To the Editor: Nonclassic congenital adrenal hyperplasia (NCAH) due to 21-hydroxylase deficiency (21-OHD) is one of the most common autosomal recessive disorders. Affected individuals typically present signs and symptoms related to excessive androgens. In the process of assisted reproductive technique (ART), the clinical features of NCAH may evade our attention and, therefore, be left untreated. Here, we present a case of NCAH, who underwent controlled ovarian hyperstimulation (COH).

A 26-year-old woman with a 4-year history of primary infertility was referred to our hospital on August 9, 2013. She had a regular menstrual cycle (3–4/29–30 days) without hirsutism or acne. Hysterosalpingography showed patent fallopian tubes with abnormal shapes. Semen analysis of her husband was normal. The patient was found to have thin endometrium at any time during menstrual cycles (3–6 mm) and hysteroscopy revealed a normal uterine cavity. Her basal hormonal levels on day 2 of menstrual cycle were as follows—follicle stimulating hormone (FSH): 6.0 IU/L, luteinizing hormone (LH): 3.1 IU/L, estradiol (E2): 231 pmol/L, prolactin: 7.9 ng/ml, testosterone (T): 3.7 nmol/L (range: 0–2.53 nmol/L), and androstanedione (A): >35 nmol/L (range: 1.4–14.3 nmol/L). Her thyroid hormones, serum cortisol levels, plasma renin, angiotensin II, aldosterone, and electrolytes levels were normal. Computed tomography of adrenals did not find an abnormality.

The patient was given compound cyproterone acetate (Diane-35, Bayer) for 3 cycles. Three months later, her androgen levels were still very high with T level of 4.0 nmol/L and A level more than 35 nmol/L. From then on, prednisone, 5 mg/d orally, was prescribed to her.

The patient underwent in vitro fertilization cycle because of a tubal factor. On the first day of menstrual cycle, she was given 3.75 mg of leuprolrelin (Beiyi, Livzon pharmaceutical, China) for pituitary down-regulation. Twenty-eight days after leuprolrelin injection, hormone measurement showed FSH: 2.8 IU/L, LH: 0.3 IU/L, E2: 116 pmol/L, progesterone (P): 10.6 nmol/L, A: >35 nmol/L, and T: 1.4 nmol/L. The thickness of endometrium was 3 mm. Two days later, the P level dropped to 1.5 nmol/L, but A level was still >35 nmol/L. She was given 1.8 mg of leuprolrelin again. Meanwhile, prednisone, 10 mg/d, was administered. Fourteen days after second injection of leuprolrelin, her P level decreased to 0.7 nmol/L and A level was <1.05 nmol/L. Recombinant FSH (Puregen, Organon) 50 IU/d + HMG (Livzon pharmaceutical) 75 IU/d was started to stimulate follicle growth. At the same time, prednisone was reduced to 5 mg/d. During COH, serum levels of P and A elevated again (P 5.6–8.1 nmol/L, A 24.7 mmol/L), whereas LH remained low. Eleven eggs were retrieved, and 9 embryos from two pronuclei fertilized eggs were obtained. All embryos were cryopreserved due to thin endometrium.

Based on the abnormal increase of P and A, further examination was conducted. Significantly increased basal and adrenocorticotropic hormone-stimulated 17-hydroxyprogesterone (17-OHP) level was found, and the patient was diagnosed as nonclassic 21-OHD. Targeted mutation analysis showed that she had one allele mutation (21-hydroxylase gene [CYP21A2] [c. 293-13C>G]). This patient took prednisone, 7.5 mg/d, continuously. Two months later, her serum 17-OHP level became normal. The thickness of her endometrium reached 9 mm in late follicular phase. Two frozen-thawed embryos were replaced, and she was confirmed to have an intrauterine singleton pregnancy. Now, the pregnancy is going very well.

Thin endometrium and elevated P levels were the main manifestations during COH that may directly affect ART success rate of this patient. It is well-known that P is converted from pregnenolone under the control of 3β-hydroxysteroid dehydrogenase both in the ovaries and the adrenals. In adrenals, P can be converted either into deoxycorticosterone under the control of 21-hydroxylase or 17-OHP by 17, 20 lyase. 17-OHP is then converted to 11-deoxycortisol by 21-hydroxylase. When
there is a deficiency of 21-hydroxylase, the accumulation of P and 17-OHP will occur in the adrenals. A and T derived from the adrenals will also increase.\(^2\)\(^3\) In this patient, the elevation of P occurred in early follicular phase accompanied with high serum A, whereas LH was low. This suggested that the increase of P was not caused by the premature elevation of LH. Thin endometrium was related to high P and 17-OHP levels. Abnormally elevated 17-OHP plays a role in the inhibition of endometrial proliferation. When 7.5 mg prednisone was prescribed to this patient in FET cycle, her 17-OHP became normal, and the thickness of endometrium reached 9 mm.

To sum up, 21-OHD NCAH should be considered in females who present hyperandrogenic symptoms and/or elevation of P during the early follicular phase. Recognition and treatment are very important for improving the success rate of ART and ensuring the safety of mother and infant.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

**REFERENCES**
1. Witchel SF. Nonclassic congenital adrenal hyperplasia. Curr Opin Endocrinol Diabetes Obes 2012;19:151-8.
2. Krone N, Braun A, Roscher AA, Knorr D, Schwarz HP. Predicting phenotype in steroid 21-hydroxylase deficiency? Comprehensive genotyping in 155 unrelated, well defined patients from southern Germany. J Clin Endocrinol Metab 2000;85:1059-65.
3. Chan AO, But WM, Ng KL, Wong LM, Lam YY, Tiu SC, et al. Molecular analysis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Hong Kong Chinese patients. Steroids 2011;76:1057-62.