Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency as a cause of infertility and miscarriages

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Abstract

Miscarriages and infertility can be presenting symptoms of non-classic congenital adrenal hyperplasia (NCAH). Two sisters are described with fertility issues and multiple miscarriages occurring up to 20 weeks of pregnancy. After diagnosing NCAH due to 21-hydroxylase deficiency and initiating glucocorticoid treatment, conception occurred within 3 months and uneventful pregnancies and deliveries ensued.

Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a disease affecting the synthesis of cortisol, and often aldosterone as well, with an increased production of steroid precursors and androgens. As a result of the elevated androgens, females are virilised at birth. In contrast, non-classic CAH (NCAH) only demonstrates a slight increase of steroid precursors and androgens with mild symptoms of androgen excess such as oligomenorrhoea, hirsutism, acne and infertility.

NCAH can easily be misdiagnosed as polycystic ovary syndrome. Sometimes NCAH is asymptomatic and may be found serendipitously. NCAH is the most frequent autosomal recessive disorder affecting 0.1–1% of the general population, however only a minority of cases is diagnosed.

Two sisters with spontaneous abortions and fertility issues subsequently diagnosed with NCAH and excellent response to glucocorticoid therapy are presented.

Case 1

A 35-year-old married woman of Middle East origin presented with miscarriages and difficulties in conceiving. Menarche was experienced at 14 years-of-age and the menstrual cycle had always been regular. She had for the last 15 years tried to become pregnant and 10 years previously she managed to conceive but had a miscarriage at 20 weeks. However, a few months later, she conceived once more and a healthy boy was delivered at term. Some years later, she once more experienced a late miscarriage, this time at 15 weeks.

She was subsequently investigated at an infertility clinic where ovaries and uterus seemed to be normal on a vaginal ultrasound, and hysterosalpingography demonstrated normal tubes and uterus. Sperm analysis on her husband was normal. Serum testosterone was markedly elevated (6.8 nmol/L; normal 0.3–3.0), serum sexual hormone binding globulin (SHBG) was normal (40nmol/L; normal 29–95), testosterone/SHBG ratio was markedly increased (0.17; normal <0.05), serum
androstenedione was elevated (22.1 nmol/L; normal 3.2–9.6) and serum dehydroepiandrosterone sulphate was normal (4.8 micromol/L; normal 1.65–9.15).

She was then referred for endocrine evaluation. At this evaluation, mild hirsutism was noted, blood pressure was 110/70 mmHg supine and 105/65 mmHg standing, height was 165 cm and weight 52 kg. Repeated bloods now showed a normal testosterone level (2.5 nmol/L), normal SHBG (46 nmol/L) and a borderline testosterone/SHBG ratio (0.051). However, elevated level was found for serum 17-hydroxyprogesterone (48 nmol/L; normal <6 in follicular phase) indicating NCAH due to 21-hydroxylase deficiency. Analysis of the CYP21A2-gene revealed the mutations V281L/Q318X confirming the diagnosis of NCAH. Prednisolone 2.5 mg twice daily was initiated.

On a subsequent review four months later she was pregnant of 6–7 weeks gestation. Prednisolone was increased to 3.75 mg twice daily. The pregnancy was otherwise normal and a healthy boy was delivered vaginally at week 39. The prednisolone dose was decreased to 2.5 mg daily after delivery. She noted that her hirsutism had improved since the initiation of prednisolone.

**Case 2**

A sister to Case 1, who still lived in the Middle East, had the same problem with multiple miscarriages and infertility. She was initiated on glucocorticoid therapy on the suspicion of also having NCAH. Within 3 months she conceived without any problems and delivered a healthy child. She soon conceived once more on glucocorticoid treatment and a second healthy child was delivered. Both pregnancies were reported to be normal.

**Discussion**

Second trimester pregnancy loss is rare and NCAH is usually not even listed as a cause in first trimester. Moran et al reported a miscarriage frequency in undiagnosed NCAH to be 25.4%, however, after the women had been diagnosed with NCAH the frequency decreased to only 6.2%. This is in accordance with a previous study reporting a miscarriage frequency of 33.3% before the diagnosis of NCAH and 0% after the diagnosis and initiation of hydrocortisone.

A recent study has described a similar miscarriage rate (7.4%) in mixed group of classic and non-classic CAH, all treated with glucocorticoids, which did not differ from an age-matched control group (6.8%, p=NS). However, no case of second trimester miscarriage has previously been reported in CAH.

Infertility is common in NCAH with a frequency of about 50%, but almost all women with CAH wishing to conceive can do so with a glucocorticoid, sometimes in combination with a mineralocorticoid and/or adding clomiphene, metformin, gonadotropins and in vitro fertilisation. The two cases presented here responded very well on glucocorticoids with conception occurring within 3 months and no complications during pregnancy and delivery.

It is controversial if all NCAH should be treated with glucocorticoids due to the increased risk of metabolic complications, osteoporosis and fractures, however, treatment should probably be initiated in all symptomatic patients, especially if desiring pregnancy.
Diagnosing NCAH is usually done by measuring early morning serum 17-hydroxyprogesterone in the follicular phase. A value of 17-hydroxyprogesterone <6.0 nmol/L will normally exclude the disorder while a value >45 nmol/L confirms it. An ACTH stimulation test with 17-hydroxyprogesterone >45 nmol/L 60 min after the injection is considered diagnostic of NCAH. Analysis of the CYP21A2-gene can be used for further classification and confirmation.

In the first case, the serum testosterone levels differed considerably without clear cause. However, two different pathology services had been used with presumably different assays. It has been suggested to exclude CAH only if testosterone >5 nmol/L, but this would have prevented Case 1 being correctly diagnosed if only the second testosterone value had been considered. Serum testosterone is largely bound to SHBG and Case 1 also demonstrates the value of calculating free testosterone, especially in the normal to mildly elevated range of testosterone, as otherwise a pathological increase of free testosterone could be overlooked.

In conclusion, the two presented sisters highlight the importance of recognising NCAH, especially in young females with infertility and/or miscarriage issues even in the second trimester. Failing to diagnose NCAH can have tragic consequences but success can be immediate if diagnosis is made and proper treatment is initiated.

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References: