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Congenital adrenal hyperplasia in adolescence — a gynecological perspective

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ABSTRACT

Objectives: Analysis of congenital adrenal hyperplasia (CAH) cases, gynaecological implications, referral reasons to gynaecologist and treatment.

Material and methods: Retrospective, longitudinal, single-centre study with female CAH paediatric patients ≥ 10 years-old, followed between 1998–2018 in gynaecology and endocrinology departments at a public university tertiary hospital.

Results: 47 patients, 34.0% (n = 16) with classic, 66.0% (n = 31) with non-classic forms (NCAH), CYP21 deficit and 46,XX karyotype. We found a normal median menarche age [11.5 IQR 2 (6–15) years-old], but significantly earlier in NCAH (p = 0.003). Precocious puberty occurred in 48.9%, n = 23. Primary amenorrhea occurred in salt-wasting form (21.4%, n = 3). Oligomenorrhea and hirsutism were significantly more prevalent in NCAH (p = 0.018, p = 0.014 respectively) and acanthosis nigricans and virilization signs in classic forms (p = 0.05, p = 0.000 respectively). Sixteen patients (34.0%) were referred to gynaecology, mostly due to menstrual irregularities (50.0%, n = 8). Medical treatment with isolated or combined corticoids, oestrogen and progestogen were chosen in all but one case. Gonadotropin-releasing hormone analogues were used in 19.0% (n = 9). Surgery was performed in 34.0% (n = 16) patients, median age 2.0 IQR 2.5 (0.6–90) years-old.

Conclusions: This paper highlights the importance of a multidisciplinary approach. Early treatment contributes to a phenotypical feminine differentiation and normalization of the hypothalamus-pituitary-ovarian axis, which is essential given the gynaecologic and obstetric consequences of untreated cases.

Key words: congenital adrenal hyperplasia; hyperandrogenism; steroid 21-hydroxylase; menstruation disorders; amenorrhea

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is one of the most frequent genetic disorders of sexual development.

According to the enzymatic activity, the most severe, or classic, form of CAH is characterized by neonatal adrenal insufficiency with salt-wasting (SW), or it may only be only in early childhood due to virilization signs (simple virilizing form — SV). In girls, the androgen excess can cause virilization of the external genitalia, and therefore sexual ambiguity typical of the classic form includes clitoromegaly, labioscrotal fold fusion, and a common urogenital sinus [1].

The non-classic form (NCAH) is less severe, the clinical features being hyperandrogenism with no neonatal sexual ambiguity. Most females with NCAH are asymptomatic during prepubertal years and premature pubarche can be the primordial sign. Different degrees of clinical hyperandrogenism usually follow (acne, hirsutism, male-pattern balding) together with precocious puberty, menstrual cycle disorders, and infertility. Some cases of NCAH remain asymptomatic [2].

Objectives

In this study our aim was to retrospectively analyze the gynaecologic healthcare management of female patients with CAH in a tertiary paediatric hospital of a Southern European country.

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MATERIAL AND METHODS

We undertook a retrospective, longitudinal, single-center study between 1998 and 2018, with a group of females with CAH who were ≥ 10 years old. The girls in our study group had been born between 1989 and 2008 and at diagnosis, each girl was entered on an electronic CAH database by the assistant endocrinologist. Forty-seven subjects were included in our study: 16 girls (34.0%) with classic CAH, and 31 girls (66.0%) with NCAH, and all with CYP21 deficiency genetically proven and 46,XX karyotype. We performed a descriptive analysis of the general sample and within each, specified the CAH form for each, and compared data for the classic and non-classic forms. Parameters evaluated include gynaecological implications and the main reasons recorded for the original referral to the childhood and adolescence gynaecologist. Statistical analysis was performed using IBM SPSS Statistics Version 24.0. Descriptive statistics were analyzed as mean and standard deviations for variables with normal distribution, and as median and interquartile ranges for variables without normal distribution. Variables were described in percentages (%) and absolute numbers (n). Nominal variables were compared using Pearson's chi-squared test or Fisher's exact test according to Cochran's rule. The comparison of continuous variables was performed with either Student's T-tests (parametric test, applied after verifying the homogeneity of variances using Levene's test) or the Mann-Whitney test (non-parametric test). The significance level is 0.05, with a corresponding confidence level of 95%.

Our study was conducted in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association.

RESULTS

The neonatal adrenal insufficiency with salt-wasting (SW) form of CAH was present in 29.8% (n = 14) of subjects, the simple virilizing (SV) form in 4.3% (n = 2), and the remainder (66.0%, n = 31) of the cases were NCAH. The diagnosis of SW was made prior to 1 year of age (plus, there was one case of prenatal diagnosis); for SV, the median age of diagnosis was 3 (2.0–4.0) years old; and for NCAH, the mean age of diagnosis was 10.6 ± 4.1 (1.0–17.0) years old. Only 8.5% (n = 4) of cases had a family history of CAH, and all of these were NCAH. Among concomitant comorbidities (Fig. 1), adrenal insufficiency was the most frequent (n = 20), corresponding to 42.6% of the patients (16 in classic form and at least one episode of adrenal insufficiency in each of four patients with NCAH forms).

Precocious puberty occurred in 48.9% (n = 23) subjects. The mean age of pubarche was 6.9 ± 2.6 (3–13 years old);

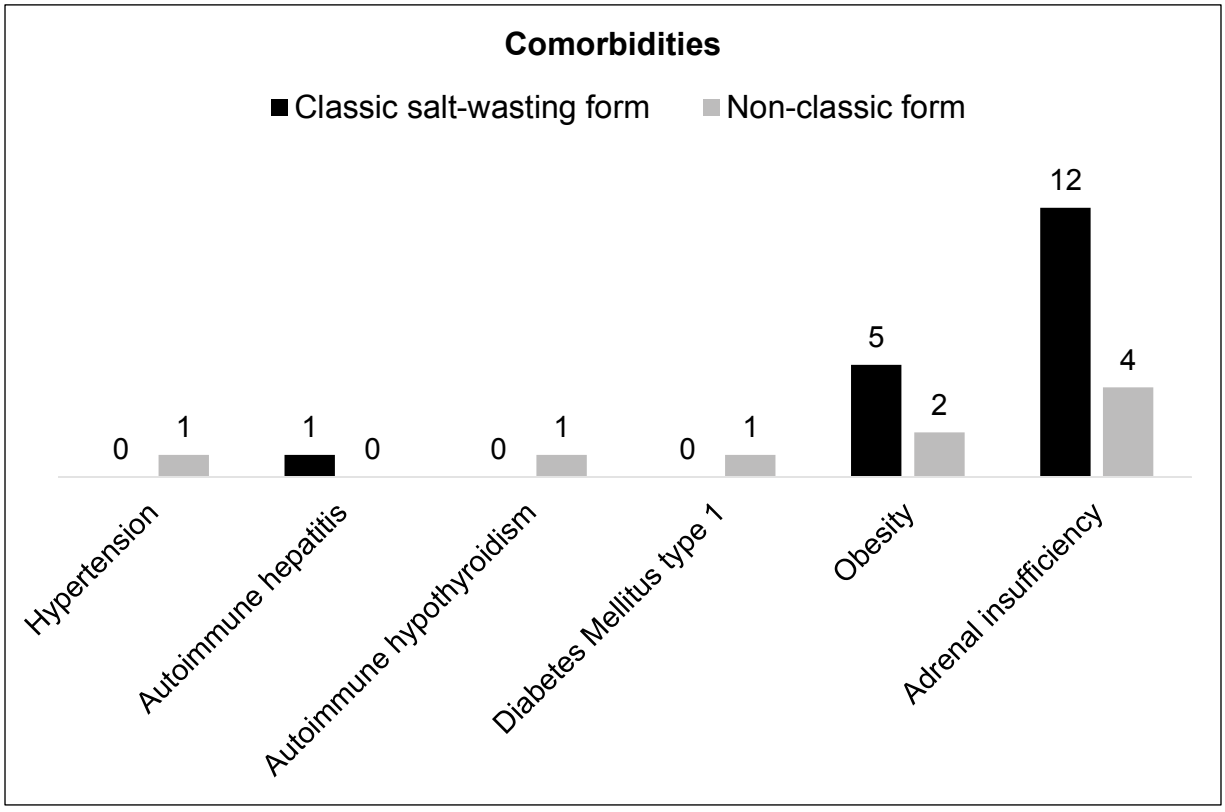

Figure 1. Patients' comorbidities

Table 1. Characterization of gynecological and therapeutic data

	All n = 47	Classic salt-wasting n = 14 (29.8%)	Classic simple virilizing n = 2 (4.3%)	Non-classic n = 31 (66.0%)	Classic vs non-classic forms (p value)
Demographic data					
Age at diagnosis, yr ($\bar{x}$,σ) or M, [range]	7.7 IQR 13 [0–17]	N/A < 1	3 [2.0–4.0]	10.6 ± 4.1 [1.0-17.0]	—
Sexual development					
Pubarche, yr ($\bar{x}$,σ) or M, IQR [range]	6.9 ± 2.6 [3.0–13.0]	9.0 IQR 7.0 [4.0–13.0]	4.0 [3.0–5.0]	6.5 ± 1.8 [4.0–11.0]	> 0.05 Mann-Whitney U
Thelarche,yr ($\bar{x}$,σ) or M, IQR [range]	8.9 ± 2.3 [4–13]	10.6 ± 2.1 [7–13]	6 [4–8]	8.4 ± 1.9 [5–11]	> 0.05 Independent samples t-test
Menarche,yr ($\bar{x}$,σ) or M, IQR [range]	11.5 IQR 2 [6–15]	13.1 ± 1.3 [11–15]	12 [11–13]	11 IQR 2 [6–14]	0.003 Mann-Whitney U
Menstrual disturbances					
Primary amenorrhea (%, n)	6.4 (3)	21.4 (3)	—	—	**0.035** Fisher's exact test
Secondary amenorrhea (%, n)	8.5 (4)	7.1 (1)	—	9.7 (3)	> 0.05 Fisher's exact test
Oligoamenorrhea (%, n)	48.9 (23)	28.6 (4)	—	61.3 (19)	**0.018** Chi-squared test
Polimenorrhea (%, n)	4.3 (2)	—	—	6.5 (2)	> 0.05 Fisher's exact test
Signs of hyperandrogenism					
Clinical hirsutism (%, n)	61.7 (29)	42.9 (6)	—	74.2 (23)	**0.014** Chi-squared test
Acne (%, n)	53.2 (25)	42.9 (6)	50.0 (1)	58.1 (18)	> 0.05 Chi-squared test
Acanthosis nigricans (%, n)	19.1 (9)	42.9 (6)	—	9.7 (3)	**0.05** Fisher's exact test
Stretch marks (%, n)	31.9 (15)	50.0 (7)	—	25.8 (8)	> 0.05 Chi-squared test
Virilization signs (%, n)	38.8 (18)	78.6 (11)	100.0 (2)	16.1 (5)	**0.000** Chi-squared test
Medical therapy					
C (%, n)	40.4 (19)	42.9 (6)	100.0 (2)	35.5 (11)	—
C + E + antiandrogenic P (%, n)	40.4 (19)	57.1 (8)	—	35.5 (11)	—
C + E + antiandrogenic P + metformin (%, n)	10.6 (5)	—	—	16.1 (5)	—
E + antiandrogenic P (%, n)	6.4 (3)	—	—	9.7 (3)	—
GnRHa (%, n)	56.3 (9)	14.3 (2)	50.0 (1)	19.4 (6)	—
Surgical intervention					
Age at first surgery (M, IQR), [range]	2.0 IQR 2.5 [0.6–9]	2 IQR 2.8 [0.6–9]	3.5 [3–4]	—	—
Surgical re-intervention (%, n)	8.5 (4)	8.5 (4)	—	—	—

C — corticoid; E — estrogen; GnRHa — gonadrotropin releasing hormone analogs; IQR — interquartile range; M— median; N/A — not applicable; P — progestogen; $\bar{x}$ — mean; σ — standard deviation

the mean age of the larche was 8.9 ± 2.3 (4–13 years old); and the median age of menarche was 11.5 IQR 2 (6–15 years old). These data are presented for each CAH form in Table 1. Regular menstrual cycles were referred to by 31.9% (n = 15) of subjects; and of the others, 6.4% (n = 3) had primary amenorrhea, 8.5% (n = 4) secondary amenorrhea, and 53.2% (n = 25) irregular cycles (48.9%, n = 23 oligomenorrhea, and 4.3%, n = 2 polymenorrhea).

Clinical hirsutism was present in 61.7% (n = 29) subjects, acne in 53.2% (n = 25), acanthosis nigricans in 19.1% (n = 9), stretch marks in 31.9% (n = 15), and virilization signs in 38.8% (n = 18). Sexual ambiguity was observed in 16 (34.0%),

and all of these were of the classic form. Signs of virilization were classified using the Prader scale as n = 4 (25.0%) at grade 1, n = 4 (25.0%) at grade 2, n = 7 (43.8%) at grade 3, and n = 1 (6.3%) at grade 4.

Sixteen patients (34.0%) were referred to a gynecologist: six with classic CAH form with a mean age 15.8 ± 2.9 (13–21 years old), and 10 with NCAH with a mean age of 15.5 ± 1.8 (13––19 years old). The main reason for the referrals was menstrual irregularities (50.0%, n = 8); and other reasons were secondary amenorrhea (18.8%, n = 3), sexual ambiguity (6.2%, n = 1), hirsutism (12.5%, n = 2), and primary amenorrhea (12.5%, n = 2). Of the 37 supra-pubic/transvaginal ultrasounds performed, 16.7% (n = 6) of subjects had polycystic ovaries, and all were NCAH patients.

Medical treatment with isolated corticotherapy was chosen for 40.4% (n = 19) of patients. Estrogen combined with an antiandrogenic progestogen was chosen for 6.4% (n = 3) patients. In a further 40.4% of patients (n = 19), corticotherapy in combination with oestrogen with an antiandrogenic progestogen were administered. Corticoid plus oestrogen plus antiandrogenic progestogen plus metformin was chosen in 10.6% (n = 5) of cases. One patient with NCAH remained under clinical follow-up. Concomitantly, in order to prevent advanced bone age, gonadotropin-releasing hormone analogs (GnRHa) were used in 19.0% subjects (n = 9) with a mean age of 6.8 ± 1.7 (3–9) years old at the start, and of 11.1 ± 1.2 (10–13) years old at the end of treatment.

Surgical treatment was performed in 34.0% of subjects (n = 16), always during childhood [median age at first surgery 2.0 IQR 2.5 (0.6–9)]. The surgical methods performed were clitoral hoodoplasty in 25.0% (n = 4), genitoplasty (vulvar and vaginal) in 6.3% (n = 1), clitoroplasty plus genitoplasty in 31.3% (n = 5), clitoroplasty plus genitoplasty with additional closure of urethrovaginal fistula in 6.3% (n = 1), and clitoroplasty plus genitoplasty with surgical repair of ureters and urethra in 31.3% (n = 5) cases. Re-intervention was needed in 25.0% of these patients (n = 4) who were at Prader 3 (n = 3) and Prader 4 stages (n = 1). The re--intervention surgeries were clitoroplasty (n = 2 patients) and vaginoplasty (n = 2 patients).

The gynaecological and therapeutic data for each CAH form are specified in Table 1.

Simultaneous assistance was provided to patients by other specialties: urology (urologic surgery) in 29.8% (n = 14), paedopsychiatry in 17.0% (n = 8), paediatrics (neurodevelopment) in 10.6% (n = 5), genetics (genetic counselling) in 59.6% (n = 28), and psychology in 4.3% (n = 2) of cases. During the follow-up of these girls, there was 1 case of evolving pregnancy.

DISCUSSION

To the best of our knowledge, patients with classic forms are usually diagnosed early in life as clinics undertake prompt investigations. However, patients with NCAH may only be diagnosed later in life, mainly due to precocious puberty, abnormally accelerated growth velocity (crossing percentiles), or menstrual cycle disorders [3].

In Portugal there is no national neonatal screening for CAH, and newborns are only investigated if there are clinical signs of this disorder or there is a family background suggesting a heightened risk. Nevertheless, neonatal screening tests can produce false-negative results, so newborns with atypical genitalia should be investigated further, regardless [4].

Our patients all had genetically confirmed CAH at the time of data analysis, so this paper will not focus on the diagnoses, except for our prenatally diagnosed case, which was detected in a mid-trimester ultrasound due to clitoris hypertrophy with the absence of testicles. A female karyotype 46,XX and high amniotic fluid 17-hydroxyprogesterone were confirmed by amniocentesis.

In terms of comorbidities, three patients had autoimmune disorders. Falhammar H. et al. [5], investigated a possible correlation between the CYP21A2 gene and these disorders, as its location is known to be highly immunologically active. In 714 patients with 21-hydroxylase deficiency, they discovered an increased prevalence of autoimmune disorders.

Although gonadotropin-dependent precocious puberty is a possible consequence of CAH, our patients had a normal median menarche age. However, the age of menarche in NCAH was statistically significantly earlier than in the classic forms. Our findings are similar to a study by Lien Trinh et al. [6], in which girls with CAH with earlier puberty showed a mean age of menarche identical to the general population, but in contrast to our findings, they found no significant differences between different CAH forms. In this and other parameters, that study's different racial and ethnic origins and treatment protocols may account for the difference between our two studies.

Premature pubarche is diagnosed when pubic or axillary hair or apocrine odor start when females are younger than eight years old [7]. In a series of 220 cases including 25 children < 10 years old with NCAH, Moran C. et al., found a premature pubarche rate of 10.5% in this sub-group [3, 8]. That rate was markedly lower than the rate of 54.8% (17 out of 31) in the same sub-population in our study. We found no significant differences in the timing of pubarche between classic and NCAH cases. The earlier onset of pubarche in classic CAH cases compared with that in the general population is also described in literature. We agree with Völkl T. et al. [9], who speculate that this might be due to an incomplete adrenal androgen suppression when attempting to avoid steroid overtreatment.

Oligomenorrhea and chronic anovulation are frequent in NCAH patients but can also arise in classic forms even with appropriate treatment [3]. In inadequately cases, the onset of menarche might be delayed [6]. During the development of puberty, evaluation of potential lower genital tract obstructions to menstrual flow should be investigated in those girls with classic CAH who have not undergone surgery previously, as these obstructions can be responsible for primary amenorrhea. Two of our three cases of primary amenorrhea (all of them classic forms) had previously undergone vulvovaginoplasty, but had not undergone any subsequent surgical intervention, so we concluded that menstrual flow obstruction was not the cause of amenorrhea [10]. Moran C. et al. [8], reported a 54% prevalence of oligomenorrhea in NCAH, which was a slightly lower result than our 61.3%. We found a higher significant prevalence of oligomenorrhea in NCAH, and we postulate that as classic form patients were diagnosed and treated earlier, the rate of these menstrual irregularities was less frequent.

Because of menstrual disorders, female adolescents might assume that they have no need for contraception. The gynaecologist has a critical role in managing family planning issues in order to avoid undesired pregnancies. Combined hormonal contraception is a first-line option.

Hirsutism and acne are common in NCAH, with hirsutism being the most commonly presenting feature [3]. Hirsutism was the most common sign of hyperandrogenism in our sample, and as expected, there was a significant difference between classic and NCAH cases, with it being more prevalent in the latter. There are reports in the literature of a 60% prevalence of hirsutism in NCAH forms, compared with our even higher prevalence of 74.2%. The prevalence of acne in NCAH forms is described in the literature as 33%, which is a lower value than our finding of 58.1% [8].

The first-line treatment for both CAH forms are glucocorticoids, and for the classic form, together with mineralocorticoids and salt supplementation. Ensuring the suppression of adrenal androgens is sometimes difficult, and one of the major risks of overtreatment is growth retardation and other features of Cushing syndrome [10]. Indeed, besides acne, hyperandrogenism can lead to other dermatologic manifestations, such as acanthosis nigricans and stretch marks [9]. We found a statistically significantly higher incidence of acanthosis nigricans in classic forms, probably due to the subjects undergoing a longer period of steroid therapy.

Virilization signs, as expected, were significantly more prevalent in classic forms and only in these cases were virilized external genitalia present at birth. Nevertheless, NCAH can also present later in life with clitoromegaly, androgenic alopecia, perianal hair, adult apocrine odor and hoarseness of voice [11]. *In utero* androgen exposure only occurs in classic forms, justifying the expected differences in virilization signs [12].

The endogenous hyperandrogenic environment of CAH can interfere with ovarian function, thus causing a polycystic ovarian morphology, which is consistent with our finding that 19.4% of our NCAH patients had these features [3]. Carmina et al. [13], reported polycystic ovarian morphology in 80% of a group of adult women with NCAH, but Pall et al. [14], found a prevalence of only 24%.

The goals of medical therapy are to prevent adrenal crisis and growth retardation, to improve sexual maturation and reproductive function, to determine the optimal timing for spontaneous puberty, regularize menstrual cycles and fertility, improve the symptoms of hyperandrogenism, and promote self-esteem [15]. These can be achieved by replacing deficient steroids and concomitantly trying to decrease adrenal sex hormones and prevent iatrogenic glucocorticoid excess [16].

Without corticoid treatment, classic forms are markedly at risk of adrenal insufficiency [17]. Nonetheless, glucocorticoids can also be part of NCAH treatment in pre- and peripubertal phases if there is an advanced bone age or early onset of pubarche [2]. Additionally, about one third of NCAH patients have partial cortisol insufficiency and may benefit from glucocorticoid supplementation. Steroid treatment can, paradoxically, lead to a secondary cortisol insufficiency, and thus in severe, stressful situations possible adrenal insufficiency must be cautiously predicted and prevented through an increase in glucocorticoid doses [18]. Steroid treatment accounted for the episodes of adrenal insufficiency in our cases of NCAH. Indeed, all our patients with classic forms and 87.1% (n = 27) NCAH patients were prescribed glucocorticoids. Towards adult age, NCAH patients should only receive this treatment if there is significant hyperandrogenism [2].

In patients with central precocious puberty, with whom there is the possibility of advanced bone age, therapy with GnRH analogs can bring benefits by preventing the small but present risk of short adult stature in NCAH patients [19]. However, GnRH analogs are not recommended as a routine treatment [2]. Nine of our patients were prescribed GnRH analogs, until they reached their normal pubertal age, because they exhibited growth velocity > 6 centimeters/year and/or bone age > 1 year than their chronological age.

In our sample, hydrocortisone and fludrocortisone were the glucocorticoid and mineralocorticoid of choice, respectively. Dexamethasone was used during pregnancy to prevent female fetus virilization in the single prenatal diagnosis case and hydrocortisone was started in the newborn after birth. In our case, a female baby was born with normal external genitalia.

Oral contraceptives combining estrogen and progestogen with antiandrogenic effects (EP) are the first-line treatment to improve hyperandrogenism and oligomenorrhea, as they suppress adrenocorticotropic hormones, and ovarian and adrenal androgens [20]. If EP are not sufficient, antiandrogens can be added, but their potential teratogenicity should be borne in mind. In our patients, antiandrogenic progestogens were the first choice among the EPs and there was no need to administer additional antiandrogens. EPs can be used over a long period, have fewer side effects than glucocorticoids, and are more effective regarding hirsutism [21]. Many of our patients with NCAH were concurrently receiving low doses of corticotherapy. Indeed, we tried to conjugate the antiandrogenic effects of glucocorticoids and EP. Long-term glucocorticoids are useful in managing hirsutism and regularizing ovulatory cycles in classic forms, but EP can, in addition, provide effective contraception. Eleven of our NCAH patients were only under corticotherapy because they did not tolerate EP, had some relative contraindication, or did not wish to take them. Glucocorticoids, as previously stated, can also be used to control menstrual cycles and signs of hirsutism.

Metformin was used in five of our patients, all with NCAH. The medication has been extensively studied in the context of hyperandrogenism caused by polycystic ovary syndrome. As NCAH is associated with insulin resistance, patients may benefit from metformin therapy as an insulin-sensitizer.

Only subjects with the classic form may be born with external genitalia malformation, including clitoral enlargement, partial or complete labial fusion or the presence of a common orifice for urethra and vagina (urogenital sinus), due to the effects of androgen excess during embryonic development [1]. Collaborating with our hospital's urology department was essential for our surgical approach.

If Prader stage ≥ 3 is identified, there is a formal indication for reconstructive clitoral and perineal surgery, performed between two and six months after birth [1]. Contrary to this, our eight patients with Prader stage 3 or 4 were submitted to surgery later than this reference period (minimum 7-months-old). Even so, there is still no consensus among experts on what is the correct surgical timing. Most authors concur that performing clitoris hypertrophy correction in early infancy is best, but patient advocacy groups disagree with this early procedure if it not essential for the patient's physical well-being [22]. Moreover, patients who have undergone earlier genital surgery are at higher risk of developing long-term complications, such as esthetic defects, urinary incontinence, vaginal stenosis, sexual dysfunction, and diminished clitoral sensation [1]. Half of our Prader ≥ 3 patients (4 of 8) underwent surgical re-interventions, reinforcing this idea. The uterus and the ovaries are unaffected in this endocrinological disorder, except for the six cases in our study with polycystic ovarian morphology on ultrasound, which were induced by the hyperandrogenic environment.

Few women with the classic form will be able to conceive. This is due to glucocorticoid undertreatment, remaining hyperandrogenism, and subsequent anovulatory cycles; or because of genital malformations that prevent fertilization [23]. One of our patients had a successful spontaneous pregnancy and another is still trying to conceive with the help of medically assisted reproduction techniques.

CONCLUSIONS

This case series study highlights the importance of undertaking a multidisciplinary approach involving endocrinology and gynaecology experts, as well as other medical and surgical specialties. Early and appropriate treatment is decisive as it contributes to a phenotypical feminine differentiation and normalization of the hypothalamus-pituitary-ovarian axis, which is essential given the gynaecological and obstetric consequences of untreated cases.

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Conflict of interest

The authors declare no conflict of interest.

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