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Correspondence

Pregnancy in a woman with congenital adrenal hyperplasia: A case report and literature review

Dear editor:

Congenital adrenocortical hyperplasia (CAH) is an autosomal recessive disease resulting from a deficiency in the cortisol synthase gene. This deficiency leads to an imbalance in adrenocortical hormones and excess androgen. 21 Hydroxylase deficiency (21-OHD) is the most common form of CAH, accounting for 90%~95% of cases.[1] This condition is primarily caused by a mutation in the CYP21A2 gene, located on chromosome 6p21.3.[2] Depending on the severity of aldosterone deficiency, CAH can be divided into classical (salt-wasting and simple-virilizing forms) and non-classical (NCCAH) types. Excess androgen, the most common factor in classical CAH and NCCAH, can negatively impact fertility in CAH patients. The spontaneous rate of pregnancy without treatment is typically very low in CAH patients.

One Han female, aged 32, experienced menarche at the age of eleven. Her menstrual cycle lasted for 3–5 days and occurred every 28–30 days. In 2010, her abdominal ultrasound revealed thickening of the left adrenal gland. At the same time, she experienced thrombocytosis, heavy body hair, and hyperandrogenism, with testosterone levels of 8.66nmol/L. Nonetheless, her other sex hormones were within normal range, and she did not suffer from hypertension. Physical examination indicated that she was slim with weak muscles, and her hairline did not exhibit significant recession. The patient exhibited a number of physical characteristics, including thick eyebrows, whiskers on her upper lip and chin, and a visible laryngeal knot. Her small breasts had no hair around the areola, but she did have body hair on her abdomen, limbs, and back. Her pubic hair was thick and her genitalia appeared normal. After being diagnosed with adrenocortical hyperplasia in the urology department, the patient underwent laparoscopic left adrenalectomy and was subsequently diagnosed with adrenal hyperplasia via pathology (Fig. 1).

Following surgery, the patient's androgen levels steadily decreased, though they remained elevated above normal levels (3.51–5.64 nmol/L). After two years of infertility, she sought medical attention and underwent monitoring of her ovulation function for six months. During this time, her sex hormone levels were found to be elevated, with an estradiol of 69.76 pg/ml, testosterone of 6.49 nmol/L, and dehydroepiandrosterone (DHEAS) of 499.71 μg/dL. The patient was prescribed prednisone 5 mg daily for treatment, and was fortunately able to conceive naturally just two months later. Throughout pregnancy, her testosterone levels fluctuated between 3.97 and 6.3 nmol/L, while 17α-hydroxyprogesterone (17α-OHP) levels fluctuated between 1623.2 and 3895 ng/dl. In the second trimester, the fetus was identified as female via ultrasound, leading to a gradual increase in the patient's prednisone dosage to 15 mg per day. The patient did not experience vaginal bleeding or hypertension during her pregnancy and declined invasive prenatal diagnosis. Non-invasive prenatal testing indicated low risk for 21, 18, and 13 trisomal syndrome. However, at 29 weeks of gestation, ultrasound revealed fetal growth restriction, although the placenta appeared normal. Premature rupture of membranes and a funnel pelvis led to a cesarean section at 37 weeks of gestation, and a healthy baby girl was delivered weighing 3kg and measuring 52cm. The newborn's female genitalia appeared normal, but her 17α-OHP levels spiked significantly on the third day after birth, gradually returning to normal levels. At 36 months, the baby's growth was normal, and genetic testing for CAH showed no significant variances compared to the general population. The mother's prednisone dose was reduced to her baseline dosage before pregnancy.

Decreased or deficient 21 Hydroxylase activity results in reduced cortisol and aldosterone synthesis. This, in turn, increases adrenocorticotropic hormone (ACTH) due to negative feedback, leading to stimulated proliferation of adrenal cortical cells and elevated levels of 17α-OHP and progesterone. The excess 17α-OHP is metabolized into androgens via an alternative pathway, leading to hyperandrogenemia and various hyperandrogenic manifestations, such as clitoral enlargement, pseudoprecocious puberty, hirsutism, and acne. Women may experience irregular menstruation or primary amenorrhea, seriously impacting their quality of life.[2] Excessive secretion of ACTH is the primary cause of secondary adrenocortical hyperplasia, leading to significant Cushing syndrome. Some patients may not show a significant increase in plasma ACTH levels, but still exhibit clinical symptoms and pathological changes in the adrenal gland. Given the patient's elevated androgen levels and lack of hypertension, primary adrenal hyperplasia was considered.

Compared to classical CAH, NCCAH presents milder symptoms. However, clinical manifestations may vary even in individuals who have been asymptomatic for an extended period. While serum cortisol and aldosterone levels in some patients with NCCAH remain stable, increases in testosterone, 17α-OHP, and progesterone are commonly observed. Diagnosis of NCCAH may occur during the evaluation of amenorrhea and infertility, as it is estimated that 90% of affected women remain undiagnosed.[3] Women with NCCAH exhibit a higher fertility rate than those with classical CAH, thanks to a more subtle hormonal imbalance.[4] Upon preparation for pregnancy, approximately 83% of women with NCCAH conceive within one year, with or without glucocorticoid therapy. However, some studies suggest that while the pregnancy rate of women with NCCAH is comparable to that of healthy women, their fertility rate remains lower than that of the general population.[5]

Excessive androgen levels have negative impacts on fertility through several complex mechanisms, including changes in the hypothalamus-pituitary-gonad (HPG) axis and direct effects on the ovaries.[6] These patients may also experience polycystic ovary syndrome as a secondary complication.[2] Furthermore, elevated progesterone concentrations over time can lead to abnormal cervical mucus and endometrial atrophy, hindering embryo implantation.[7] Psychological factors also have a significant

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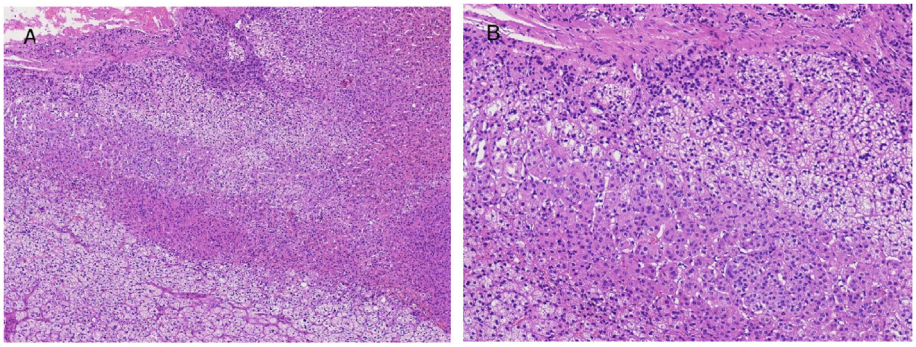

Fig. 1. Adrenal excision specimen after surgery: adrenal hyperplasia. (A) × 40; (B) × 200.

impact on the pregnancy of female patients.[8] Some CAH patients who undergo genital plastic surgery may experience poor outcomes, leading to dissatisfaction with their sexual life and affecting their chances of getting pregnant.[9]

Currently, hormone therapy is recommended as a treatment for CAH due to the potential risk of iatrogenic adrenal crisis following adrenalectomy.[1] Glucocorticoid replacement therapy not only addresses insufficient cortisol secretion but also curbs excessive ACTH production.[2] Moreover, it can reduce androgen stimulation, preventing further masculinization of female CAH patients and promoting normal growth and development. However, excessive use of glucocorticoids should be avoided to prevent growth inhibition and iatrogenic Cushing syndrome.

In classical CAH, the chance of spontaneous pregnancy without treatment is quite low, and thus, glucocorticoid replacement therapy is typically necessary for ovulation.[6] According to research,[4] NCCAH patients who don't receive glucocorticoid replacement therapy have a higher likelihood of spontaneous pregnancy. However, for those who need assistance with fertility, ovulation induction or other assisted reproductive technologies can be used, including preimplantation genetic screening during in vitro fertilization-embryo transfer (IVF-ET), to select embryos unaffected by CAH. In this case study, the patient initially experienced primary infertility after marriage and began taking 5 mg of prednisone orally each day. After only two months, the patient became pregnant naturally, which highlights the effectiveness of glucocorticoid treatment for CAH-related infertility.

During pregnancy, patients with CAH may require hormone replacement therapy like Prednisone. However, Dexamethasone is not recommended due to its inability to be metabolized by the placenta, which could harm the fetus. The dosage of adrenocortical hormone should be adjusted based on testosterone and 17α-OHP levels. Despite this, there is no universal consensus on glucocorticoid dosage management during pregnancy. The fetal reproductive system begins developing at 9 weeks of gestation. Therefore, it is recommended to start hormone therapy as early as possible to prevent female fetuses from virilizing in the uterus.[10–12] Studies indicate that the use of glucocorticoid replacement therapy in CAH female fetuses decreases the possibility of male genitalia,[13] and lowers the rate of abortion in CAH patients.[6] However, glucocorticoid therapy may have some side effects, such as low placental weight, low birth weight, gestational hypertension, and impaired glucose tolerance. The medical plan for patients with CAH should be tailored to each individual. Inadequate diagnosis and treatment of CAH can have serious consequences for both maternal pregnancy outcomes and fetal health, including virilization of female fetuses, neonatal salt wasting, and even neonatal death or brain damage.

Prenatal diagnosis and treatment are crucial interventions to reduce the adverse outcomes associated with salt-wasting CAH.[14] Amniotic fluid testing can detect 17α-OHP levels and diagnose fetal CAH.[15,16] Gene sequencing technology is essential for prenatal genetic diagnosis, which can be done through amniocentesis or chorionic villus sampling. This method is especially suitable for high-risk patients who have a family history of CAH, those who are CAH patients themselves, or those who have previously given birth to a CAH child. Detecting the fetal genetic phenotype can help determine whether replacement therapy is necessary during pregnancy and whether the dosage should be increased. Non-invasive prenatal diagnosis technology is now available, allowing for the inference of fetal CAH status from maternal plasma as early as 5 weeks of gestation.[17] This eliminates the need for invasive prenatal diagnosis methods and helps ensure that ill female fetuses receive prompt prenatal treatment, while avoiding unnecessary hormone therapy for healthy female and male fetuses.[17] However, in this particular case, the patient declined prenatal diagnosis due to concerns about the risks of invasive prenatal testing. Therefore, the baby's genetic sequence can only be tested after birth.

Despite exhibiting normal menstruation and external genitalia, the patient's androgen and 17α-OHP levels were elevated, indicating a diagnosis of NCCAH. With glucocorticoid treatment, the patient became pregnant spontaneously. While some NCCAH patients can achieve spontaneous pregnancy through optimized glucocorticoid and mineralocorticoid therapy, the incidence of such cases is relatively low in China.

This study provides guidance for clinicians encountering similar patients by describing the treatment and clinical indicators during pregnancy complicated with CAH. Hormonal therapy requires careful monitoring, with regular clinical and laboratory follow-ups to ensure optimal treatment outcomes.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Peking University People's Hospital Ethics Committee.

Consent to participate

Informed consent was obtained from the patient included in the study.

Consent to publish

All authors consent for publication.

Conflicts of interest

The authors declare no conflicts of interest.

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