MANAGEMENT OF ENDOCRINE DISEASE

Gonadal dysfunction in congenital adrenal hyperplasia

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Abstract

Gonadal dysfunction is an adverse outcome in patients with congenital adrenal hyperplasia (CAH), which may become apparent already during puberty. Clinical consequences of gonadal dysfunction include menstrual disturbances in females and hypogonadism and impaired fertility in males and females. In males, gonadal dysfunction can be caused by primary gonadal failure due to testicular adrenal rest tumours (TART), and by secondary gonadal failure due to poor hormonal control. In females, gonadal dysfunction can result from an overproduction of adrenal androgens including 11-oxygenated C-19 androgens and progestins, and rarely from ovarian adrenal rest tumours. In all patients with CAH, optimal hormonal control is the key for adequate gonadal function. Therefore, regular measurements of adrenal steroids and/or their metabolites should be performed. In addition, markers of the hypothalamus–pituitary–gonadal axis need to be assessed. In females, the regularity of the menstrual cycle should be evaluated. In males, regular evaluation for TART using ultrasonography is recommended from the start of puberty or even earlier when poor hormonal control is present. When TART is present, counselling on cryopreservation of semen should be offered.

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Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of the adrenal cortex

caused by a defect of one of the enzymes involved in the adrenal steroidogenesis (1, 2). The most common enzyme deficiency (90–99%) causing CAH is 21-hydroxylase deficiency (21OHD, *CYP21A2* mutation), with an

Invited Author's profile

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incidence of around 1:15 000 but more common in certain ethnicities (1, 3, 4). The prevalence of non-classic (NC) CAH is higher and can be found in up to 1:200 across multiple ethnicities (5). The other rarer forms of CAH are 11 β -hydroxylase deficiency, 17 α -hydroxylase/17,20-lyase deficiency, 3 β -hydroxy-steroid dehydrogenase type 2 deficiency, P450 oxidoreductase deficiency, lipid CAH and cholesterol side-chain cleavage enzyme deficiency (6, 7, 8). Patients with CAH caused by 21OHD have impaired cortisol production and consequently elevated ACTH concentrations due to the lack of the negative feedback on the pituitary gland. The increased ACTH concentrations lead to chronic stimulation of the adrenal cortex and increased production of steroid precursors before the enzymatic block (mostly 17-hydroxyprogesterone). These steroids are subsequently shunted to the unaffected androgen pathway and alternative pathways producing elevated concentrations of the precursor steroid as 21-deoxycortisol, 11-hydroxyprogesterone, 16-hydroxyprogesterone, 11-hydroxylated androgens, and dihydrotestosterone. Treatment consists of glucocorticoid supplementation and in the case of mineralocorticoid deficiency also aldosterone (1). By treating patients with CAH with glucocorticoids the negative feedback system on the pituitary gland is restored with a decrease in ACTH production and consequently also lowering androgen production. Adequate monitoring is necessary to prevent over- and undertreatment.

Gonadal dysfunction is one of the most important long-term complications in both sexes in CAH, which may become apparent already during puberty. Clinical manifestations of gonadal dysfunction include signs of hypogonadism and infertility in males and females (9, 10). In addition to hormonal imbalances, in females anatomical and psychological issues, as well as homosexuality and uninterest in pursuing parenthood, may contribute to lower fertility rate in this patient group (11).

In this review, the main causes of gonadal dysfunction in male and female with CAH will be discussed.

Gonadal dysfunction in males with CAH

In males with CAH, the reproductive function can be impaired due to primary gonadal failure, mainly caused by the presence of testicular tumours (9, 12, 13, 14). Hypogonadism is a common finding and males with CAH and hypogonadism often have small testes on physical examination (Table 1). Another important factor

contributing to testicular dysfunction is the suppression of the hypothalamic–pituitary–gonadal axis due to high circulating levels of androgens but also by aromatisation to estrogens and elevated progesterone and 17OHP concentrations as discussed later in the section secondary gonadal failure, resulting in secondary gonadal failure (9).

Testicular adrenal rest tumours (TART)

Benign testicular tumours are typical lesions in male patients with CAH and were first described in 1940 by Wilkins *et al.* (15). Since then, several case reports and larger studies have been published (3, 9, 12, 14, 16, 17). Histologically, these benign tumours resemble adrenocortical cells and they were originally thought to arise from aberrant adrenal cells in the testes. Therefore, they were named testicular adrenal rest tumours (TART). Clinically TART typically present as bilateral (>80% of the cases), painless lesions (12). Only a few patients report pain or discomfort, especially in larger tumours. TART lesions below 2 cm are generally not detectable by palpation due to the typical central location adjacent to the mediastinum testes (3, 14). Imaging techniques such as ultrasound or MRI are necessary to detect smaller lesions (Fig. 1A and B). Ultrasound is the preferred method to detect the tumours as it is as sensitive as MRI and more accessible in most clinics (18, 19). With ultrasound, even small lesions of several millimetres can be detected as hypoechogenic well-delineated masses, often multi-lobular, located around the mediastinum testes. In most publications using ultrasound, a prevalence of about 30–50% is reported in adult CAH patients (12). However, TART can already be detected during childhood with increase in prevalence during puberty and adulthood (14, 20, 21, 22, 23, 24) and have been reported in autopsy material of patients with CAH less than eight weeks old (25). TART are mainly present in males with classic forms of CAH (salt wasting (SW) and simple virilising (SV)). Only few papers describe patients with non-classic (NC) CAH with TART (12, 14, 26).

Histologically, TART have features of steroid producing tissue (Fig. 1C). It is thought that elevated ACTH levels play an important role in the pathogenesis of TART. Several case reports describe shrinkage of the tumour after intensifying glucocorticoid therapy and consequently suppression of ACTH (27, 28, 29, 30, 31, 32, 33). As ACTH and angiotensin (AII) receptors, as well as adrenal specific enzymes and hormones, were found in TART tissue, an adrenal origin of TART was deemed very likely. However, several unsolved questions remain. TART are also found in

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Table 1 Causes of gonadal dysfunction, clinical and hormonal findings and recommendations for males and females with CAH.

	Causes of gonadal dysfunction	Clinical findings	Hormonal findings	Recommendations
Males	Testicular adrenal rest tumours (TART), common	Small (irregular) testes In case of large tumours, increased testicular volume Mostly difficult to detect on palpation On imaging typically bilateral Hypogonadism Subfertility	Testosterone decreased LH and FSH increased (rare) LH and FSH (low) normal (see below) Azoospermia/oligozoospermia	Early detection: ultrasonography from puberty (yearly), in adulthood every 2–5 years (in case of small or no TART) Consider cryopreservation semen (12) Intensify glucocorticoid treatment Surgery not beneficial for fertility but can be considered if pronounced local pain/discomfort (33)
	Insufficient therapeutic control in CAH, excess adrenal androgens and progestins lead to suppression HPG axis	Hypogonadotropic hypogonadism Subfertility	Testosterone decreased LH and FSH (low)normal (with normal prolactin and estradiol) Low inhibin B level A4/testosterone ratio > 1 Azoospermia/oligozoospermia	Intensify glucocorticoid treatment Gonadotrophin therapy
Females	Insufficient therapeutic control in CAH, excess adrenal androgens and progestins lead to suppression HPG axis	Irregular menses Acne, hirsutism Hypogonadotropic hypogonadism Subfertility	Testosterone and/or A4 increased Progesterone increased Polycystic ovarian appearance on ultrasonography (occasionally)	Intensify glucocorticoid treatment Early follicular phase progesterone < 2 nmol/L (to achieve pregnancy) (80) Avoid dexamethasone in pregnancy
	Ovarian adrenal rest tumours (OART), rare	Associated with bilateral adrenalectomy	Testosterone and/or A4 increased	Routine ultrasonography not recommended (83, 84, 85, 86, 87)

A4, androsten.edione; HPG-axis, hypothalamic-pituitary-gonadal axis.

Figure 1

Ultrasound (A) and MRI (B) and histology of a testicular adrenal rest tumour (TART). (A) Scrotal ultrasound of a 19-year-old male with congenital adrenal hyperplasia. The transverse image shows a hypoechogenic rounded lesion (between the white indicators) in the left testis. (B) T2-weighted MR image of longstanding bilateral TART in a 33-year-old patient with congenital adrenal hyperplasia. Heterogeneous low-signal intensity tumours (between the white indicators) are displacing surrounding high signal normal testicular tissue. (C) H&E staining of TART tissue: large polygonal cells with abundant eosinophilic cytoplasm. Reprinted with permission from (13); © 2019 .

well-controlled patients and a clear correlation between hormonal control and prevalence or tumour size has not been found although a positive correlation with ACTH levels has been described (34, 35, 36). Gene expression of adrenal specific genes, such as *CYP11B1*, *CYP11B2*, *CYP21A2*, and *DLK*, and adrenal receptors MC2R and AGTR2 in TART tissue were described in several papers (26, 37). More recently, also Leydig cell specific features of TART tissue were described suggesting that TART consist of a more totipotent cell type (38). Recently, *GATA3* and *GATA6* expression in TART and adrenals, and *GATA4* expression was found in TART and testis (39, 40). Furthermore, also testis-specific gene expression of the LH receptor (*LHCGR*), *INSL3*, and *HSD17B3* has been described in TART (12). Thus, the aetiology of TART has still not been completely clarified.

Other testicular tumours beside TART such as Leydig cell tumours (LCTs) have been incidentally described in patients with CAH and it is challenging to discriminate TART from LCT (41, 42, 43, 44, 45, 46, 47, 48, 49, 50). This is clinically important as LCT can have malignant features. Unfortunately, neither palpation nor imaging techniques can clearly discriminate clinically between TART and LCT. However, there are some differences that may help in the diagnostic process: the presence of TART in both testes is reported in >80% of patients with TART, while only one testes is affected in >90% of the LCT-patients (12, 50). TART size might decrease after intensifying glucocorticoid treatment in some although not all cases (27, 28, 51). Furthermore, histologically Reinke crystalloids are sometimes present in LCTs, but never in TART (12, 18, 28).

Azoospermia is common in patients with CAH and TART. Due to the central location of TART within the testes adjacent to the mediastinum testes it is likely that TART will lead to mechanical obstruction of the seminiferous tubules with consequently obstructive azoospermia. It has been hypothesized that due to obstruction proximal to the epididymis, as in the presence of TART, the efferent flow in the seminiferous tubules is chronically obstructed leading to reduced spermatogenesis and peritubular fibrosis with irreversible damage of the surrounding tissue (52). In addition, paracrine effects of the steroids produced by TART on the surrounding tissue have been described, that may damage the Sertoli or germ cells (12, 28).

As TART is most often described in patients with poor hormonal control, intensifying glucocorticoid treatment is the first choice of treatment. An increase of glucocorticoid dosage and/or change to synthetic long-acting dexamethasone will lead to a decrease of

ACTH levels and in some patients, this results in tumour reduction (29, 30, 31, 32, 33, 35). However, medical treatment is not always successful and with higher glucocorticoid doses the risk of serious side effects such as hypertension and weight gain may increase. Treatment with mitotane has been described in one case report to restore fertility (53). However, this remains experimental as mitotane requires close drug monitoring, may cause irreversible chemical adrenalectomy and severe adverse effects that might not be justified in this benign tumour entity. Another case report describes the use of human chorionic gonadotropin (HCG) combined with follicle-stimulating hormone (FSH) in one patient with CAH and TART and hypogonadotropic hypogonadism, resulting in restored testicular testosterone production and consequently fertility (54).

Testis sparing surgery as a treatment option for TART has been described in several papers (55, 56). In one study eight adult male patients with longstanding TART were treated with testis sparing surgery (56). However, no significant improvement of gonadal function after surgery was found, suggesting irreversible damage to the testicular tissue had already occurred. This was confirmed by testis biopsies. Furthermore, surgery may contribute to irreversible damage of the testes due to scarring of the testicular tissue (52, 57). Therefore, patients should be carefully informed by a multidisciplinary team about the consequences of large TART, and cryopreservation of sperm should be considered. Patients should also be informed about the possible costs of the storage of sperm. As TART can already occur in childhood with a clear increase in prevalence during puberty, we recommend yearly ultrasound of the testes in patients with classic CAH in adolescence. Initiation of earlier screening during childhood can be considered in children with poor hormonal control (1, 22). However, if no TART or only small stable TART are found in a well-controlled adult male with CAH, ultrasound screening every 2–5 years may be sufficient (14).

Secondary gonadal failure in male patients with CAH

Male patients with poorly controlled CAH exhibit a higher risk to develop gonadal failure due to hypogonadotropic hypogonadism (9). High concentrations of adrenal androgens steroids are aromatised to oestrogens which will suppress the hypothalamic–pituitary–gonadal (HPG) axis, leading to hypogonadotropic hypogonadism and small testes in adolescence undergoing pubertal maturation of the testes (58). Moreover, glucocorticoid therapy in CAH

may cause HPG-axis suppression. Some authors suggest that also steroids produced by TART may contribute to the suppression of gonadotropins (17, 20, 59, 60). However, clinically these two conditions cannot be distinguished. Moreover, a number of studies have shown a hypogonadotropic effect of progestins in males and the combined administration of progestins and testosterone are the basis of the proposed male hormonal contraception (61). Given the synergistic hypogonadotropic effect of progestogens and testosterone in males, it is likely that excessive and combined secretion of androgens together with progesterone and 17OHP, will contribute to the gonadotropic inhibition in men with classic CAH.

In contrast to other forms of secondary hypogonadism, most patients with CAH do not report any complaints from testosterone deficiency as males with CAH and poor hormonal control usually have substantial amount of androgens from adrenal origin. A typical biochemical profile in this situation, is suppressed or normal gonadotropins with testosterone levels within the lower normal range, but low inhibin B levels (9, 17). Therefore, even in patients with apparently normal gonadotropin and testosterone levels, gonadal function can be severely impaired. Therefore, inhibin B can serve as an additional marker for Sertoli cell function beside FSH (14, 17). To distinguish testosterone from adrenal or testicular origin in male with CAH it has been suggested to use the serum androstenedione to testosterone ratio (A/T ratio), as androstenedione is elevated when the androgens are predominantly of adrenal origin (62, 63). It can be hypothesized that well-controlled males with CAH produce mainly testosterone from the testes with only a small amount of androstenedione leading to a low A/T ratio (A/T ratio < 0.5). In poorly controlled males the androstenedione levels will increase resulting in suppression of gonadotropins and an A/T > 1, indicating that a significant fraction of testosterone is of adrenal origin (62). One has to be aware that serum total testosterone can be decreased due to low serum SHBG concentrations, for example in obese patients, or elevated in some conditions such as hepatitis or hyperthyroidism. Therefore, in this situation free testosterone could be measured or calculated from total testosterone, SHBG and albumin concentrations. However, most direct free testosterone assays lack adequate sensitivity and specificity. Moreover, in the vast majority of cases total testosterone measurements are sufficient as long as it is measured by a sensitive and specific assay such as a specific RIA or LC-MS/MS assay. On the other hand, male patients with hypogonadotropic hypogonadism and apparently low testosterone surprisingly may not

complain of clinical symptoms of hypogonadism. An explanation for this may be an excess of 11-oxygenated C19 steroids in CAH. In particular 11-ketotestosterone (11KT) and 11 β -hydroxy androstenedione seem to play a role in CAH (63). It has been demonstrated that 11KT and its derivate 11KT-dihydrotestosterone act at the androgen receptor with equal potency to the classic testosterone and dihydrotestosterone (64, 65). In the absence of TART, most reports show reversible hypogonadism and improved fertility after initiating or increasing glucocorticoid therapy (66, 67).

Child rate in males with CAH

Most studies of gonadal function in CAH males do not report on fatherhood and if doing so no comparisons with controls have been made. In 1978 fatherhood was reported for the first time in 25 adult males with CAH of whom 10 had 19 living children (68). Some did not have any glucocorticoid supplementation at the time of conception, however, none of the patients had had any genetic confirmation of CAH and there was no control group which make the report difficult to interpret. A Finnish study of 21 males with classic CAH found a child rate of 0.07 compared to 0.34 in the entire Finnish male population with a similar age distribution (69). A Swedish study of 30 adult males with CAH showed a child rate of 0.9 compared to 1.8 in the entire Swedish population with equal age distribution (14). In a US study of 30 males aged 17–43 years only 7% had children (27), while in a German study of 22 males with CAH aged 19–48 years 23% had fathered children (70). Moreover, in a UK study of 65 adult males with CAH 25% had become fathers, two after fertility treatment, however, only 37% had tried to conceive their partner (3). Furthermore, in a French study of 219 males with classic CAH aged 18–70 years 24% had fathered at least one child, 11% after IVF (9). This fertility rate was lower than French reference population. At last, in a Swedish epidemiological study including 221 males with CAH aged 15–81 years and 22 024 age-, sex- and municipally matched controls only those born before the neonatal screening had reduced fatherhood rate (odds ratio 0.5) while those born after the introduction of screening had normalised fatherhood rate (16). Adoption was more common in the males with CAH (odds ratio 2.9). Males with NC phenotype had also normalised fatherhood rate. Of those CAH males who had succeeded in becoming fathers the number of children was the same as in controls (16). Thus, males with classic CAH seemed

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less likely to be fathers, however, with early diagnosis of classic CAH, thanks to neonatal screening programs, fertility may be normalised (16).

Gonadal dysfunction in females with CAH

Gonadal dysfunction in female adolescent and young adults with CAH can result in abnormal pubertal development, amenorrhoea and irregular menses (Table 1). Timing of puberty and age at menarche is usually not significantly different in females with and without CAH (10, 71, 72). However, elevated adrenal steroids can lead to menstrual irregularity. Therefore, regular monthly menses generally indicate appropriate hormone replacement therapy. It should be noted that menstruation disturbances are common in the general female population and in one study of 62 adult women with CAH irregular menstruations was in fact as common in patients as in age-matched controls (both 28%) (10). In general, the gonadal function in females with CAH can be impaired due to several factors: overproduction of adrenal androgens including 11-oxygenated C19 steroids, elevated adrenal precursor steroid (17-hydroxyprogesterone and progesterone), polycystic ovaries and ovarian adrenal rest tumours. Furthermore, as described previously in males with CAH, hypogonadotropic hypogonadism can interfere with gonadal function (see 'Secondary gonadal failure in male patients with CAH' section).

Adrenal overproduction of androgens in females with CAH

In case of poor hormonal control, elevated adrenal C-19 steroids can affect ovarian function, resulting in menstrual disturbances (1). Suppression of adrenal androgen secretion by increasing the glucocorticoid dose can restore ovulation and normalise the menstrual cycle (73). More recently, the potential contributions of the alternative backdoor steroid and the 11-oxo-steroid pathways to androgen excess in patients with CAH have been described (63, 74, 75). Turcu *et al.* showed that C19 steroids were associated with menstrual disorders in females with CAH and may therefore serve as additional biomarkers in disease control (63).

Adrenal overproduction of progestins

In some females with CAH, adequate suppression of adrenal androgen levels seems to be insufficient to

correct menstrual abnormalities. It has been described that increased levels of adrenal steroid precursors (such as progesterone and 17-hydroxyprogesterone) may interfere with the normal menstrual cycle (73, 76, 77). In addition, elevated progesterone levels from adrenal origin can cause impermeability of the cervical mucus and failure of implantation contributing to infertility. Thus, adequate suppression of adrenal progestins, as well as androgens, are needed for menarche and for a regular menstrual cycle. The degree of suppression of progesterone, especially in the follicular phase, has been suggested to be less than 2 nmol/L (76). However, lowering of 17-hydroxyprogesterone and progesterone levels can often only be achieved with supraphysiological glucocorticoid doses. The degree of suppression of follicular phase progesterone that is required to allow optimal endometrial receptivity is uncertain (76). Therefore, finding the balance between over- and undertreatment is an important task (78). Furthermore, beside optimising glucocorticoid therapy also optimising mineralocorticoid treatment based on renin levels is considered to be an important factor (78). Beside local effects, elevated progesterone has also direct and indirect effects on the pituitary production of gonadotropins that may interfere with the normal menstrual cycle.

Ovarian adrenal rest tumours

In contrast to the high prevalence of TART in males with CAH, the presence of ovarian adrenal rest tumours (OART) seems to be very rare (Fig. 2). So far only a few case reports have been published (79, 80, 81, 82, 83). The low prevalence may be explained by the difficulty to detect these tumours by ultrasound due to the abdominal location of the ovaries in contrast to the scrotal position of the testes. In a small study of 13 adult females with CAH no ovarian adrenal rests were detected by ultrasound or MRI (84). ¹⁸F-FDG PET/CT was used to study ectopic ovarian rests in females with CAH in two case reports (79, 80). In addition, ¹³¹I-noriodocholesterol imaging might help to identify occult OART (85). Selective venous sampling and complete pelvic venous sampling to localise virilising ovarian tumours has also been described (81). When routine imaging techniques fail to detect these lesions, pelvic venous sampling might effectively localise the tumours. This may be especially important when females with CAH suffer from an unexplained increase of adrenal C-19 steroids. One case report describes a young adult female with CAH who underwent bilateral adrenalectomy because of

Figure 2

Ovarian adrenal rest tumour in the right ovary of a 19-year-old female with congenital adrenal hyperplasia. Two sectioned sharply circumscribed green-yellow nodules of ectopic adrenal cortical tissue. Reprinted from (81) copyright 2019 with permission.

poorly controlled CAH (81). Several years after successful surgery, she developed secondary amenorrhea and hair loss. These signs of adrenal androgen excess were caused by ovarian adrenal rests only detectable by pelvic venous sampling. This case clearly illustrates that chronically elevated ACTH may induce proliferation of adrenal rest cells also in females within the ovaries, leading to androgen excess and thereby undoing the beneficial effect of bilateral adrenalectomy. Routine imaging to detect ovarian adrenal rests and polycystic ovaries is, however, not recommended. Though in the case of, for example, increased androgen levels after adrenalectomy additional methods such as a PET CT or venous sampling may be necessary.

Gonadal aspects in non-classic CAH (NCCAH)

In a multicentre cohort study by Moran *et al.* the presenting symptoms in 193 females with NCCAH at the age of 10 years and older were hirsutism (59%), oligomenorrhea (54%), acne (33%), infertility (13%), clitoromegaly (10%), alopecia (8%), primary amenorrhea (4%), and premature pubarche (4%) (86). However, many females with NCCAH are asymptomatic and spontaneous pregnancy may occur even before a NCCAH diagnosis is made. This was demonstrated in another multicentre study by Moran *et al.* (87): of 203 pregnancies, 138 (68%)

occurred before the mother's diagnosis of NCCAH and 65 (32%) after the diagnosis. Bidet *et al.* reported about a cohort of 190 females with NCCAH and of the 187 pregnancies (in 85/95 women desiring pregnancy) 99 (52.9%) occurred before the diagnosis of NCCAH (96/99 spontaneous), and 88 (47%) after the diagnosis (11/88 spontaneous) (88).

Thus, in NCCAH the likelihood of spontaneous pregnancy is much higher than in classic CAH. There is a strong correlation between the severity of CAH and the level of gonadal dysfunction: gonadal impairment is, therefore, lower in NCCAH compared to classic CAH (89). But it is likely that the underlying mechanisms of subfertility are identical. Treatment with glucocorticoids is effective in females with NCCAH seeking fertility. It shortens the time to conception and seems to reduce the risk for miscarriage (87, 88, 90). Dexamethasone is not recommended because it crosses the fetoplacental barrier.

Pregnancy in females with CAH including child rate

It is important to stress that patients with classic CAH have normal pregnancy rates. This was shown by Casteras *et al.* and needs to be distinguished from low fertility rates that were observed in the patient cohort (76). In a recent Swedish study based on different national registers, 272 females with CAH (aged 14 years or older) and 27 200 matched controls were studied and far fewer females with 21OHD had given birth than controls (25.4% vs 45.8%, $P < 0.001$) (91). Moreover, mothers with CAH were older at first pregnancy and had fewer children in total compared to controls. Women with SW CAH were less likely to be mothers than those with SV or NC CAH (8.1% vs 41.8% vs 40.8%), the SV and NC groups were as likely to be mothers as the controls.

The low child rate compared to the general population has multiple reasons including hormonal, anatomical, psychological and psychosexual reasons (92). In difficult-to-control hyperandrogenism in CAH bilateral adrenalectomy has been described in case reports successfully resulting in pregnancies. Apart from the increased risk of adrenal crisis, the development of ovarian or paraovarian adrenal rest tumours have been observed as long-term complication following bilateral adrenalectomy in females with CAH (93). For a more detailed description of fertility in females with CAH we refer to the literature (94, 95, 96).

Several cohort studies as well as case reports also show that the course of pregnancy and the outcome of pregnancies are mostly uneventful (92). As dexamethasone crosses the placenta, it is essential that only hydrocortisone and prednisolone are used for hormone replacement during pregnancy to avoid adverse effects on the foetus. Usually the hormone replacement dose used pre-conceptionally can be continued throughout pregnancy. An increase of glucocorticoid dose of 20–40% in the second- and third-trimester might be considered similarly as in primary adrenal insufficiency although personal experience shows that in most cases this is not necessary. During labour and delivery, however, stress doses are clearly indicated (92, 97). All patients need to be aware of sick day rules and equipped with emergency kits, thus re-education of patients is recommended. Evidence-based disease monitoring parameters during pregnancy are, however, lacking. Patients therefore are mainly monitored according to clinical signs of over- and undertreatment with glucocorticoids. Physicians need to be aware of pregnancy-associated changes in hormone parameters. Two main parameters of disease control as 17-hydroxyprogesterone for glucocorticoid dosing and renin for mineralocorticoid dose adjustment dramatically increase during pregnancy and thus cannot be used for monitoring purposes. Instead androgens, in particular free testosterone, might be better hormonal disease monitoring parameters, however, pregnancy-caused changes need to be taken into consideration (98).

Gonadal dysfunction and paternity in rare CAH variants

TART has been described in CAH patients with 11 β -hydroxylase deficiency and 3 β -hydroxy-steroid dehydrogenase type 2 deficiency (7, 12, 99, 100). In contrast to 11 β -hydroxylase deficiency, which only affects the adrenal steroidogenesis, 3 β -hydroxy-steroid dehydrogenase type 2 deficiency reduce both adrenal and gonadal steroidogenesis (7, 8). Occasional males and females with 11 β -hydroxylase deficiency have been able to have children of their own (101, 102). Only one male with 3 β -hydroxy-steroid dehydrogenase type 2 deficiency has been reported to father children but there was no genetic testing to confirm his paternity (103). If any female with 3 β -hydroxy-steroid dehydrogenase type 2 deficiency has been able to be a biological mother is unclear (8). Since 17 α -hydroxylase/17,20-lyase deficiency usually presents as a sexually infantile adolescent phenotypic female (either

46,XX or 46,XY) sex steroid replacement is necessary according to the sex of rearing (104). Although patients with 17 α -hydroxylase/17,20-lyase deficiency are normally considered infertile a few cases of successful pregnancies after fertility treatment (frozen embryo transfer (FET)) have been reported (105, 102, 106). The majority of patients with P450 oxidoreductase deficiency have atypical genitalia (6). Patients with P450 oxidoreductase deficiency, at least classic, are also considered infertile, but successful pregnancies have been documented after fertility treatment (FET) (107, 108). Lipoid CAH and cholesterol side-chain cleavage enzyme deficiency are the most severe forms of CAH with impaired production of cortisol, aldosterone and sex steroids (104). One woman with lipoid CAH has after fertility treatment (clomiphene stimulation) been able to have two successful pregnancies (109). It should be noted that even though gonadal dysfunction seems to be present in almost all cases and paternity infrequent in rare CAH variants, normal gonadal function and fertility have occurred in sporadic cases (102, 103). In milder NC form of rare CAH variants, some of these patients may not have been diagnosed, the gonadal function and fertility is more unclear (95).

Conclusions and practice recommendations

Optimal hormonal control is a key factor for adequate gonadal function in males and females with CAH, already during adolescence and young adulthood.

In all adolescent with CAH

Evaluation of hormonal control by regular measurements of adrenal steroids and parameters of the HPG axis should be performed.

In females with CAH

Assess the regularity of the menstrual cycle during each visit. When amenorrhea or irregular menstruation is present, measurement of androstenedione, 17-hydroxyprogesterone, LH, FSH, testosterone, oestradiol and progesterone is recommended to rule out hormonal causes of gonadal dysfunction. Consider intensifying glucocorticoid treatment with careful monitoring of 17-hydroxyprogesterone and androstenedione as well as adverse effects from supraphysiological dosages of glucocorticoids. Routine imaging to detect OART

and polycystic ovaries is not recommended. Low dose glucocorticoid treatment with hydrocortisone or prednisolone in NCCAH may be considered when patients seek fertility since it can shorten the time to conception and seems to reduce the risk for miscarriage. As dexamethasone traverses the placenta, it should not be given during pregnancy.

In males with CAH

Yearly evaluation for TART using ultrasonography is recommended during adolescence in classic forms of CAH or even earlier in poorly controlled patients. However, if no TART or only small stable TART are found in a well-controlled adult male with CAH, ultrasound screening every 2–5 years may be enough. We recommend yearly evaluation of gonadal function by measuring LH, FSH, testosterone, oestradiol and SHBG, androstenedione. Inhibin B could be considered. Normal levels of gonadotropins and testosterone do not rule out gonadal dysfunction especially in patients with small testis volumes. Consider using the androstenedione to testosterone ratio to differentiate between an adrenal and a testicular origin of the androgens. When TART is present cryopreservation of semen should be considered.

Declaration of interest

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