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Improvement in semen parameters by switching steroids in a male congenital adrenal hyperplasia patient with severe oligozoospermia

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ABSTRACT

Congenital adrenal hyperplasia (CAH) causes hypogonadotropic hypogonadism due to the excessive production of adrenal androgens, which results in hypospermatogenesis in some male patients. We herein present a CAH case with hypogonadotropic hypogonadism and male infertility. A 26-year-old male receiving steroid therapy for 21 hydroxylase deficiency was diagnosed with low gonadotropin levels, an elevated ACTH level, and severe oligozoospermia. The switching from hydrocortisone to dexamethasone resulted in the normalization of gonadotropin levels and semen findings. The couple underwent ICSI-ET, resulting in a live birth. In cases of CAH with hypospermatogenesis, the continuous suppression of ACTH by dexamethasone may restore spermatogenesis.

1. Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited congenital disorder that causes a lack of cortisol secretion from the adrenal glands. The incidence of CAH is 1 in about 16,000 people.[1] The majority of CAH cases are caused by 21-hydroxylase deficiency, which leads to the excessive production of corticotrophin (ACTH).

In males with CAH, fertility may be impaired,[1] and one of the underlying causes is hypogonadotropic hypogonadism due to negative feedback by the excessive production of adrenal androgens. We herein present a case of male infertility with CAH in which ACTH was suppressed by the switching of steroids, which resulted in a successful pregnancy and live birth.

2. Case presentation

A 26-year-old male was diagnosed with the classical salt-wasting form of CAH in a newborn screening test. Since then, he had been treated with hydrocortisone and fludrocortisone. He got married and the couple wanted a baby, he was referred to our department.

He was obese (height: 1.67 m; weight: 85 kg; body mass index: 30.48 kg/m^2). Sexual maturity was Tanner Stage 5 for both genital and pubic hair development. Testicular volumes were normal (right; 26 mL, left; 20 ml) with no varicoceles or indurations in either testis. Ultrasonography showed no obvious tumors, varicoceles, or microcalcifications. A semen analysis revealed severe oligozoospermia (average of two separate analyses: volume: 4.4 mL; concentration: 2.0 $\times$ 10^6/mL; motility: 69%). Hormonal tests showed high ACTH level (1229 pg/ml) and extremely low gonadotropins (FSH 0.2 mIU/ml, LH $<$ 0.1 mIU/ml). The total testosterone and cortisol level were 3.2 ng/ml and 2.5 μg/dL, respectively. MRI revealed no testicular adrenal rest tumors (TART) in the testes.

Based on these results, hypogonadotropic hypogonadism and hypospermatogenesis were caused by the negative feedback of gonadotropins due to the excessive production of adrenal androgens.

Long-acting steroids were administered to reduce adrenal androgens. Treatment was switched from hydrocortisone at 20 mg/day to dexamethasone at 0.25 mg/day. After 3 months of treatment, ACTH decreased to 475.9 pg/ml; however, there were no obvious improvements in gonadotropin levels or semen findings (Tables 1 and 2). The dose of dexamethasone was increased to 0.5 mg/day. After 6 months of treatment, gonadotropins recovered to normal levels. After 9 months of treatment, semen findings finally improved. Due to the side effects of dexamethasone, body weight increased by 7 kg; therefore, the dose of dexamethasone was reduced to 0.25 mg. After the dose reduction in dexamethasone, the level of ACTH gradually increased, whereas

Abbreviations: CAH, congenital adrenal hyperplasia; TART, testicular adrenal tumors.

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Table 1
Changes in hormone levels
Dexamethasone was increased to 0.5 mg/day from 0.25mg/day 4 months later. Suppression of ACTH and normalization of FSH and LH were observed 6 months after switching steroids. However, 3 months later dexamethasone was reduced to 0.25 mg/day.

Hormonal parameters	Before therapy	3 months after therapy	6 months after therapy	9 months after therapy	12 months after therapy
FSH (mIU/ml)	0.2	0.1	3.6	4.3	3.0
LH (mIU/ml)	<0.1	<0.1	3.3	3.0	2.8
ACTH (pg/ml)	1229.4	475.9	5.7	94.8	706.8
Total testosterone (ng/ml)	3.2	4.6	3.9	3.9	3.4

Table 2
Changes in semen findings
A marked improvement in semen findings was observed 9 months after therapy. 12 months after therapy, the couple underwent ICSI-ET, resulting in a successful pregnancy and live birth.

Semen parameters	Before therapy	3 months after therapy	6 months after therapy	9 months after therapy	12 months after therapy
Volume (ml)	4.4	3.87	4.6	6.1	4.0
Concentration (Million/ml)	2.0	0.4	4.0	82	28
Motility (%)	69	75	5.7	58.5	78

gonadotropin levels and semen findings remained within normal limits. The couple attempted timing therapy for several month but were unable to conceive. Therefore, ICSI-ET was performed and one year later, a healthy male baby weighing 2650g was successfully delivered.

3. Discussion

It has been reported that males with CAH may have decreased fertility.[1] There are two main causes of male infertility: hypogonadotropic hypogonadism and TART.[2]

Adrenal androgens are overproduced in patients with CAH, whereas endogenous cortisol levels are very low. This leads to a compensatory increase in ACTH, the further production of adrenal androgens, and the suppression of gonadotropins in the hypothalamic-pituitary-gonadal (HPG) axis. The inhibition of the HPG system ultimately leads to hypogonadotropic hypogonadism.[2]

TART is a benign tumor that develops in the testis.[1] The incidence of TART in CAH was reported to be from 14% to 86% and it has been suggested that elevated ACTH levels may be involved in its development.[1] TART has been suggested to result in the mechanical obstruction of the definite ducts, and strong parenchymal impairments in the testes may lead to hypergonadotropic hypogonadism.[3]

If TART or hypogonadotropic hypogonadism is present in a male CAH patient, the first step of fertility treatment is the continuous suppression of ACTH, resulting in tumor mass reductions and the normalization of the HPG system.[4] Hydrocortisone, which is often used to treat CAH, has a short half-life and does not sustainably suppress ACTH; therefore, a switch to dexamethasone, a long-acting steroid, may be effective.[5] Long-acting steroids are more likely to suppress ACTH, and the HPG system is more likely to be inhibited when steroids are administered at night rather than in the morning.

In the present case, the level of ACTH was markedly elevated, TART was not present, gonadotropins were suppressed, and the patient had hypogonadotropic hypogonadism. The switch to dexamethasone increased gonadotropin levels and improved semen findings (Tables 1 and 2). Since a side effect of dexamethasone was weight gain, steroids were immediately changed back to hydrocortisone after the end of fertility treatment.

In hypogonadotropic hypogonadism cases, such as the present case, there have been few reports of gonadotropin improvements and the restoration of fertility by increasing the steroid dosage or switching to a steroid with a long half-life.[4] In males with CAH, the impact on fertility may be often overlooked.

4. Conclusion

In conclusion, switching to a steroid with a long half-life may effectively overcome male infertility in some CAH patients. There is a trade-off between improvements in gonadal function and the side effects of intensified steroid therapy. It is also important to thoroughly manage steroids from childhood and to perform imaging searches for TART.

Consent

Informed consent for publication was provided by the patient.

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Declaration of competing interest

None.

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References

1. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, et al. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. *Endocr Rev*. 2022 Jan 12;43(1):91–159. https://doi.org/10.1210/endrev/bnab016. PMID: 33961029; PMCID: PMC8755999.
2. King TF, Lee MC, Williamson EE, Conway GS. Experience in optimizing fertility outcomes in men with congenital adrenal hyperplasia due to 21 hydroxylase deficiency. *Clin Endocrinol*. 2016 Jun;84(6):830–836. https://doi.org/10.1111/cen.13001. Epub 2016 Feb 15. PMID: 26666213.
3. Fouques C, Fatfouta I, Hieronimus S, Sadoul JL, Bongain A. Two cases of male patients followed for a classical form of congenital adrenal hyperplasia (CAH), presenting an azoospermia: analysis and review of the literature. *Basic Clin Androl*. 2019 Mar 12;29:10. https://doi.org/10.1186/s12610-019-0084-8. PMID: 31143447; PMCID: PMC6532123.
4. Tiitinen A, Välimäki M. Primary infertility in 45-year-old man with untreated 21-hydroxylase deficiency: successful outcome with glucocorticoid therapy. *J Clin Endocrinol Metab*. 2002 Jun;87(6):2442–2445. https://doi.org/10.1210/jcem.87.6.8616. PMID: 12050196.
5. Claahsen-van der Grinten HL, Otten BJ, Sweep FC, Hermus AR. Repeated successful induction of fertility after replacing hydrocortisone with dexamethasone in a patient with congenital adrenal hyperplasia and testicular adrenal rest tumors. *Fertil Steril*. 2007 Sep;88(3):705.e5–705.e8. https://doi.org/10.1016/j.fertnstert.2006.11.148. Epub 2007 May 22. PMID: 17517401.