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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;
21 Hydroxylase deficiency;
Fertility;
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