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ORIGINAL ARTICLE

Fertility outcome in male and female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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KEYWORDS

Congenital adrenal hyperplasia;
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Testicular adrenal rest tumours;
Hyperandrogenism

Abstract *Objective:* To investigate fertility in a sample of Tunisian patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency.

Design: Tunisian bicentric prospective study.

Setting: Endocrinology department, Hedi Chaker Hospital, Sfax, Tunisia and Department of Endocrinology and Internal Medicine, Tahar Sfar Hospital, Mahdia, Tunisia.

Materials and methods: Twenty-six patients (11 M; 15 F), aged 16.5–48 years, were enrolled. Clinical, biological, hormonal and ultrasound examinations were performed to assess fertility.

Results: Eighteen had the classical form and eight the non classic. One patient had palpable testicular nodule. Inhibin B level was decreased in four male patients. Semen analysis showed abnormalities in four of 10 patients. Testicular adrenal rest tumors (TARTs) were detected in 6/11 patients. Menstrual disorders and hirsutism were noted in four and nine female patients, respectively. Six

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patients showed polycystic ovary syndrome. Anti-Mullerian hormone level was reduced in four female patients. Among four female patients who wished to get pregnant, two of them achieved one successful pregnancy, miscarriage occurred in one patient and the remaining patient was sterile. Fertility issues in our patients appeared to be related to poor hormonal control and a result of noncompliance with medication schedules.

Conclusion: Fertility in male and female patients with CAH is reduced. Early and adequate glucocorticoid therapy along with good compliance, careful monitoring of androgen levels and continuous psychological management could contribute to improved fertility rates in this population, even among those with the severe variant.

1. Introduction

Congenital adrenal hyperplasia (CAH) describes a group of inherited autosomal recessive disorders that cause deficiency in an adrenal enzyme resulting in the impairment of cortisol and aldosterone biosynthesis. 21-Hydroxylase deficiency (21-OHD) accounts for 95% of all affected patients, and is caused by inactivating mutations in the 21-hydroxylase gene (CYP21A2) (1). The loss of negative feedback inhibition by cortisol leads to increased hypothalamic–pituitary–adrenal axis activity, and subsequent hyperplasia of the adrenal gland. There are different clinical forms of CAH associated with 21-OHD: classical CAH, the most severe form comprises both salt-wasting (SW) and simple virilizing (SV) forms, and the non-classical (NC) form which may be asymptomatic or associated with signs of postnatal or even adult onset androgen excess. With the availability of glucocorticoid replacement allowing patients to reach adulthood, recent attention has been paid toward long-term health problems such as fertility (2). Several lines of evidence indicate that CAH patients had impaired fertility and fecundity (2–5). In males, the most obvious cause of subfertility is the occurrence of testicular adrenal rest tumours (TARTs), but other causes probably contribute (2,3). In females, several hormonal, structural and psychological factors have been suggested to contribute to the disturbed reproductive axis (4,5).

The aim of this study was to investigate fertility in a sample of Tunisian CAH patients with CAH due to 21-OHD.

2. Patients and methods

2.1. Patients

This descriptive study enrolled 26 patients (11 M; 15 F, mean age ± SD = 27.4 ± 8.2 years, range: 16.5–48 years) who were regularly followed in two clinics: Sfax and Mahdia, Tunisia. All these individuals had CAH with 21-OHD. The diagnosis of CAH was based on clinical and biochemical criteria (i.e. elevated levels of 17-hydroxyprogesterone (17-OHP) and androstenedione, ACTH stimulation test). None of the patients was treated in utero with dexamethasone.

Ten patients (6 M, 4 F) had the SW form of CAH, and they had been diagnosed in their first year of life. Eight patients (5 M, 3 F, age at diagnosis: between birth and 6 years) were diagnosed as classical SV patients. In the other eight patients (women only in this group), the NC form was diagnosed during between 15 and 44 years of age.

All patients had been treated from the time of diagnosis. Twenty-one patients, 16 with the classical form and five with the NC form, were started on a regimen of hydrocortisone (HC), given two or three times daily, while the remaining five patients (three with the NC form and two with the classic SV form) were treated with dexamethasone (once daily). Salt wasters were treated with 27.9 ± 9.6 mg/m^2 per day of HC for the first 2 years of life, and the doses were decreased to 17.6 ± 6.6 mg/m^2 per day during childhood. Daily doses of HC in patients with classical and NC forms were respectively 17.3 ± 4.6 mg/m^2 and 16.04 ± 3.4 mg/m^2 during adulthood. For dexamethasone, the prescribed doses ranged from 0.25 to 0.75 mg per day. Fifteen patients (10 with the SW form and five with the SV form) additionally received 9α-fludrocortisone (FC; twice daily).

A single stage clitoroplasty, vaginoplasty and labiaplasty were performed in all female patients with classic CAH. Patient age at the time of surgery ranged from 6 month to 6 years. During follow-up, no complications such as fistulas or vaginal strictures were noted, and all patients had a good genital cosmetic appearance.

The adequacy of therapy was monitored periodically on the basis of clinical and laboratory data, in accordance with 2002 guidelines (6). Patients were classified as under adequate hormonal control if 50% or more of the total serum androgen levels were within normal limits for age or if 50% or more of the baseline serum 17-OHP concentrations were 2.0–10 ng/mL (6–30 nmol/L). Possible overtreatment was defined as suppressed androgen and 17-OHP levels in serum.

The mean duration of follow-up period was 18.5 ± 9.3 (range 3–41.5) years. Seven patients had experienced a salt-wasting adrenal crisis in the neonatal period. The onset of puberty (defined by onset of breast development in females and increased testicular volumes in males) was 10.8 ± 1.4 years for girls and 11.2 ± 1.2 years for boys. Menarche occurred spontaneously in all patients, at an average age of 12.8 ± 1.1 years. One female patient with the NC form (patient No. 23) had a history of previously diagnosed congenital hypothyroidism. She was started on L-thyroxine 10 μg/kg per day at the age of 6 month, but she was irregular in follow-up and was not compliant with the treatment.

2.2. Clinical assessment

Data related to fertility were collected in a standardized fashion, either prospectively or by retrospective review of the clinical file. In male patients (n = 11), testicular palpation was

performed in order to detect any mass. For female patients ($n = 15$), menstrual history; pregnancy desire; number of pregnancies obtained; spontaneously or with treatment; and outcome (birth or miscarriage) were collected. The degree of hirsutism was assessed using the Ferriman–Gallwey scoring method, and hirsutism was considered to be present when a score of at least eight was evident (7). Prader score was used to classify abnormalities of the external female genitalia (8).

2.3. Hormone assays

For women, blood samples were collected during the follicular phase of those with regular menstrual cycle and at any time in the amenorrheic patients. Circulating concentrations of Δ4-androstenedione, testosterone, LH, FSH, ACTH and 17-OHP were measured by commercially available assays. Reference ranges of Δ4-androstenedione, age adjusted, were 0.65–2.1 ng/mL for males and 0.8–2.4 ng/mL for females. Supine plasma renin concentrations were measured using a commercial radioimmunoassay kit (RIA kit; CIS Bio International). Inhibin B concentration was measured in duplicate in serum samples using a solid-phase sandwich ELISA (DSL-10-84100 ACTIVE® Inhibin-B ELISA kit). Serum level of AMH was measured by the ELISA technique (DSL-10-14400 ACTIVE® MIS/AMH ELISA kit). Reference values were between 94 and 327 pg/mL for the inhibin B, and between 2.2 and 6.8 ng/mL for AMH. The lower limit of detection was 10 pg/mL for Inhibin B and 0.1 ng/mL for AMH.

2.4. Fertility assessment

In addition to clinical exam, all male patients underwent a testicular ultrasonogram. Doppler and B-mode studies were performed using a high-frequency linear-array transducer. Indeed, seminal fluid was collected by 10 of 11 patients after 2–3 days of ejaculatory abstinence. The analysis included estimation of semen volume, sperm concentration, total sperm count, motility and morphology. Semen was evaluated according to the WHO standard (9). For female patients, following the clinical examination, pelvic ultrasonography was performed for the diagnosis of polycystic ovary syndrome (PCOS), as proposed by the Rotterdam consensus (10).

3. Results

3.1. Hormonal control

At the time of the study, mean morning baseline 17-OHP in serum for the whole cohort was 22.51 ng/mL (range, 1.1–77); mean morning Δ4-androstenedione levels were 5.25 ng/mL (range, 1.6–24) and mean morning plasma ACTH levels were 118.31 pg/mL (range, 6.5–537).

During the treatment period, nine patients (34.6%) showed well controlled CAH. Poor hormonal control, with elevation of 50% or more of Δ4-androstenedione and 17-OHP serum measurements, was present in 16 patients (61.5%). These were chronically non compliant patients, mainly because of ignorance and lack of understanding. The remaining patient (patient No. 8) had suppressed androgen and 17-OHP levels indicating possible overtreatment.

3.2. Male fertility

Palpation of the testes revealed bilateral testicular atrophy and a 2 cm bilateral, firm and irregular nodule in patient No. 1. This patient had also a low level of testosterone (1.3 ng/mL), FSH (0.72 U/L) and LH (0.27 U/L). All these parameters were within the reference range in the 10 remaining patients. The mean serum inhibin B level was 117.74 ± 75.25 pg/mL (range, 15.36–222.91). Inhibin B concentrations were below the reference range in 4/11 patients. Testicular sonography detected TARTs in 6/11 patients, all showed poor hormonal control and non-compliance to steroid therapy. The maximal diameter of these tumours ranged from 0.8 to 2.6 cm. In all cases, these tumours were bilateral, hypoechoic, and seemed to originate from the mediastinum testis (Fig. 1). Indeed, sperm abnormalities were found in 4/10 patients: azoospermia in two patients (patients No. 1 and 5), oligoasthenospermia in one patient (patient No. 2), and oligo-astheno-teratospermia in one patient (patient No. 10). One patient (patient No. 11) successfully fathered two normal children, while another (patient No. 11) had unsuccessfully tried to conceive since the age of 26 years. Data related to fertility outcome in male patients are summarized in Table 1.

3.3. Female fertility

Hirsutism was present in 9/15 female patients (60%), and the median Ferriman-Gallwey score was 15.8 (range, 10–20). In addition, three female patients (two with the NC form and one with the SV form) presented with mild clitoromegaly (Prader score stage 1). Irregular menses (oligomenorrhea or spaniomenorrhea) were noted in four patients (two with the NC form, one with the SW form and one with the SV form). Serum oestradiol concentration was reduced in one patient with the SV form (patient No. 18, <9 pg/mL). This patient was noncompliant with her treatment, and had also low serum FSH and LH levels (1.26 and 1.66 U/L, respectively). Mean AMH serum level was 2.92 ± 2.1 ng/mL (range, 0.1–6.06) and was reduced in four patients (one with the SV form and three with the NC form). Mean serum testosterone level was 1.95 ± 2.21 ng/mL (range, 0.26–6.4). Pelvic ultrasound showed polycystic ovaries in five patients. According to the Rotterdam criteria, six patients (40%) had PCOS: one with SW form, one with the SV form, and four with the NC form. All female patients with either PCOS or reduced AMH levels were noncompliant with their medication, and showed poor hormonal control.

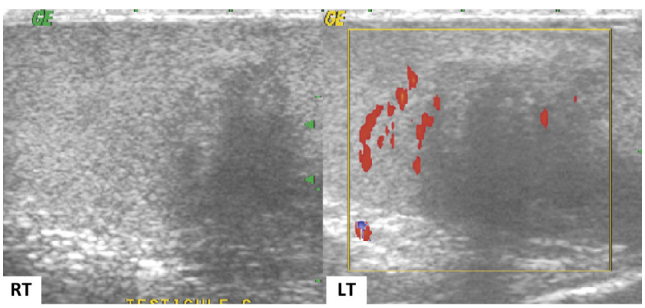

Figure 1 Bilateral testicular adrenal rest tumors in patient 2.

Table 1 Data related to fertility outcome in male patients.

Patient No./age (yr)/phenotype	Hormonal control*	Testicular exam	Hormonal profile				Semen analysis	Testicular sonographic findings ± TART size (mm)
			FSH (U/L)	LH (U/L)	T (ng/mL)	Inhibin B (pg/mL)		
1/21/SW	Poor	Palpable nodule	0.72	0.27	1.3	15.36	ASP	Hypoechoic nodules RT: 21 × 18 LT: 19 × 18
2/18/SW	Poor	N	6.89	2.98	6.78	46.8	OAS	Hypoechoic nodules RT: 22 × 20 LT: 20 × 18
3/23/SW	Poor	N	5.33	2.21	9.17	78.25	N	Hypoechoic nodules RT: 12 × 10 LT: 8 × 8
4/16.5/SW	Poor	N	2.15	1.7	3.89	183.84	ND	Hypoechoic nodules RT: 11 × 9 LT: 8 × 6
5/22.5/SW	Poor	N	3.46	3.75	8.49	19.16	ASP	Hypoechoic nodules RT: 26 × 12 LT: 24 × 19
6/22.5/SW	Adequate	N	4.8	3.1	3.5	222.91	N	N
7/31/SV	Adequate	N	5.7	2.9	4.1	105.7	N	N
8/17.5/SV	Poor	N	2	4	4.5	207.18	N	N
9/18/SV	Adequate	N	6.28	3.5	6.6	195.6	N	N
10/28/SV	Poor	N	5.04	1.99	5.56	103.52	OATS	Hypoechoic nodules RT: 18 × 10 LT: 15 × 6
11/47.5/SV	Adequate	N	7.1	5.2	3.7	116.83	N	N

SW: salt wasting; SV: simple virilizing; FSH: follicle-stimulating hormone; LH: luteinizing hormone; T: testosterone; RT: right testicle; LF: left testicle; N: normal; ASP: azoospermia; OATS: oligo-astheno-teratospermia; OAS: oligoasthenospermia; TART: testicular adrenal rest tumors.

* Hormonal control was considered adequate if 50% or more of the total serum androgen levels during follow-up were within normal limits for age or if 50% or more of the baseline serum 17-OHP concentrations were 2.0–10 ng/mL (6–30 nmol/L).

Table 2 Data related to fertility outcome in female patients.

Patient No./age (yr)/phenotype	Hormonal control*	Clinical exam	Hormonal profile					Pelvic sonographic findings
			FSH (U/L)	LH (U/L)	E2 (pg/mL)	T (ng/mL)	AMH (ng/mL)	
12/21/SV	Poor	Hirsutism	7.1	4.3	76	0.44	3.9	N
13/26/SV	Poor	Clitoridomegaly	5.2	3.1	77	0.62	3.7	N
14/25/SW	Adequate	N	6.02	2.2	85	0.69	4.7	N
15/23.5/SW	Poor	N	5.15	2.47	97	0.27	6.06	N
16/22/SW	Adequate	N (with 1 successful pregnancy)	5.55	3.89	144	0.26	4.4	N
17/27/SW	Poor	Hirsutism Menstrual disorders One miscarriage	7.24	4.4	98	0.82	4.8	N
18/33/SV	Poor	Hirsutism Menstrual disorders	1.66	0.34	< 9	5.82	1.8	Polycystic ovaries
19/28/NC	Poor	Hirsutism Sterility	4.54	3.48	90	0.68	5.12	N
20/26/NC	Adequate	N	5.94	2.78	104	0.54	3.7	N
21/30.5/NC	Poor	Hirsutism 2 successful pregnancies	6.48	4.06	78.9	0.66	2.95	N
22/48/NC	Poor	Clitoridomegaly Menstrual disorders	6.2	2.7	128	2.18	0.11	Polycystic ovaries
23/36/NC	Poor	Hirsutism	7.3	2.1	36.1	2.7	2.3	Polycystic ovaries
24/36/NC	Poor	Hirsutism Clitoridomegaly	7.2	6.1	53	0.33	0.01	N
25/34/NC	Poor	Hirsutism	5.9	7.4	71	6.4	0	Polycystic ovaries
26/32/NC	Poor	Hirsutism Menstrual disorders	6.9	3.86	56	0.77	3.05	Polycystic ovaries

SW: salt wasting; SV: simple virilizing; NC: non-classical; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estrogen; T: testosterone; AMH: Anti-Müllerian Hormone; N: normal.
* Hormonal control was considered adequate if 50% or more of the total serum androgen levels during follow-up were within normal limits for age or if 50% or more of the baseline serum 17-OHP concentrations were 2.0–10 ng/mL (6–30 nmol/L).

Four female patients were married and wished to get pregnant. Three of them became pregnant spontaneously: patient No. 17 had a spontaneous miscarriage, patient No. 16 had one healthy child, and patient No. 21 had two healthy children. All deliveries were done with elective cesarean section. The remaining patient (patient No. 19) was sterile. This patient was very noncompliant with her daily glucocorticoid treatment. She complained of spaniomenorrhea, and presented with moderate hirsutism associated with bilaterally enlarged, cystic ovaries. Absolute causes of sterility, such as bilateral tubal obstruction and azoospermia of the male partner, were previously excluded. Data related to fertility outcome in female patients are summarized in Table 2.

4. Discussion

In the current study, markers of gonadal function, involving both Sertoli and Leydig cells, were reduced in 4/11 patients and abnormalities in semen analysis were noted in 4/10 patients. Furthermore, testicular sonograms revealed testicular adrenal rests in 6/11 subjects, all of whom were noncompliant with their glucocorticoid replacement, with subsequent chronic elevation of ACTH. Our findings confirm and extend previous studies showing that men with CAH have reduced fertility (11).

Some patients, as was our case No. 1, may develop hypogonadotropic hypogonadism due to high levels of steroids which suppress the hypothalamic–pituitary–gonadal axis (12). More frequently, men with CAH have infertility because of TARTs. Most authors now agree that TARTs develop from ectopic remnants of intratesticular adrenal tissue stimulated by ACTH hypersecretion (13). These tumors may be prevalent in up to 94% of CAH adults and may already appear during childhood (13).

TARTs produce adrenal-specific steroids, contain adrenal-specific enzymes, and express ACTH and angiotensin II receptors.

All our patients with TARTs showed poor hormonal control with subsequent chronic elevation of ACTH. Our findings corroborate the hypothesis that poor hormonal control and inadequate suppression of ACTH secretion are dominant etiological factors in the development of TARTs. However such tumors were also reported in adequately or even over-treated patients with suppressed ACTH levels, and other factors such as mineralocorticoid replacement adequacy could be involved in this tumorogenesis (13).

TARTs can affect testicular function directly through mechanical compression of adjacent seminiferous tubules and/or indirectly (paracrine effect) via local steroid production which may be toxic to the Leydig cells and germ cells (13). Indeed, long-standing TARTs can lead to peritubular fibrosis and tubular hyalinization, which confirms irreversible testicular damage. Thus, these tumors should be periodically screened from adolescence by ultrasound (13). Increased glucocorticoid doses and effective suppression with dexamethasone can reduce the size of the TARTs in the early stages and can also induce a rise in sperm count (12). When there is no response to dexamethasone, testis sparing surgery may be considered (13,14).

In our cohort of 15 female patients, one had sterility, one presented with hypogonadotropic hypogonadism and six showed POCS. Indeed, 4 women had low level of AMH, which is considered now as an important clinical marker of ovarian functioning, as well as a useful predictor of fertility outcomes (15). These results provide corroborating evidence of a low frequency of pregnancy among women with CAH compared with their age-matched controls and this is especially true in the salt-wasting form of classical CAH (2,4,5).

This subfertility seems to be due to several contributing factors. Tonic oversecretion of androgens (partly aromatized to estrogens) results in a continuous steroidal feedback and thus, loss of gonadotropin cyclicity, leading to anovulation or dysovulation (16). Progesterone hypersecretion; seen even in women with adequate hormonal control; may have a mini-pill-like effect on the endometrium leading to anovulatory cycles and could also affect the quality of cervical mucus (17). Secondary polycystic ovary syndrome, common in this disease, could represent an additional factor contributing to infertility (18,19). Genital surgery may result in the impairment of clitoral sensation, vaginal stenosis, poor cosmesis, anorgasmia, and painful intercourse. These complications are thought to be more common after clitorectomy than after new techniques which preserve innervation and clitoral sensation (20).

Psychosexual factors may also play a role in the overall reduction in childbirth rates in classic 21-OHD. In childhood, girls with CAH have masculinized behavior and are more likely to use physical aggression in conflict situations; possibly due to the effects of the prenatal exposure to high androgen levels. Adult females with 21-OHD have often a less favorable sexual self-image, less partnership and reduced heterosexual activity (21,22).

In contrast to reduced fertility in classic CAH, pregnancies are commonly normal and uneventful. Current evidence suggests that fertility rather than pregnancy rates seems to be reduced compared to the general population (23). Among four females trying to conceive, we report one patient with spontaneous miscarriage, two patients who achieved uneventful pregnancies resulting in one birth for one patient and two for the other, and one patient with sterility. The latter showed poor compliance with treatment with subsequent chronic hyperandrogenism.

Fertility in NC CAH is only mildly reduced, and seems to be mainly due to hormonal imbalance. However, without glucocorticoid treatment, an increased miscarriage rate has been reported (24).

The main causes of fertility issues in our female patients seem to be medication non compliance and subsequent hyperandrogenism. Thus, better compliance with therapy and careful monitoring of androgen levels could contribute to improving fertility rates among women with CAH.

In conclusion, fertility in male and female patients with CAH is reduced, especially in those with poor disease control. Prevention of subfertility requires a multidisciplinary approach from infancy through adulthood. Early and adequate glucocorticoid therapy along with good compliance, careful monitoring of androgen levels and continuous psychological management could contribute to improved fertility rates in this population, even among those with the severe variant.

Conflict of interest

None to declare.

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