients, with special attention to side effects.

If tumour size does not decrease with increasing glucocorticoid therapy or if there is persistent azoospermia despite tumour shrinkage, surgical intervention may be considered. In the past orchiectomy was performed. However the malignant potential of these tumours is negligible. Walker et al. performed testis sparing surgery in three patients with CAH. Postoperatively there was good vascular flow and no recurrence of the tumour. However investigations to assess fertility were not performed. Tiryaki et al. reported two male CAH patients with steroid unresponsive testicular tumours who were also treated by testis sparing tumour enucleation. Again no data about fertility before and after operation were reported. Because fertility prognosis in CAH males with testicular tumours remains uncertain, cryopreservation of semen could be proposed to young adult male patients. In case of unwanted infertility, assisted reproduction could be considered. When there is obstructive azoospermia, testicular aspiration and intracytoplasmatic sperm injection may offer a solution. At least in some cases deterioration of fertility by testicular tumour growth can be prevented by early increase of glucocorticoid therapy. Furthermore, early testis sparing surgery as soon as testicular tumours are detected has the potential to prevent damage to the testicular tissue. Therefore it may be that detection of the tumours by ultrasonography at an early stage (prepubertal) is useful. However, further investigations are necessary to support this hypothesis.

**Hypogonadotropic hypogonadism**

In poorly controlled patients with CAH the elevated ACTH levels induce high levels of androstenedione, which is partly aromatised to oestrone. These high levels of androgens and oestrone will suppress the hypothalamic-pituitary-gonadal axis, leading to hypogonadotropic hypogonadism and small testes. It may be that steroids produced by testicular adrenal rest tumours contribute to the suppression of the hypothalamic-pituitary-gonadal axis. However this effect cannot be separated from the effects resulting from adrenal androgen excess. Hypogonadotropic hypogonadism may also occur in males with previously undiagnosed late onset 21-hydroxylase deficiency. In this condition adrenal rest tumours are not a common finding. Most reports show reversible hypogonadism and improved fertility after initiating or increasing glucocorticoid therapy.
FERTILITY IN WOMEN WITH CONGENITAL ADRENAL HYPERPLASIA

In women with CAH due to 21-hydroxylase deficiency, fertility seems to be reduced, based on reports of decreased pregnancy rates, decreased live-birth rates and menstrual disorders. Most reports about pregnancies in female patients with classic 21-hydroxylase deficiency are case studies. There are only a few reports providing pregnancy rates or live-birth rates in large populations of patients with CAH: the live-birth rate in patients with classic salt-wasting CAH is 0-10% (n = 64), in simple virilizing patients 33-50% (n = 83) and in non-classic patients 63-90% (n = 18). In the general population or in age-matched controls, pregnancy rates or live-birth rates are 65-91%. Thus, compared with a non-CAH female population, pregnancy and live-birth rates are severely reduced in patients with salt-wasting CAH, mildly reduced in patients with simple virilizing CAH, and normal in patients with non-classic CAH. Pregnancy outcomes in women with classic CAH have been reviewed by Lo and Grumbach. They found 105 reported pregnancies in 73 women with CAH (20 salt-wasting patients, 53 simple virilizing patients), resulting in 74 live-born children. Of these 105 pregnancies, 11 (10%) led to spontaneous abortion and 11 (10%) were electively terminated.

Data on fertility in patients with non-classic 21-hydroxylase deficiency are predominantly derived from studies in patients in whom the diagnosis of CAH was made after they had presented with subfertility and/or other symptoms of hyperandrogenism. As a result, these fertility data represent only the symptomatic subset of the non-classic CAH population, and this introduces substantial bias. It has become clear that the prevalence of non-classic CAH is relatively high, but when the disease is mild, patients may never come to clinical presentation. In two reports on fertility in non-classic patients presenting with subfertility, the corrected pregnancy rate was 93% and 100%, spontaneously or after glucocorticoid treatment (with or without clomiphene citrate).

Instead of pregnancy rates and live-birth rates as direct markers of fertility, regularity of menstrual cycles can be used as an indirect marker of fertility, particularly in adolescent girls. In most reports, a normal mean age of menarche was observed in girls with CAH, but these data are misleading because by definition only the patients who did experience menarche were included. In women with CAH, delayed menarche can be associated with poor therapeutic control. Menstrual irregularity in women with CAH has also been associated with poor therapeutic control and in non-classical CAH, menstrual irregularity is typically one of the presenting signs.

Several factors have been suggested to contribute to impaired fertility in females with CAH: adrenal overproduction of androgens and progestins (17-hydroxyprogesterone and progesterone), ovarian hyperandrogenism (polycystic ovary syndrome), ovarian adrenal rest tumours, genital surgery, and psychological factors such as delayed psychosexual development, reduced sexual activity and low maternal feelings.

Adrenal overproduction of androgens and progestins

Androgen overproduction by the adrenal gland can directly and indirectly affect ovarian activity. Directly, androgen excess inhibits ovarian folliculogenesis. The hypothesis that androgen excess has a negative (direct and/or indirect) effect on ovulation is supported by the finding that suppression of adrenal androgen secretion by increasing the glucocorticoid dose can restore ovulation in patients with CAH. However, in some patients adequate suppression of androgen levels was not sufficient to correct menstrual abnormalities. In these patients, increased levels of progestins (progesterone and 17-hydroxyprogesterone) as a result of adrenal overproduction interfered with normal menstrual cycles.

Elevated progestin levels may cause persistent inhibition of follicular growth, inhibition of endometrial proliferation and failure of endometrial breakdown, resulting in menstrual disorders. In addition, even if regular ovulation and menstruation is achieved, elevated progesterone levels from adrenal origin can still prevent conception in women with CAH, by causing involution of the endometrium and impermeability of the cervical mucus.
Thus, adequate suppression of adrenal androgens and progestins is needed for menarche and regular menstrual cycles. In reverse, the regularity of menstrual cycles can be considered as a measure of therapeutic control in females with CAH and should be aimed at from pubertal years on.

**Hypogonadotropic hypogonadism**

Similar to male patients with CAH, oversecretion of androgens, which are mostly aromatized to oestrone, can result in hypogonadotropism, contributing to anovulation or dysovulation. Adequate suppression of androgens can help to restore gonadotrophin cyclicity and therefore regular menstrual cycles. However, in contrast to the experience in male patients with CAH, these findings are rare in female patients\(^46,47\).

**Polycystic ovarian syndrome (PCOS)**

PCOS is characterized by ovulatory dysfunction and hyperandrogenism with irregular menstrual cycles, hirsutism and acne, leading to subfertility. In the classic form polycystic ovariies are detected. The pathogenesis of PCOS is still uncertain but there is evidence that the androgens result from ovarian overproduction\(^48\). Female patients with CAH with poor hormonal control as well as untreated women with the non-classic form of CAH can have a similar clinical presentation, including sonographic evidence of ovarian cysts resulting from adrenal hyperandrogenism. In both conditions significantly elevated levels of androgens, 17-hydroxyprogesterone and insulin insensitivity have been described\(^49-52\). So the distinction between these two conditions can be difficult. Differentiation can be made upon post-ACTH rise in 17-hydroxyprogesterone and molecular analysis\(^52,53\). Because PCOS is associated with reduced fertility\(^54\) it is suggested that the presence of PCOS in patients with CAH can be an additional factor in the mechanism of subfertility in women with CAH\(^1,55\). Stikkelbroeck et al. investigated the prevalence of PCOS in 13 female patients with CAH. Polycystic ovaries were found in two patients (15.4%) reflecting a prevalence corresponding to the general population\(^56\). Therefore it is unlikely that PCOS is a frequent cause of infertility in women with CAH.

**Ovarian adrenal rest tumours**

In contrast to the high prevalence of testicular tumours in male patients with CAH, ovarian adrenal rest tumours have been described only in case reports\(^57,59\). In our own study of 13 women with CAH, no ovarian adrenal rest tumours could be detected either by ultrasonography or by magnetic resonance imaging (MRI), which suggests that ovarian adrenal tumours are rare and do not frequently contribute to female subfertility\(^56\). Therefore routine ovarian imaging in these patients is not indicated.

**Genital surgery**

Besides the endocrine factors described above, the effects of genital surgery in early life also play an important role in impaired fertility in women with CAH. Surgical reconstruction of ambiguous genitalia in 46,XX neonates consists of reduction of clitoral size, creation of labia minora and exteriorisation of the vagina, thereby creating a functional vagina to allow menstruation and sexual activity\(^60,61\). The most important factors related to surgery that can interfere with sexual disturbance are loss of clitoral sensitivity, intravaginal stenosis and disturbed vaginal arousal\(^62\). In the past in female neonates with clitoromegaly, clitoridectomy was performed with loss of sensitivity due to damage to the neurovascular supply. Currently the preferred technique is clitoroplasty with excision of the erectile tissue preserving the neurovascular supply to the glans\(^63\). However, recent data show that there is still abnormal clitoral sensation even after optimising the surgical technique\(^62\). The incidence of vaginal stenosis after surgery varies dependent on the type of operation\(^64,65\). In the past stenosis was reported in up to 77%\(^61\). Krege et al. reported vaginal stenosis in 36% of patients, with a requirement for additional treatment (manual dilatation, secondary vaginoplasty)\(^66\). Therefore modern surgical techniques performed by experienced surgeons can improve the functional results of the surgery.
Psychosexual factors

Several studies show gender atypical behaviour in female patients with CAH. It is suggested that biological and social factors contribute to the development of gender identity disorders in these patients. Pre- and postnatal exposure to androgens can cause gender atypical behaviour resulting in more boyish behaviour, such as preference for male typical toys and admiration for male characters. Furthermore, significantly less satisfaction with the female sex of assignment is reported. However, social factors can also influence the development of gender identity, such as inability of parents to accept the sex assignment. These gender identity disorders can contribute to subfertility in female patients with CAH. There is controversy about the rate of bisexuality or homosexuality. Other psycho-social factors can be anxiety about sexual activity and inability to achieve orgasm.

CONCLUSION

Congenital adrenal hyperplasia and its treatment have a considerable impact on fertility in both males and females. It is important to recognize that the majority of causes impairing fertility are already present in childhood, and therefore should be a treatment goal already in (peri)pubertal years. CAH should therefore be regarded as a lifelong disease: the implications of CAH and its treatment reach beyond childhood.

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