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# Clinical characteristics and treatment during preconception and perinatal period of infertile women with non-classical 21-hydroxylase deficiency

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## Abstract

**Objective** A single-center observational study to determine the clinical characteristics and therapeutic dose adjustments in women of reproductive age with infertility and non-classical 21-hydroxylase deficiency (NC-21OHD).

**Design** A retrospective analysis of 20 women of reproductive age who were diagnosed with NC-21OHD during an infertility evaluation at Shengjing Hospital of China Medical University from January 2013 to May 2024 was performed. The clinical manifestations, auxiliary examinations, adjustment of glucocorticoid (GC) treatment during preconception and perinatal period, and pregnancy outcomes were analyzed.

**Results** 14 of 16 patients (87.5%) had inappropriately elevated progesterone levels during the follicular phase. The average levels of 17α-hydroxyprogesterone, testosterone, androstenedione, and dehydroepiandrosterone sulfate in the follicular phase were also significantly increased. All 20 infertile patients received GC treatment before preparing for pregnancy. During the follow-up, six of 20 patients had seven conceptions. three patients had spontaneous abortions in the first trimester and four patients delivered babies (4/20). Three patients had a GC dose that was maintained throughout pregnancy and one had an increase in the GC dose starting in the second trimester. Of the remaining 16 patients, seven are still trying to conceive and nine had discontinued treatment.

**Conclusions** An abnormal increase in the follicular phase progesterone level is the most common serologic marker for NC-21OHD among infertile women. Ovulation can be restored after GC treatment, but the proportion of successful conceptions remains low. The dose of GCs in most pregnant women remained unchanged throughout pregnancy.

**Keywords** Non-classical 21-hydroxylase deficiency, Congenital adrenal hyperplasia, Infertility, Glucocorticoids, Pregnancy outcome

## Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic disorders. The synthesis of multiple steroid hormones in the adrenal cortex is insufficient in patients with CAH due to a deficiency of steroid synthetase. As a result, the adrenocorticotropic hormone (ACTH) level is increased, the adrenal cortex is hyperplastic, and steroid precursors accumulate, which leads to a deficiency of corticosteroids and secondary

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hyperandrogenism [1]. The reported incidence of CAH in China and internationally is 1/14,000 ~ 1/18,000 [1]. CAH can be divided into classical (including simple masculinization, salt loss type) and non-classical; the latter is more common. The most common type of CAH is 21-hydroxylase deficiency (21-OHD), which accounts for ~ 95% of cases [1, 2], and is one of the most common causes of abnormal sexual differentiation in women. CAH due to 21-OHD is caused by homozygous or compound heterozygous mutations in the human 21-hydroxylase gene (*CYP21A2*).

Adult women with non-classic 21-OHD (NC-21OHD) have menstrual disorders and anovulation due to elevated androgens [3, 4]. The persistent elevation of progesterone leads to infertility [5, 6]. *CYP21A2* genotyping has revealed a 1:200 prevalence of NC-21OHD in the United States population [7]. It is difficult to diagnose NC-21OHD due to insidious symptoms or misdiagnosis as polycystic ovary syndrome (PCOS) due to the clinical manifestations of hyperandrogenism, infertility, and polycystic ovaries. Such patients do not receive timely treatment [8]. Ultrasound reveals polycystic ovaries in 25% of women with NC-21OHD [9]. The risk of NC-21OHD in female offspring of women with classic 21-OHD is 1.4–2.5%, while the risk of NC-21OHD in female offspring is as high as 14% [10, 11]. Therefore, the clinical significance of prenatal diagnosis and correct treatment is evident.

Data from developed countries have shown that most women with NC-21OHD conceive naturally [10, 11]; 10–30% have decreased fertility or need assisted reproduction [12, 13]. It is not known, however, if women of childbearing age with NC-21OHD who are infertile and undergo treatment can also conceive and deliver, especially in economically underdeveloped geographic areas with limited knowledge and understanding of rare diseases. Glucocorticoid (GC) treatment can improve hormone status and promote conception in women with NC-21OHD [6, 14], and it is widely believed that GC doses need to be increased during pregnancy. The 2018 Endocrinology Society guidelines (Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline) reminds clinicians that due to the lack of serologic parameters for accurate assessment of the GC dose during pregnancy, the GC dose should be carefully evaluated and adjusted [1]. Therefore, it is not clear whether and how the dose of GCs should be adjusted in the preconception and perinatal periods.

The current study retrospectively analyzed the clinical data, auxiliary examination findings, periconception and perinatal treatment, and pregnancy outcomes among 20 infertile women of childbearing age with NC-21OHD as the main clinical manifestation who were treated in Shengjing Hospital of China Medical University from January 2013 to May 2024. The relevant literature was also reviewed. The aim of the current study was to ascertain the conception potential of women with NC-21OHD in northeast China, analyze the influencing factors, and analyze the hormone adjustment strategies during pregnancy.

## Methods

### Source of data

Clinical data from 20 women of reproductive age with NC-21OHD who were diagnosed and treated in Shengjing Hospital of China Medical University from January 2013 to May 2024 were retrospectively analyzed. All of the women were infertile and sought evaluation at the assisted reproductive center of local hospitals and/or our hospital (Fig. 1). Infertility was defined by the World Health Organization as the inability to conceive after one year of trying without any contraceptive measures and having normal sexual intercourse. Fourteen women were referred to the Department of Endocrinology Outpatient Clinic due to the inappropriate increase in the follicular phase progesterone level.

## Methods

### Case data collection and diagnostic criteria

Clinical data, including age at first visit (hereinafter referred to as baseline), age at menarche, menstrual pattern, marital status, and family history were recorded in detail. Blood pressure, height, weight, distribution of body hair, and development of external genitalia were examined and recorded. The modified Ferriman-Gallwey (mF-G) score was used to evaluate body hair distribution. Hirsutism was defined as an mF-G score > 6.

The serum endocrine hormone levels in the follicular phase were measured. Specifically, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), testosterone (Testo), progesterone (Prog), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S) (DXI800, Beckman, USA); androstenedione (AND) (IMMULITE 2000XPi, Siemens, German), free testosterone (F-T) (maglumiX8, New Instruments, China), cortisol (COR) and adrenocorticotropin hormone (ACTH) (e801, Roche, Switzerland) levels were measured by chemiluminescence immunoassay (CLIA). The level of 17-hydroxyprogesterone (OHP) (DRG Instruments GmbH, German) was measured by Enzyme-linked immunosorbent assay (ELISA). The free androgen index (FAI [%]) was calculated as follows: Testo * 3.47 * 100/SHBG. An adrenal computed tomography (CT) scan was obtained in 12 of 20 women.

The women who needed or requested to have genetic testing were referred to the Genetics Department of our

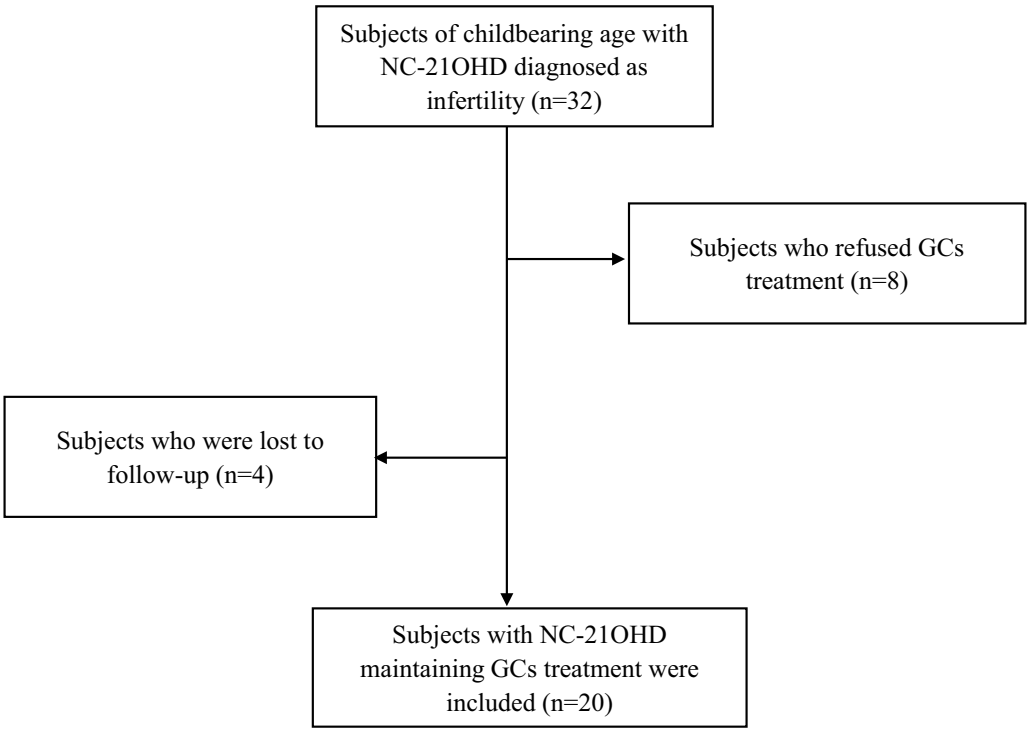


**Fig. 1** Flowchart of subjects inclusion

hospital. DNA was obtained from the patients and the results of the genetic testing were obtained by multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing (3730xl, Thermo Fisher Scientific, USA).

According to the 2016 consensus statement on the diagnosis and treatment of CAH due to 21-OHD issued by the Endocrine Genetic Metabolic Disease Group of the Chinese Medical Association Pediatrics Branch [15] and Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline in 2018 [1], all 20 women in this study met the diagnostic criteria for NC-21OHD ( i.e., 17-OHP > 10 ng/mL in the morning follicular phase or after an ACTH stimulation test, or based on genetic analysis). Because ACTH injection is not available in most parts of China, three women with a baseline 17-OHP level = 2 ~ 10 ng/mL in the follicular phase were diagnosed by *CYP21A2* gene analysis. Another 10 women with a baseline 17-OHP > 10 ng/mL volunteered for genetic analysis.

### GC treatment and pregnancy outcomes

All 20 women were treated with GCs before pregnancy, including hydrocortisone (HC), prednisone (Pred), or dexamethasone (DEX). The dosage of GCs was adjusted by monitoring the improvement in menstruation and ovulation, 17-OHP, Prog, and Testo levels in the follicular phase, and serum potassium, sodium, chlorine, and glucose levels. For infertile women, the goal of adjusting medication is to keep 17-OHP and AND levels within normal or slightly above normal ranges, and keep Prog level in the follicular phase below 0.6 ng/mL (2.0 nmol/L) [1]. In principle, DEX should be converted to HC (followed by Pred) orally before entering the pregnancy preparation state to reduce the risk of placental penetration during pregnancy. The method of conception, GC dose adjustment during pregnancy, and the pregnancy outcome data were collected.

### Literature pertaining to the treatment of infertile women of reproductive age with NC-21OHD

The literature was searched on Pubmed using the title or abstract for keywords [nonclassic congenital adrenal hyperplasia or non-classic congenital adrenal hyperplasia or CYP21A2 mutation or 17-hydroxyprogesterone]. The initial search yielded a total of 311 references, screening out those references that were redundant or irrelevant and searching through the reference lists of the relevant reviews, which in turn yielded additional material, resulting in the inclusion of 10 references (13 cases) related to the GC treatment of infertile women of reproductive age with NC-21OHD [16–25] (Supplementary Table 1).

### Statistics

SPSS26.0 software was used for statistical analysis of the data. The metrological data are presented as the mean ± SEM for normally distributed data, and frequency and percentage for counting data.

## Results

### Clinical data

Twenty women of childbearing age with NC-21OHD were treated for infertility in the Assisted Reproductive Department. The average age was 30.60 ± 4.51 years (range, 20–38 years), the age of menarche was 13.62 ± 2.39 years (range, 12–21 years), and the duration of infertility was 7.08 ± 2.53 years (range, 3–10 years; Table 3). Seven of 20 women (35%) had irregular menstruation, 12 of 20 (60%) with hirsutism, five of 20 (25%) with acanthosis nigricans, nine of 20 (45%) with isolated clitoral hypertrophy, and 11 of 20 (55%) with polycystic ovaries (Table 1).

The average height was 158.56 ± 4.35 cm (range, 150.0–169.0 cm), the weight was 66.75 ± 12.51 kg (range, 47.5–95.00 kg), and the body mass index was 24.79 ± 3.97 kg/$m^2$ (range, 16.80–33.10 kg/$m^2$; Table 3) for the 20 women. According to the diagnostic criteria for overweight and obesity in the 2022 Expert Consensus on Obesity Prevention and Treatment in China [26], 40% (8/20) of the women were overweight (24.0 kg/$m^2$ ≤ BMI < 28.0 kg/$m^2$) and 15% (3/20) were obese (BMI ≥ 28.0 kg/$m^2$).

The specific endocrine hormone detection of the subjects is shown in Table 2. Fourteen women were referred to the Endocrinology Department for evaluation of a significant increase in the follicular phase Prog level (10.79 ± 12.27 ng/mL). A significant increase in the follicular phase 17-OHP (15.65 ± 5.75 ng/mL) was also detected. In addition, the Testo (1.72 ± 0.77 ng/mL) level, AND (8.76 ± 2.29 ng/mL) level, and the calculated FAI (20.26 ± 20.00%) were increased (Table 3). The average levels of SHBG (46.52 ± 50.92 nmol/L) and F-T (8.43 ± 7.78 pg/mL) were within the normal range. Ten of 20 women had elevated DHEA-S levels (444.93 ± 235.50 ug/dL). Additional hormone levels were determined in 19 of 20 women, as follows: E2, 77.12 ± 101.11 pg/mL; FSH, 6.61 ± 2.05 mIU/mL; LH, 7.48 ± 8.78 mIU/mL; PRL, 14.87 ± 5.9 ng/ mL; ACTH, 67.12 ± 73.76 pg/mL; and COR, 10.16 ± 5.95 ug/dL (Table 3).

### *CYP21A2* gene analysis and adrenal imaging

*CYP21A2* gene analysis was performed in 13 women. Ten women had compound heterozygous mutations, including three with three gene locus mutations and seven with two gene locus mutations. Three women had homozygous mutations (Table 4).

Adrenal imaging was performed in 12 women, of whom 10 had bilateral/unilateral adrenal enlargement and one had bilateral adrenal adenoma (maximum diameter = 7 mm); no abnormalities were detected in the adrenal glands in one woman (Table 1).

### Treatment and pregnancy outcome

In this study GC treatment was indicated in 20 women with a chief complaint of infertility. All 20 women began preparing for pregnancy after receiving GCs, which improved hormone levels and ovulation. Eleven women were treated with HC, one was treated with Pred, six were treated with DEX, and two were treated with HC and Pred. In this study when the patient conceived, the dose of GCs was as following: HC, 10–60 mg/d; Pred, 2.5 mg/d; and DEX, 0.375–0.625 mg/d (Table 1).

During the follow-up after GCs treatment, six of the 20 women had seven conceptions, of which three had spontaneous abortions in early pregnancy. Compared to healthy women of childbearing age, the proportion of successful pregnancies (30% [6/20]) was significantly reduced and the abortion rate (42.9% [3/7]) was significantly increased. Four women delivered babies successfully (4/20); three were natural conceptions and one was via in vitro fertilization and embryo transfer (IVF-ET). Among the four pregnant women, three had a constant HC dose throughout pregnancy (average, 21.6 mg/d; range, 20–25 mg/d). One woman had a pre-pregnancy HC dose of 20 mg/d and the dose was increased at 11 weeks gestation to 30 mg/d. All four women had vaginal deliveries of singletons with an average birth weight of 3312.5 g. There were no adverse obstetric outcomes, such as premature delivery and malformations. Two women had gestational diabetes mellitus (GDM) during pregnancy. None of offspring have symptoms suggestive of 21-OHD; no genotyping was performed. Among the 16 women who did not conceive, seven are still preparing for pregnancy, and the other nine have discontinued attempting pregnancy (Table 1). The reason given was that the patient and/or spouse had a misunderstanding about the genetics of NC-21OHD and panicked, thus giving up the desire to conceive.

## Discussion

A total of 20 women of childbearing age with NC-21OHD who complained of infertility were included in this study. Of the 20 women, 87.5% were shown to have inappropriate progesterone elevation in the follicular phase as the earliest finding to diagnosis. Despite hormone therapy during the preconception and perinatal periods, the success rate of assisted reproduction or natural conception is still significantly lower in women with NC-21OHD than healthy women. Specifically, women with NC-21OHD

**Table 1** Clinical characteristics of the subjects

| | Age | BMI | Pregnancy history | Menstrual cycle | PCO | Hirsutism/ Acne/ Alopecia | Acanthosis nigricans | Clitorism | Adrenal imaging | Pregnancy outcome | Daily dose of GCs before pregnancy | Daily dose of GCs during pregnancy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case1 | 35 | 22.6 | G1P0 | Regular | + | + | − | + | Left adrenal enlargement | Natural conception, GDM, 37 weeks + 5 cesarean section a healthy 3700 g baby girl | HC 10 mg bid | Same before pregnancy |
| Case2 | 29 | 19.5 | G0P0 | Regular | + | + | − | + | Bilateral adrenal enlargement | Natural conception, GDM, 38 weeks + 5 cesarean section a healthy 3100 g baby boy | HC 6.6 mg tid | Same before pregnancy |
| Case3 | 31 | 27.1 | G0P0 | Regular | − | + | + | − | Left adrenal enlargement | Natural conception, 39 weeks + 2 cesarean section a healthy 3100 g baby boy | HC 10 m bid + HC 5 mg qn | Same before pregnancy |
| Case4 | 32 | 25.3 | G0P0 | Delayed | + | + | + | + | Left adrenal enlargement | IVF-ET, cesarean section a healthy 3350 g baby boy | HC 10 mg bid | HC 10 mg tid |
| Case5 | 35 | 23.6 | G0P0 | Regular | − | − | − | − | Left adrenal enlargement | 2 years still failed to conceive naturally, preparing for pregnancy | HC 10 mg tid | |
| Case6 | 34 | 23.6 | G0P0 | Delayed or frequent | + | + | + | − | No abnormality in bilateral adrenal glands | 1 years still failed to conceive naturally, preparing for pregnancy | HC 13 mg tid | |
| Case7 | 34 | 24.6 | G1P0 | Regular | − | + | + | + | Bilateral adrenal enlargement | Preparing for pregnancy | HC 10 mg bid + Pred 2.5 mg qn | |
| Case8 | 33 | 20.7 | G0P0 | Delayed | + | + | − | + | Bilateral adrenal enlargement | 2 years still failed to conceive naturally, preparing for pregnancy | HC 10 mg tid | |
| Case9 | 30 | 16.8 | G0P0 | Delayed | + | − | − | + | Bilateral adrenal enlargement | Preparing for pregnancy, planning IVF-ET | DEX 0.25 mg qd + DEX 0.375 mg qn | |
| Case10 | 38 | 31.8 | G3P0 | Regular | + | + | + | + | − | Preparing for pregnancy | HC 10 mg qd + Pred 2.5 mg qn | |
| Case11 | 37 | | G0P0 | Regular | + | − | − | − | − | Preparing for pregnancy, planning IVF-ET | DEX 0.375 mg qd | |

**Table 1** (continued)

| | Age | BMI | Pregnancy history | Menstrual cycle | PCO | Hirsutism/ Acne/ Alopecia | Acanthosis nigricans | Clitorism | Adrenal imaging | Pregnancy outcome | Daily dose of GCs before pregnancy | Daily dose of GCs during pregnancy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case12 | 28 | 24.1 | G2P0 | Regular | + | + | − | + | − | After IVF-ET failure, stop GCs, give up pregnancy | HC 6.5 mg tid | |
| Case13 | 32 | 22.3 | G2P0 | Regular | + | + | − | − | Left adrenal enlargement | After 2 IVF-ET failure, stop GCs, give up pregnancy | HC 5 mg bid | |
| Case14 | 25 | 26.6 | G0P0 | Delayed | − | + | − | − | Bilateral adrenal adenoma? | Give up pregnancy | DEX 0.375 mg qn | |
| Case15 | 29 | 26.7 | G0P0 | Regular | − | + | − | + | Bilateral adrenal enlargement | Give up pregnancy | DEX 0.375 mg qn | |
| Case16 | 24 | 33.1 | G0P0 | Amenorrhea | + | − | − | − | − | Give up pregnancy | Pred 2.5 mg qn | |
| Case17 | 27 | 26.4 | G0P0 | Delayed or frequent | − | − | − | − | − | Give up pregnancy | DEX 0.375 mg qn | |
| Case18 | 28 | 27.1 | G0P0 | Regular | − | − | − | − | − | Give up pregnancy | HC 40 mg qd + HC 20 mg qn | |
| Case19 | 20 | 21.2 | G0P0 | Regular | − | − | − | − | − | Give up pregnancy | DEX 0.375 mg qn | |
| Case20 | 31 | 28.0 | G3P0 | − | − | − | − | − | − | Give up pregnancy | HC 10 mg qd | |

*PCOS* polycystic ovarian syndrome, *GCs* glucocorticoids, *HC* hydrocortisone, *Pred* prednisone, *DEX* dexamethasone, *GDM* gestational diabetes mellitus, *IVF-ET* in vitro fertilization and embryo transfer

**Table 2** Endocrine hormone testing of the subjects

| | 17-OHP (ng/mL) | FSH (mIU/mL) | LH (mIU/mL) | E2 (pg/mL) | PRL (ng/mL) | Prog (ng/mL) | Testo (ng/mL) | SHBG (nmol/L) | FAI | DHEA-S (μg/dL) | AND (ng/mL) | F-T (pg/mL) | AMH (ng/mL) | ACTH (pg/mL) | COR (μg/dL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case1 | > 20↑ | 5.55 | 10.67 | 430 | 10.38 | 9.98↑ | 2.34↑ | | | 557↑ | > 10.0↑ | | | 23.19 | 21.36↑ |
| Case2 | 17.19↑ | 7.45 | 4.93 | 69 | 33↑ | 7.96↑ | 2.68↑ | 57.5 | 1.39 | 632.9↑ | | 11.89↑ | | 24.95 | 9 |
| Case3 | 6.7↑ | 6.47 | 4.18 | 33.64 | 14.11 | 1.10 | 1.28↑ | 32.9 | 16.66↑ | 308.2↑ | | 5.04 | 1.51 | 32.88 | 11.27 |
| Case4 | 2.86↑ | | | | | | 1.78↑ | | 1.78 | 395.2↑ | > 10.0↑ | 3.41 | 10.89↑ | 12.31 | 15.37 |
| Case5 | > 20↑ | 8.76 | 5.12 | 37.74 | 14.41 | 8.18↑ | 1.2↑ | 49.1 | 8.48 | 364.9↑ | > 10.0↑ | 9.53↑ | | 24.07 | 9.93 |
| Case6 | > 20↑ | 4.17 | 11.37 | 68.48 | 14.91 | 2.46↑ | 1.53↑ | 26.4 | 20.11↑ | | | | 11.83↑ | 28.97 | 12.89 |
| Case7 | 14.64↑ | 6.67 | 3.84 | 39.44 | 10.93 | 1.9↑ | 2.16↑ | 46.6 | 16.08↑ | | | 5.66 | | 108.8↑ | 17.08 |
| Case8 | 19.27↑ | 7.06 | 1.28 | 61 | 17.38 | 4.52↑ | 0.8↑ | 184.2↑ | 1.51 | 66 | 5.63 ↑ | 1.94 | 1.74 | 295.4↑ | 4.49↓ |
| Case9 | > 20↑ | | | | | | | | | 296↑ | > 10.0↑ | 8.6 | | 51.73 | 11.6 |
| Case10 | 17.14↑ | 7.02 | 8.57 | 64 | 15.02 | 0.9 | 1.45↑ | 17.7↓ | 28.43↑ | 475.6↑ | > 10.0↑ | 5.36 | 2.71 | 40.83 | 20.35↑ |
| Case11 | 19.85↑ | 6.22 | 37.2 | 59 | 10.55 | 1.62↑ | 0.98↑ | | | 389.8↑ | 4.52↑ | | | | |
| Case12 | 14.06↑ | 6.54 | 3.77 | 21 | 10.42 | 7.6↑ | 0.77↑ | 7.4↓ | 36.11↑ | | | | | 75.40↑ | 10.86 |
| Case13 | 12.81↑ | 8 | 3.99 | 52 | 19.49 | 3.67↑ | 1.03↑ | | | | | | 1.16 | 29.76 | 13.75 |
| Case14 | > 20↑ | 11.08 | 7.76 | 42.1 | 18.44 | 28.73↑ | 3.12↑ | 15.5↓ | 69.85↑ | > 1000.0↑ | > 10.0↑ | 28.87↑ | 3.92 | 81.11↑ | 0.98↓ |
| Case15 | | 7.56 | 2.41 | 32 | 13.76 | 10.04↑ | 2.23↑ | | | | | | | 39.41 | 6.6↓ |
| Case16 | 6.02↑ | | | | | 9.98↑ | 1.05↑ | | | 408.7↑ | | 4.05 | | 19.23 | 7.1 |
| Case17 | | 2.43 | 0.89 | < 20 | 10.09 | > 40↑ | 3.13↑ | | | | | | | 89.97↑ | 5.86↓ |
| Case18 | | 4.2 | 6.34 | 127.51 | 10.2 | 34.08↑ | 1.81↑ | 27.9 | 22.51↑ | | | | | 216.1↑ | 3.29↓ |
| Case19 | | | | | | | | | | | | | | < 1↓ | < 0.054↓ |
| Case20 | 20.00↑ | | | | | | | | | | | | | 80.26↑ | 11.3 |

Reference values

17-OHP, 2(ng/mL)

FSH, adult female: follicular phase: 3.85–8.78 (mIU/mL); ovulation phase: 4.54–22.51 (mIU/mL); luteal phase: 1.79–5.12 (mIU/mL); menopause: 16.24–113.59 (mIU/mL);

LH, adult female: follicular phase: 2.12–10.89 (mIU/mL); ovulation phase: 19.18–100.03 (mIU/mL); luteal phase: 1.2–12.86 (mIU/mL); menopause: 10.87–58.64 (mIU/mL);

E2, adult female: follicular phase: 27–122(pg/mL); ovulation phase: 95–433(pg/mL); luteal phase: 49–291(pg/mL); menopause: < 20–40(pg/mL);

PRL, adult female: 3.34–26.72(ng/mL);

Prog, adult female: follicular phase: 0.31–1.52(ng/mL); Luteal phase: 5.16–18.56(ng/mL);

Testo, adult female: < 0.1–0.75 (ng/mL);

SHBG, female 20–46 years old:18.2–135.5 (nmol/L); post-menopausal 47–91 years old:16.8–125.2 (nmol/L);

FAI, female 20–46 years old: 0.65–10.93; post-menopausal 47–91 years old: 0.23–6.80;

DHEA-S, 23–266 (ug/dL);

AND, 0.3–3.3 (ng/mL);

F-T, < 9.0(pg/mL);

AMH, 0.07–7.35(ng/mL);

ACTH, 7.2–63.3(pg/mL) (8:00 am); 3.6–31.7(pg/mL) (16:00 pm);

COR, 6.02–18.4 (ug/dL) (8:00 am); 2.68–10.5(ug/dL) (16:00 pm)

**Table 3** Summary of the subjects' clinical variables

| Indicators | Detection value |
|---|---|
| Age (years) | 30.60 ± 4.51 |
| Age of menarche (years) | 13.62 ± 2.39 |
| Duration of infertility (years) | 7.08 ± 2.53 |
| BMI (kg/m$^2$) | 24.79 ± 3.97 |
| 17-OHP (ng/mL) | 15.65 ± 5.75 |
| FSH (mIU/mL) | 6.61 ± 2.05 |
| LH (mIU/mL) | 7.48 ± 8.78 |
| E2 (pg/mL) | 77.12 ± 101.11 |
| PRL (ng/mL) | 14.87 ± 5.91 |
| Prog (ng/mL) | 10.79 ± 12.27 |
| Testo (ng/mL) | 1.72 ± .77 |
| SHBG (nmol/L) | 46.52 ± 50.92 |
| FAI | 20.26 ± 20.00 |
| DHEA-S (ug/dL) | 444.93 ± 235.50 |
| AND (ng/mL) | 8.76 ± 2.29 |
| F-T (pg/mL) | 8.43 ± 7.78 |
| AMH (ng/mL) | 4.82 ± 4.56 |
| ACTH (pg/mL) | 67.12 ± 73.76 |
| COR (ug/dL) | 10.16 ± 5.95 |

are characterized by a low rate of conception and a high rate of spontaneous abortion, and nearly one-half of affected women give up pregnancy preparation due to an inadequate understanding of the genetic disease. Indeed, factors influencing the low fertility rate are not only NC-21OHD, but psychological and social factors. By reviewing the literature and summarizing GC treatment in the four women who delivered babies, it was found that the dose of GCs post-conception does not usually need to be increased.

The adverse effects of NC-21OHD-related hormone disorders on female fertility may be multifaceted and include the following: (1) a high androgen level interferes with the pulsatile secretion of GnRH or LH and inhibits ovarian follicular development; (2) there is co-localization of androgen and FSH receptors in granulosa cells, and a high androgen level affects the production of ovarian steroid hormones; (3) a high progesterone level thickens the cervical mucus, which is not conducive to sperm penetration; (4) a high progesterone level inhibits endometrial growth and affects endometrial receptivity; and (5) an elevated progesterone level inhibits tubal peristalsis, but also inhibits follicular development, thereby increasing the risk of infertility [6, 11–13, 27–29]. Nevertheless, most women with NC-21OHD are able to conceive naturally, so GC therapy is not recommended

**Table 4** Genetic testing results of the subjects

| Case | Genovariation | Protein change | Variation type |
|---|---|---|---|
| Case1 | c.710 T > A<br>c.713 T > A<br>c.719 T > A | p.Ile237Asn<br>p.Val238Glu<br>p.Met240Lys | Compound heterozygous mutation |
| Case2 | c.710 T > A<br>c.713 T > A<br>c.719 T > A | p.Ile237Asn<br>Val238Glu<br>Met240Lys | Compound heterozygous mutation |
| Case3 | c.884G > T<br>c.293-13A /C > G | p.V282L<br>Splicing | Compound heterozygous mutation |
| Case4 | c.844G > T<br>c.923_924insT<br>c.955C > T | p.Val282Leu<br>p.Leu308Phefs*6<br>p.Gln319* | Compound heterozygous mutation |
| Case5 | c.92C > T | p.Pro31Leu | Homozygous mutation |
| Case6 | c.844G > T | p.Val282Leu | Homozygous mutation |
| Case7 | c.92C > T<br>c.923dupT | p.Pro31Leu<br>p.Leu308fs | Compound heterozygous mutation |
| Case8 | c.92C > T<br>c.293-13C > G | p.Pro31Leu<br>p? | Compound heterozygous mutation |
| Case9 | c.1294G > A<br>c.293-13A/C > G | p.Glu-432Lys<br>p? | Compound heterozygous mutation |
| Case12 | c.293-13C > G<br>c.1455delG | p?<br>p.Met486Trpfs*56 | Compound heterozygous mutation |
| Case13 | c.92C > T<br>c.844G > T | p.Pro31Leu<br>p.Val282Leu | Compound heterozygous mutation |
| Case14 | c.293–13A/C > G | p? | Homozygous mutation |
| Case16 | c.1432C > T<br>c.371C > T | p.Q478X<br>p.T 124I | Compound heterozygous mutation |

in asymptomatic non-pregnant NC-21OHD patients. In fact, studies have shown that 53–68% of women with NC-21OHD can conceive naturally before diagnosis and treatment [10, 11]. A multicenter study by Moran et al. [10] confirmed that of 203 pregnant women with NC-21OHD, 138 (68%) had a pregnancy before the diagnosis of NC-21OHD and 65 (32%) had a pregnancy after the diagnosis. Bidet et al. [11] reported that of 187 pregnancies in 190 women with NC-21OHD, 99 (52.9%) occurred before NC-21OHD was diagnosed (96/99 were natural pregnancies) and 88 (47%) pregnancies occurred after the diagnosis of NC-21OHD (11/88 were natural pregnancies). NC-21OHD is associated with lower gonadal damage than classical 21-OHD [30]. Therefore, the possibility of natural pregnancy in women with NC-21OHD is much higher than women with classical 21-OHD.

For women with NC-21OHD and excessive androgens, infertility, or a history of an abortion, GC treatment can shorten the time-to-conception and reduce the abortion rate [31]. Studies have confirmed that the risk of pregnancy loss in women with NC-21OHD after GC treatment is significantly lower than before treatment (26% vs. 6%) [10, 11]. A retrospective study in Israel included 75 infertile women with NC-21OHD, 72 of whom conceived (187 pregnancies). The time-to-pregnancy of the untreated group was 4.0 ± 7 months compared to 3.3 ± 3 months in the GC-treated group. After assisted conception, there were 17 pregnancies in women treated with GCs. The time-to-conception before treatment was 10.2 ± 11.4 months compared to 3.3 ± 3.4 months after treatment. Of the 187 pregnancies, 135 (72%) were live births, 38 (20.3%) were spontaneous abortions in the first trimester, seven (3.7%) were elective terminations, three (1.6%) were ectopic gestations, and four (2.1%) are under investigation. The study showed that there is no correlation between women with NC-21OHD who receive GC treatment and the abortion rate, but in NC-21OHD women who had failed to conceive without GC therapy, the time to conceive after they received it was significantly shorter [31]. Another retrospective study showed that of the 173 female patients with NC-21OHD, 78 had no pregnancy plans, 86 of 95 patients with a pregnancy plan had 176 pregnancies, and nine did not conceive. Of the patients, 56% were treated with GCs, 44% were untreated, and there were 128 live births in 76 patients. Of the patients treated with GCs, 66% had regular menstrual cycles and significantly lower levels of androgens and Prog, and the treatment was associated with a shorter duration of pregnancy. Androgen levels and duration of pregnancy were positively associated with pregnancy loss rates [32]. These studies suggest that GCs may be beneficial for conception among infertile women with NC-21OHD, and is often recommended before a pregnancy is contemplated. In this study, three women conceived naturally after taking GCs and all three gave birth to healthy babies.

High androgen levels are corrected by GC treatment alone and ovulation is restored. Anovulatory patients can treated with clomiphene or gonadotropins to induce ovulation [5, 6, 28, 33]. IVF-ET may be considered if the patient is not pregnant after the above treatment or in patients with tubal obstruction and/or endometriosis. To avoid the adverse effects of a high Prog level induced by ovulation induction on pregnancy, frozen-thawed embryo transfer can be performed at the best time [34, 35]. In this study one woman who did not conceive after GCs treatment successfully conceived by IVF-ET and one healthy baby was delivered. Searched by Pubmed, 10 case reports were included in present study, involving 13 NC-21OHD infertile women of childbearing age treated with GCs. Twelve women conceived after receiving GC treatment before pregnancy, including nine natural conceptions, two pregnancies after IVF-ET, and one pregnancy after ovulation induction.

Women with NC-21OHD who conceive without GC treatment do not need to receive GCs during pregnancy [34]. The early pregnancy loss rate is likely to be lower when patients are treated with GCs, so the continued use of GCs during pregnancy is recommended [36]. In some cases antenatal treatment failure can be attributed to the late start of treatment, an insufficient dose of GCs, and poor maternal tolerance leading to drug reduction or early withdrawal [37]. Commonly used GCs include DEX, Pred, and HC. The safety of DEX during pregnancy has not been determined [38]. DEX can inhibit the hypothalamus–pituitary–adrenal axis (HPA) of the fetus through the placenta and can effectively inhibit adrenal gland androgens in children with 21-OHD, avoiding masculinization of the female fetal external genitalia and reducing the need for reconstruction surgery. However, prenatal use of DEX may be associated with fetal developmental defects [3, 39, 40]、low birth weight [41]、decreased fetal length [42]、cognitive impairment [43], and may even permanently affect the expression of carbohydrate homeostasis-related genes that alter the normal effects of the HPA [44]. However, a 2019 meta-analysis concluded that prenatal DEX treatment reduced fetal masculinization in women at high risk for 21-OHD, with no significant differences in neonatal physical, cognitive, behavioral, or temperament outcomes [45]. At present, the prenatal application of DEX has not been established. To ensure that the risk-to-benefit ratio is minimized for pregnant women with NC-21OHD who are at high risk for a fetus with 21OHD and are considering prenatal treatment, it is recommended to use a program approved by the relevant institutional review committee with a

large sample size for prenatal treatment. DEX treatment must be started nine weeks before pregnancy (reported in the literature seven weeks ago) to prevent fetal genital malformations or reduce clitoral hypertrophy in female fetuses [46, 47]. Combined with the cases in this report and the literature, the therapeutic dose of DEX ranges from 0.25 to 1 mg/d. Pred is sometimes more effective in establishing regular cycles and ovulation and can be used prior to conception [33]. Pred can also be used during pregnancy and Pred does not cross the placental barrier. Combined with the cases in this report and the literature, the therapeutic dose of Pred is between 2.5 and 7.5 mg/d, and can be combined with HC. HC is inactivated by placental 11βHSD2 and does not cross the placenta. After the initiation of HC treatment, most women with NC-21OHD (78%) became pregnant without ovulation induction [11]. The initial dose of HC is 10–60 mg/d, which can be combined with Pred. DEX crosses the placenta, so it is critical to use only HC and Pred for GC substitution during pregnancy to avoid adverse effects on the fetus.

In this study 20 women were treated with GCs, including 11 treated with HC, one treated with Pred, six treated with DEX, and two treated with HC combined with Pred. Four women with NC-21OHD who had delivered babies were all treated with HC before pregnancy was confirmed. The dose of HC during pregnancy was unchanged in three women and increased in one woman. Through Pubmed search, 10 case reports were included in present study, involving 13 NC-21OHD infertile women of childbearing age treated with GCs. 12 were treated with GCs before pregnancy, five were treated with DEX, four were treated with Pred, and three were treated with HC. After pregnancy, 11 women continued to receive GC treatment; two were treated with DEX, four were treated with HC, and five were treated with Pred. After pregnancy, the dose of GCs was reduced in one woman, not adjusted or similar in four women, and increased in three women. Current studies and the present study suggest that not all infertile women with NC-21OHD need to increase the dose of GC after conception, and some patients may not increase the dose of GCs or even reduce the dose. Another retrospective study also showed that the dose of GCs did not need to be increased after conception. The dose of HC was decreased significantly from 7.5 ± 3.8 mg in the first three months of pregnancy to 6.4 ± 3.3 mg in the 2nd trimester and to 5.5 ± 4.4 mg in the 3rd trimester [31]. This finding is in contrast to the Lo et al. [48] and Witchel et al. [5] studies. Some studies suggest that the dose of HC in early pregnancy does not need to be increased but increased by 25% ~ 40% (5–7.5 mg) from the 24th week of gestation [5, 25, 49]. Stress doses should be used during delivery [50]. There is still a lack of guidelines for GC treatment during pregnancy in women with NC-21OHD; how to adjust GCs during pregnancy needs to be further verified.

Women with NC-21OHD have a 1.4%-2.5% risk of having a child with classic 21-OHD and up to 14% risk of having a child with NC-21OHD [10, 11]. Offspring of women with NC-21OHD generally do very well in school [51]. To reduce the above risks, it is recommended that women with NC-21OHD should be genotyped for *CYP21A2* before planning a pregnancy and their spouses should also be tested for the *CYP21A2* gene. Using RT-PCR to analyze cell-free fetal DNA (circulating DNA) from maternal blood can determine fetal gender and the *CYP21A2* genotype in the 6th week of pregnancy, which reduces unnecessary treatment. Unfortunately, none of the four women who delivered babies in this study underwent such testing, and therefore continued HC treatment during pregnancy and no offspring were diagnosed with 21-OHD.

There were some shortcomings in this study, such as a small sample size, more patients discontinuing pregnancy plans, observation of only a few cases during the entire course of pregnancy with respect to the GC dose, a lack of long-term follow-up of patients and their offspring. Relevant cases should be collected and analyzed to provide reference for endocrine management endocrinology and/or assisted reproduction.

## Conclusion

This study focused on the fertility potential and the factors influencing infertile women with NC-21OHD childbearing age as the main complaint in northeast China. We analyzed the GC treatment strategies during the preconception and perinatal periods, and summarized the relevant literature, especially the literature on dose adjustment of GCs during pregnancy. The results of this study showed that even if infertile women with NC-21OHD symptoms were treated during the preconception period, the ability to conceive was significantly lower than healthy women and the risk of spontaneous abortion increased. In addition to the pathophysiologic characteristics of NC-21OHD, infertility is likely related to psychosocial factors. Indeed, patients and their spouses give up on pregnancy due to inappropriate panic about the disease. This finding suggests that clinicians should pay particular attention to educating pregnant women with NC-21OHD, their spouses, and the entire family about the disease, which requires the full cooperation of endocrinologists, obstetricians, and genetic counselors. In addition, high follicular phase Prog levels may be a marker for the disease, and timely GC intervention may be helpful to improve the fertility rate. This study showed that the dose of GCs in women with NC-21OHD after

pregnancy may not need to be increased, and according to some reports in the literature, the GC dose may even be reduced without affecting the pregnancy outcome. Unfortunately, there are few studies on the adjustment strategies of GC treatment in infertile patients with NC-21OHD, and there is a lack of clinical features or serologic indicators to guide the dose adjustment of GCs, which we consider to have an urgent research need.

## Supplementary Information

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Supplementary material 1.

### Author contributions

Xuejiao Cui: Writing original manuscript, data analysis; Ping Li: Design and modify this manuscript. All authors have approved the submitted version.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article or in the data repositories listed in the references. No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

This study was carefully reviewed and approved by the Medical Ethics. Committee of Shengjing Hospital of China Medical University (Number: 2024PS024K). All subjects agreed on the survey and signed written consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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