Classic congenital adrenal hyperplasia and its impact on reproduction

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Women with classic congenital adrenal hyperplasia (CAH) can suffer from impaired fertility rates as a result of increased androgen secretion or impaired sex steroid production. In virilizing CAH forms, such as 21-hydroxylase and 11β-hydroxylase deficiency, the low reported pregnancy rate is mainly secondary to a diminished desire to conceive. Optimal glucocorticoid and/or mineralocorticoid replacement, sufficient to normalize androgen and P levels in the follicular phase, allows natural conception in most cases. The remaining CAH forms exemplified by StAR, P450scc, P450-oxidoreductase, and 17α-hydroxylase/17-20 lyase deficiencies are associated with impaired sex steroid production. Several factors are involved in the true low fertility rate in this group: folliculogenesis arrest, uterine hypoplasia, and inadequate endometrial thickness related to aberrant androgen, estrogen, and P secretion. There are several reports of successful term pregnancies achieved through controlled ovarian hyperstimulation, followed by estrogen replacement and IVF. Progress in female genitalia reconstructive surgery, individualized hormonal therapies, psychosexual evaluation, and assisted reproductive technology have improved fertility and pregnancy outcomes in women with classic CAH. Finally, successful gestational management in CAH patients requires the close coordination of care between endocrinologists and obstetricians. (Fertil Steril® 2019;111:7–12. ©2018 by American Society for Reproductive Medicine.)

Key Words: Congenital adrenal hyperplasia, fertility, reproduction

Congenital adrenal hyperplasia (CAH) (1) comprises a group of endocrine autosomal recessive disorders characterized by a deficiency in one of the enzymes or proteins involved in cortisol biosynthesis. Decreased cortisol production leads to increased ACTH levels, chronic adrenal stimulation, and consequently, elevated steroid precursors that are distinctive for each form of CAH (Table 1).

The most prevalent CAH involves enzymatic deficiencies associated with high androgen production in prenatal life, leading to virilization of external genitalia in females. In all of these conditions, girls generally present with atypical genitalia, and female reconstructive surgery is often required (Table 1). Adrenal 21-hydroxylase deficiency (21OHD) is the most common enzymatic defect, accounting for 95% of all CAH cases (1). The clinical phenotype depends on the degree of enzymatic impairment. In classic 21OHD simple virilizing (SV) form, girls are born with virilized external genitalia; both sexes display androgen excess and postnatal virilization. In the classic salt-wasting (SW) form, both cortisol and aldosterone are deficient. In addition to virilization, neonates present with SW crises (2). Other rare, virilizing CAH forms are 11β-hydroxylase deficiency (11OHD) and type II 3β-hydroxysteroid dehydrogenase deficiency (3βHSDIID).

The other CAH form includes enzymatic or protein deficiencies—StAR deficiency, P450scc deficiency, and 17α-hydroxylase/17-20 lyase deficiency (17OHD)—that are associated with decreased androgen and/or estrogen (E) production. All of these CAH forms disrupt sexual steroid production, causing absence or incomplete pubertal development and infertility in both sexes (Table 1). In girls, P450-oxidoreductase (a flavoprotein that donates electrons to the P450s enzymes) deficiency presents with nonprogressive prenatal virilization of external genitalia and later with decreased sex steroid production, leading to incomplete pubertal development.

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TABLE 1

Clinical features related to gonadal function in women with CAH.

Variable	CAH group					
	Androgen excess			Estrogen deficiency		
Deficiency	21OH	11OH	3βHSD	17αOH	StAR/P450scc	POR
Gene	*CYP21A2*	*CYP11B1*	*HSD3B2*	*CYP17A1*	*StAR, CYP11A1*	*POR*
Elevated precursor	17OHP	DOC, 11-deoxycortisol	17OH-Preg	P, DOC	None	P, 17OHP
External genitalia	Virilized	Virilized	Mildly virilized/normal	Normal	Normal	Mildly virilized
Pubertal development	Normal	Normal	Incomplete or normal	Absent or incomplete	Incomplete or normal	Incomplete or normal
Fertility treatment	Spontaneous on optimized gluco-/mineralocorticoid replacement	Spontaneous on optimized glucocorticoid replacement	Possible but not described	COH + individualized E/P therapy	COH + individualized E/P therapy	COH individualized E/P therapy

Note: 17OH-Preg = 17OH-pregnenolone; COH = controlled ovary hyperstimulation; DOC = deoxicorticosterone; Gluco = glucocorticoid.

Gomes. Reproduction in congenital adrenal hyperplasia. Fertil Steril 2018.

In childhood, treatment focuses on preventing virilization and/or adrenal crisis, controlling hypertension in 11OHD and 17OHD, and promoting normal growth and pubertal development. In adulthood, treatments aim at preventing metabolic abnormalities and osteoporosis secondary to excessive glucocorticoid administration and improving fertility outcomes. In this Views and Reviews, we explore female fertility outcomes in the various forms of classic CAH.

FERTILITY IN 21OHD

Initial studies indicated a low fertility rate for female patients with classic 21OHD, especially among those with the SW form. In 1987, Mulaikal et al. (3) reported the fertility rate in their cohort of 80 female 21OHD patients as 38% in the SV form and 2.5% in the SW form. Additionally, lower fertility rates were observed in a cohort of 29 women with CAH reported by Jääskeläinen (4). Thirteen pregnancies were confirmed in 9 women (in 1 of 9 women with the SW form and in 8 of 20 women with the SV form); among these pregnancies, seven were conceived naturally and six were achieved after hCG stimulation (4). A recent larger, cross-sectional, multicenter study in Europe called dsd-LIFE, which investigated fertility outcomes in patients with various disorders of sex development, found that 15% of CAH patients (28 of 221) conceived naturally, and 2% (4 of 221) conceived through some form of assisted reproductive technology (5). The above-mentioned and subsequent studies consistently demonstrated that these women were less sexually active and less likely to pursue motherhood (3–6).

Several factors have been proposed to explain this low delivery rate in female patients with 21OHD. The most obvious is the adrenal steroid excess present in poorly controlled patients. Progesterone, an androgen precursor, has a critical role in regulating GnRH pulse frequency. Bachelot et al. (7) reported normal LH pulses in well-controlled women with 21OHD and reduced LH pulse frequency and amplitude in poorly controlled anovulatory patients, most likely due to P over-secretion. High P levels in the follicular phase, despite optimal glucocorticoid replacement, have been associated with amenorrhea and infertility in 21OHD patients (8). Increased P concentrations alter the GnRH pulse generator, disrupt endometrial thickening, and make the cervical mucus thicker, disrupting ovulation, embryo implantation, and/or sperm migration, respectively.

In contrast, elevated androgen concentrations impair the ability of P to lower the activity of the GnRH/LH pulse generator (9, 10). Therefore, in a subset of patients, the neuroendocrine abnormality in 21OHD might include increased GnRH pulse frequency, which increases the frequency and pulse amplitude of LH over FSH production, leading to elevated androgen secretion by ovarian theca cells and polycystic ovarian morphology, similar to the polycystic ovarian syndrome phenotype (11, 12). Androgen excess also has a direct effect on the ovaries, suppressing later stages of follicular development and further compromising ovulation (13, 14). Both androgen and/or P, when elevated, could cause several endometrial molecular alterations, disrupting embryo implantation (15).

Unfavorable anatomical and/or functional genital reconstruction in women with CAH may contribute to the lower sexual activity reported for this group of patients (16). Initial studies showed that 35%–50% of these patients had an inadequate vaginal opening, making sexual intercourse virtually impossible (2). Advances in genital reconstruction techniques have led to an increase in the percentage of patients who are sexually active (17). Single-stage reconstruction, consisting of vulvoplasty, clitoroplasty, and Y-V perineal flap, resulted in 68% good morphological and functional results in our cohort (18). Notably, advances in clitoral reconstruction have been made. Newer techniques preserve the clitoris dorsal nerve as well as the vessel and ventral mucosa that supply the glans, maintaining clitoral sensory input and facilitating orgasm (18). In addition, vaginal dilations with acrylic molds instead of surgery in adult women with introitus stenosis result in good sexual outcomes (19).

Psychosexual factors may also decrease the fertility rate in women with 21OHD. Women with 21OHD frequently present with typically masculine behavior, and approximately one-third do not have any sexual interest and fantasies (16, 17, 20, 21). Prenatal androgen exposure might affect the central nervous system, contributing to this behavior (16). Of note, women with 21OHD harboring the null genotype seem to have lower sexual interest and less satisfaction with their surgical outcome, illustrating that there are more surgical complications related to the severity of the disease in this group of women—including, but not limited to, urinary leakage, decreased clitoral sensitivity, and dissatisfaction with sexual intercourse (22).

Moreover, CAH patients may have an inadequate understanding of their fertility potential. In the dsd-LIFE study, 40% of 211 female CAH respondents did not remember receiving any information about their fertility. Additionally, among those who had received information, only 50% were satisfied with it, and only 60% knew about the possibility of having their own biological children (5). These results emphasize the need to improve the education of CAH patients regarding their fertility potential.

Despite these issues, the pregnancy rate among CAH women who wish to conceive is much more optimistic than reported previously. A study evaluating 106 women with classic 21OHD showed a 91% pregnancy rate in the CAH group, which was similar to the rate found in the normal control population (95%) (23). There was no significant difference in the pregnancy rate between women with the SV and SW forms (93% and 89%, respectively). However, the women with the SV form were six times more likely to seek motherhood compared with the women with the SW form (64% vs. 11%, respectively) (23).

FERTILITY IN 11OHD

11β-Hydroxylase deficiency is the second most common enzymatic defect resulting in classic CAH. This deficiency accounts for 5%–8% of CAH cases (24, 25). Female patients with the classic 11OHD form are exposed to intrauterine androgen excess, which may result in atypical genitalia, menstrual abnormalities, subfertility, and hypertension due to the accumulation of mineralocorticoid precursors (24).

Women with genetically confirmed 11OHD are reported to have impaired fertility unless properly treated. In 2007, Simm and Zacharin (26) reported on a woman with classic 11OHD who became pregnant after receiving dexamethasone at 0.75 mg/d and clomiphene citrate at 50 mg/5 days (26). During gestation the patient had significant worsening of hyperandrogenic acne and hirsutism. The dexamethasone dose was increased to up to 2.0 mg/d.

FERTILITY IN 3βHSDIID

In contrast to 21OHD and 11OHD deficiencies, which are restricted to adrenal steroidogenesis, 3βHSDIID is a rare disorder resulting in impairment of both adrenal and gonadal steroidogenesis. Clinical manifestations are variable, ranging from the severe SW form with or without atypical genitalia, to the non-SW form with hirsutism and menstrual abnormalities (27).

There are two types of 3βHSD. Type I isoenzyme is expressed in the peripheral tissues. Type II is expressed in the gonads and adrenal glands. Women with 3βHSD type II deficiency have excess production of androgen precursors, which are converted to active androgens in the peripheral tissues by the normal 3βHSD type I isoenzyme. This explains the excess androgens observed in these women (28). In most 3βHSD type II–deficient patients, the female external genitalia are normal or mildly virilized. However, the gonadal function is not well understood, and hypergonadotropic hypogonadism has been described. Interestingly, Alos et al. (29) described a patient with severe neonatal dehydration, normal external genitalia, and normal pubertal development, with regular menstrual cycles and evidence of P secretion. On the other hand, the SW patient described by Zachmann et al. (30, 31) required E therapy to undergo complete feminization, including menses. After stopping the E/P therapy, menses ceased, and multiple ovarian cysts were observed. These cases demonstrate the great variability of 3βHSD type II deficiency. Fertility rates in this population have not been reported.

FERTILITY IN 17OHD

17α-Hydroxylase and 17,20 lyase catalyze the synthesis of glucocorticoids and sex steroids in the adrenal glands and gonads, respectively. 17α-Hydroxylase/17,20 lyase deficiency accounts for $<$1% of all CAH cases (32); however, it is the second most frequent adrenal enzymatic defect in the Brazilian population owing to gene founder effect mutations (33).

46,XX patients present with normal prenatal sexual development, resulting in normal internal and external genitalia (34–36). The diagnosis is generally recognized at puberty, when patients develop hypergonadotropic hypogonadism, usually associated with hypokalemic hypertension, secondary to the deficiency of sex steroids and the accumulation of the following precursors: 11-deoxycorticosterone, corticosterone, and 18-deoxycorticosterone, respectively. A multicenter study comprising a large cohort of 46,XX patients reported primary amenorrhea in 71%, hypertension in 87.5%, and spontaneous

development of breasts in 50% of the cases. Interestingly, ovarian torsion was the first symptom in 3 of 16 cases, and multiple ovarian cysts were observed in 10 of 16 patients, ranging from <1 to 6 cm in diameter (33). Excessive gonadotropin-mediated ovarian stimulation in hypogonadal women with 17OHD is a potential underlying mechanism leading to the development of ovarian cysts. In these cases, the development of ovarian cysts was avoided through dexamethasone, E, and P therapies (37), or, in one case, by the use of GnRH analogues. It is worth mentioning that all patients had reduced uterine volume at diagnosis. Reports of female patients with 17OHD presenting with spontaneous menarche with cyclic menses suggest that there can be partial impairment of enzymatic activity (38).

Pregnancy is rarely reported in women with 17OHD. Infertility is most likely due to arrested folliculogenesis resulting from anovulatory cycles, lack of E, and P excess. Adrenal P secretion may be inhibited by the use of glucocorticoids, but conventional therapies for infertility do not replace the deficient secretion of sex steroids. Treatment with stimulatory gonadotropins increases ovarian P secretion secondary to enzyme blockage. Uterine hypoplasia and inadequate endometrial development may impair embryo implantation. No pregnancies have been reported after fresh IVF cycles in women with partial 17OHD (32).

Levran et al. (39) reported a pregnancy resulting in three live births after the transfer of cryopreserved embryos. The patient received dexamethasone and GnRH agonists, hMGs, and hCG during her controlled ovarian hyperstimulation. In 2016, another successful pregnancy was described in a Brazilian woman with 17OHD (40). The first IVF cycle failed despite the production of viable embryos. For the second IVF attempt, all viable embryos were frozen owing to inadequate endometrial development associated with prematurely elevated serum P levels during ovarian stimulation. Long-acting GnRH agonist and oral dexamethasone were used to lower ovarian and adrenal P secretion. Serum P levels of <1 ng/mL were achieved, E_2 valerate was used for the endometrial preparation, and frozen–thawed embryo transfer was performed, resulting in a singleton pregnancy.

FERTILITY IN P450 OXIDOREDUCTASE DEFICIENCY

P450 oxidoreductase (POR) transfers electrons from nicotinamide adenine dinucleotide phosphate to all microsomal type II P450 mutations, including those involved in steroidogenesis, such as 17α-hydroxylase, 21-hydroxylase, and aromatase. P450 oxidoreductase mutations were first described in 2004 in patients with steroid abnormalities, suggesting combined 17OH and 21OH deficiencies. Impairment of 17OH activity caused by the *POR* gene mutation disrupts sex steroid production in both sexes, resulting in failure of pubertal development and infertility in females. Impairment of aromatase activity causes decreased conversion of androgen precursors to Es in the ovaries and fetal androgen precursors to estriol and estrone in the feto-placental unit, which account for virilization of both the fetus and mother.

46,XX POR deficiency patients present with atypical genitalia at birth, and, in contrast to those with virilizing CAH forms, their postnatal androgen levels are low. This mild prenatal virilization is explained by the conversion of 17OH-P to dihydrotestosterone through the backdoor pathway, bypassing conventional androgen precursors (41). P450 oxidoreductase deficiency patients may develop bone defects that are characteristic of Antley-Bixler syndrome owing to impairment in sterol synthesis (*CYP51A1*) (42).

There are few reports about gonadal function in female patients with POR deficiency (43–45). Recently we described the long-term follow-up of a 46,XX patient who presented with partial pubertal development (breasts TII), infantile uterus, and a large ovarian cyst (2.8 cm) at 14 years of age; menses only occurred after E replacement, and the ovarian cyst regressed (46).

It was suggested that POR deficiency should be investigated in infertile female patients with normal androgen levels. We described a POR deficiency patient with normal external genitalia, amenorrhea, and large ovaries with multiple cysts, mimicking normoandrogenic polycystic ovarian syndrome phenotype (47). In a patient with a history of vaginal atresia, POR deficiency was suspected during controlled ovarian stimulation, after the patient exhibited low serum E response associated with high P levels. This patient received letrozole and gonadotropins to induce ovulation, and a successful IVF frozen embryo transfer was achieved (48).

FERTILITY IN CONGENITAL LIPOID ADRENAL HYPERPLASIA

Congenital lipoid adrenal hyperplasia (lipoid CAH) is the most severe form of CAH. Although rare, it is most prevalent in Japanese and Korean populations (49). The disease is characterized by disruption of adrenal and gonadal steroidogenesis in the conversion of cholesterol to pregnenolone, resulting in impaired production of glucocorticoid, mineralocorticoid, and sex steroids.

Lipoid CAH is most commonly caused by a mutation in the StAR (steroidogenic acute regulatory) protein, which transports cholesterol from the outer to the inner mitochondrial membrane. These patients generally develop severe SW crises with hyperpigmentation in the first months of life. Interestingly, 46,XX females present normal pubertal development, followed by anovulatory menstrual cycles (50, 51). Because the ovaries have low steroidogenic activity during fetal life, they retain some steroidogenic activity for years, probably through a StAR-independent pathway, enabling normal pubertal development (52). However, these low E levels may be insufficient to promote ovulation and/or embryo implantation (53).

In 2009 Khoury et al. (54) reported on a 25-year-old patient with regular menstrual cycles and infertility. Pregnancy was achieved after clomiphene stimulation, but miscarriage occurred at 6 weeks of gestation. In a subsequent pregnancy attempt, P was added, which resulted in a twin full-term pregnancy. In contrast, IVF may not be successful in infertile lipoid CAH patients owing to inadequate endometrial

thickness. To correct the E deficiency and achieve optimum endometrium preparation (53), high doses of E_2 valerate can be added during the ovarian hyperstimulation phase, whereas P can be added in the luteal phase and continued until the initiation of placental function (55).

A less severe lipoid CAH form was described in a female patient diagnosed with dehydration in the first months of life (51). This patient had normal pubertal development, and at age 32 years maintained regular menses and normal gonadotropin levels in the follicular phase. She did not attempt to conceive, and fertility issues remained unknown. These above-mentioned cases indicate the wide phenotypic variability in the gonadal function of female patients with lipoid CAH.

Lipoid CAH could also be caused by mutations in the *CYP11A1* gene. The clinical manifestations of P450scc deficiency are similar to those presented in patients affected by StAR mutations, except for the smaller adrenal size (49, 56). Fertility outcome is unknown in humans, but Cyp11a1 transgenic female mice have displayed reduced pregnancy rates and impaired embryo implantation due to low P levels (57).

FERTILITY TREATMENT IN CAH

To optimize fertility outcomes in virilized women with CAH, glucocorticoid and mineralocorticoid replacement must be achieved to normalize androgen and P levels. Casteràs et al. (23) improved the rate of natural conception of women with 21OHD in up to 76% of cases after the introduction of optimized glucocorticoid and mineralocorticoid regimes. These regimens achieved serum P levels of <2 nmol/L in the follicular phase and renin within the normal range. In cases of nonsuppressible androgen and P, bilateral adrenalectomy can restore normal steroid concentrations and can result in successful pregnancies (58). This is a hazardous treatment option, because it will abolish any residual cortisol and aldosterone production, increasing the risk of acute adrenal insufficiency.

Improving factors that impact sexual function, such as psychological conflicts and genitoplasty procedures, might increase the fertility rate among CAH patients. Interestingly, the perceptions of women with CAH of the appearance of their genitalia have been shown to be worse than their physicians' impressions (59). New genital reconstruction techniques result in normal external genitalia and adequate vaginal introitus and clitoris sensitivity, contributing to improved sexual activity in patients with virilized CAH forms. Moreover, improved education about sexual function and fertility potential will improve fertility rates. Among CAH patients with impaired sex steroid production, successful full-term pregnancies may be achieved using controlled ovarian hyperstimulation followed by IVF and adequate hormone replacement. The addition of E therapy in these patients has improved endometrial development and endometrial thickness, resulting in improved pregnancy outcomes.

There is scarce information regarding glucocorticoid use during pregnancy in women with CAH, and both dexamethasone and prednisolone have been used. To avoid fetal exposure, the CAH guidelines from the American Endocrine Society recommend the use of glucocorticoid, which does not traverse the placenta; in general, preconception doses are maintained during pregnancy (60). Successful gestational management of CAH patients requires the close coordination of care between obstetricians and endocrinologists.

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