CASE REPORT

Congenital adrenal hyperplasia and pregnancy

Soulmaz Shorakae, Helena Teede

Monash Health, Clayton,
Victoria, Australia

Correspondence to
Dr Soulmaz Shorakae,
solshoraka@yahoo.com

SUMMARY

A 32-year-old woman with classical congenital adrenal hyperplasia (CAH) secondary to 21-hydroxylase deficiency presented with infertility. She was treated with different steroid replacement regimens together with fludrocortisone. The aim of this case report is to discuss fertility barriers in women with classical CAH, and emphasise the risks and benefits of available steroid treatment options. Clinical considerations covered include preconception health and fertility planning, optimising fertility through suppression of excess hormone production, reducing fetal androgen exposure in utero and limiting maternal and fetal side effects of therapy and limiting chances of CAH in the baby. In this case suppression of androgen and progesterone levels was challenging but eventually was achieved and resulted in a spontaneous pregnancy. However, she miscarried in the first trimester, and fetal biopsy revealed a complete hydatiform mole. She is advised not to conceive while she is under investigation to determine the extent of the disease.

BACKGROUND

Congenital adrenal hyperplasia (CAH) is an inherited autosomal recessive disorder of adrenal steroidogenesis and is usually caused by 21-hydroxylase deficiency. Cortisol and less frequently aldosterone production is decreased or absent, resulting in an increased adrenocorticotrophic hormone (ACTH) secretion by pituitary and consequently, excessive production of adrenal androgen and progesterone, including 17-OH-progesterone.

Since 1987, several authors have reported increased infertility in women with classical CAH.¹⁻⁵ Androgen excess can inhibit ovarian folliculogenesis and elevated progesterone levels can cause persistent inhibition of follicular growth and endometrial proliferation, failure of endometrial breakdown and impermeability of the cervical mucus.⁶

Ovarian adrenal rest tumours can displace normal tissue in the ovary and produce steroids which also disturb ovarian function.⁷

Other contributors to reduced fertility include homo/bisexuality, low sexual self-esteem, lack of motivation and low maternal feelings as a result of abnormal sex steroid levels,⁷ complications of prior genital reconstruction surgery and dyspareunia.⁸

Optimal glucocorticoid therapy, targeting the lowering of ACTH levels, can markedly decrease androgen and progesterone levels and ovarian adrenal rest tumour size, improve fertility outcomes and reduce fetal androgen exposure.

CASE PRESENTATION

A 32-year-old woman from Asian background with classical CAH secondary to 21-hydroxylase

deficiency was referred to the reproductive unit in a large tertiary referral centre in Melbourne, Australia for management of infertility in 2010. Her CAH was treated at the time with dexamethasone and fludrocortisone.

She had menarche at the age of 10 years, and used to have regular menses until she started oral contraceptives at the age of 17. Following cessation of oral contraceptives at the age of 25, she developed secondary amenorrhoea and subsequently infertility.

Her incidental medical history included septated uterus diagnosed on hysteroscopy during her infertility work-up, which did not warrant surgical correction, and a slow-growing interosseous epidermoid cyst in the left parietal region which was stable on imaging surveillance without causing neurological symptoms. She had no previous smoking history.

Her partner was also investigated and was found to have normal semen analysis and did not carry a CAH genetic defect on screening.

TREATMENT

On presentation in 2010, she was on dexamethasone 0.5 mg in the morning and fludrocortisone 100 µg daily. In preparation for conception in February 2011, the steroid replacement was changed to prednisolone 5 mg in the morning and 2.5 mg in the evening. Subsequently treatment was changed to prednisolone 2.5 mg in the morning and 5 mg in the evening towards the end of 2011 and was up titrated to 2.5 mg in the morning and 7.5 mg in the evening in February 2012 with targets being suppression of ACTH, androgen and 17-OH-progesterone levels. She resumed regular menstruation in April 2012, two months after the prednisolone dose was up titrated. However, as androgen, 17-OH-progesterone and renin levels were not satisfactory her treatment regimen was changed in June 2012 to dexamethasone 0.5 mg in the morning and fludrocortisone dose was increased to 150 µg daily (table 1).

OUTCOME AND FOLLOW-UP

Our patient conceived naturally in late 2012; however, she miscarried at 10 weeks of gestation, and fetal biopsy revealed a complete hydatiform mole. She is now being investigated to determine the extent of her trophoblastic disease, and is not attempting to conceive.

DISCUSSION

In patients with CAH, preconception health should focus on preparation many years in advance of desired pregnancy. Relevant clinical considerations

To cite: Shorakae S, Teede H. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010299

Table 1 Steroid replacement regimens and associated hormonal changes between June 2010 and January 2013

	June 2010	February 2011	September 2011	November 2011	February 2012	April 2012	June 2012	January 2013
17-OH-progesterone (0–8) nmol/L	–	14.5	>151	131.4	119.6	N/A	1.4	16.4
Testosterone (0–2.7) nmol/L	0.6	1.8	9.0	7	6.3	5.3	0.7	2.6
Renin (4.5–46) mU/L	25.3	43	151.4	95.1	71.8	94.8	4.7	47.8
Treatment regime	Dex* 0.5 mg	Dex* 0.5 mg	Pred† 5 mg/2.5 mg	Pred† 2.5 mg/5 mg	Pred† 2.5 mg/7.5 mg	Pred† 2.5 mg/ 7.5 mg	Dex* 0.5 mg	Dex* 0.5 mg
	Florinef 150 µg	Florinef 150 µg	Florinef 100 µg	Florinef 100 µg	Florinef 100 µg	Florinef 100 µg	Florinef 150 µg	Florinef 150 µg

*Dexamethasone.

†Prednisolone.

must include optimising steroid replacement to resume regular menstruation, status of genital anatomy and the vaginal introitus, screening for psychosexual disorders, discussion around desire for pregnancy and potential barriers to fertility.⁹ Casteràs *et al*⁹ reported that only about 20% of women with CAH actively tried to conceive.⁴ Individuals with CAH also need to be counselled about the inheritance pattern of the condition, and risk of having an affected child.

Prior literature regarding the mechanism of reduced fertility includes that by Bachelot *et al* who reported reduced leutinising hormone (LH) pulse frequency and amplitude in women with CAH who had irregular or absent menstrual cycles. This report suggests predominance of progesterone rather than androgen action on the gonadotropic axis. They also demonstrated hormonal control of CAH as the best predictor of LH pulsatility, which highlights the importance of careful monitoring and suppression of progesterone production to obtain regulation of menstrual cycles, and subsequently optimise fertility.¹⁰ However, the progesterone and 17-OH-progesterone concentrations may be difficult to suppress even with excessive glucocorticoid doses.¹¹

Choosing the appropriate type and dose of steroid replacement is quite challenging in the treatment of women with classical CAH desiring pregnancy. Over and under replacement of steroids both result in reduced fertility.¹² Assuring adequate mineralocorticoid replacement is essential as progesterone is also the substrate for 21-hydroxylase in the zona glomerulosa.⁹

It is recommended to use steroids such as hydrocortisone, prednisone and prednisolone, which are metabolised by placental 11b-hydroxysteroid dehydrogenase type 2. Casteràs *et al*¹³ suggest to aim progesterone concentrations less than 63 ng/dL (2 nmol/L)⁴ and to achieve this goal, they recommend prednisolone 2–5 mg every 8 h. Dexamethasone is not recommended because it is not inactivated by placenta. Poulain *et al*¹⁴ demonstrated that exposure to high doses of dexamethasone in vitro impairs human fetal oogenesis through an increase in apoptosis; however, future studies are required to investigate the fertility of women who have been exposed to dexamethasone during fetal life to confirm such effect of dexamethasone in vivo.

Assisted reproductive therapies such as ovulation induction, intrauterine insemination and in vitro fertilisation (IVF) may be necessary for some women.⁵ If adrenal androgen and progestin excess are the major causes for subfertility, bilateral adrenalectomy has been described as a treatment option. However, this procedure presents anaesthetic and surgical risks and leaves the patient completely adrenally insufficient. Moreover, adrenal rest

tissue may become hyperplastic and overproduce androgens postoperatively, due to increased ACTH.¹⁵

Once conception occurs, steroid doses may need to be increased slightly during pregnancy; however, higher glucocorticoid doses put the pregnant woman at risk of fluid overload, excessive weight gain, cushingoid features, hypertension, glucose intolerance and hyperglycaemia.⁹

Monitoring steroid replacement during pregnancy is challenging due to confounding factors with sex hormone-binding-globulin and other steroid hormones potentially affecting the assay specificity. It is advisable to use laboratories with expertise in steroid immunoassay and to compare these results with laboratory-specific reference values for pregnancy. Free or bioavailable testosterone levels should be used as the primary method of monitoring androgen status throughout pregnancy, with aim to maintain levels in the high normal range for normal pregnancies.^{2 15}

Human placental tissue serves as a metabolic barrier to reduce fetal exposure to circulating maternal androgens and androgen precursors. However, in pregnancies with an affected female fetus, prenatal treatment with dexamethasone has been used to prevent or ameliorate genital virilisation of the female infants with classical CAH, with the goal of reducing the need for feminising genital reconstructive surgery. The Endocrine Society's 2010 Clinical Practice Guideline for CAH indicates that prenatal treatment of affected offspring poses unique and unresolved ethical issues¹⁶; therefore, this treatment remains controversial.⁹

Depending on prior reconstructive genital surgery, delivery by caesarean section is preferred for most women with classical CAH. Stress doses of steroids should be started at the onset of labour and continued until after delivery.⁹

Available data do not support an increased rate of spontaneous abortion among glucocorticoid-treated women with classic CAH.¹² Also we could not establish any evidence supporting association between CAH, steroid replacement and trophoblastic disease in our literature review. The two main risk factors for gestational trophoblastic disease include woman's age under 20 or over 35 years, and prior history of molar pregnancy. Other factors, including smoking, maternal blood group AB, A or B, history of infertility, nulliparity and use of oral contraceptive pills have also been described in literature.^{17 18} Our patient carries risk factors, including nulliparity, age above 30, previous oral contraceptive use and history of infertility. Asian background may also contribute as an additional risk factor based on a study reported by Tham *et al*.¹⁹

Learning points

- ▶ Preconception health, including hormonal, psychosexual and anatomical barriers to fertility should be addressed early in women with classical congenital adrenal hyperplasia (CAH).
- ▶ Fertility and pregnancy outcomes improve with adequate replacement of glucocorticoids and suppression of adrenocorticotrophic hormone (ACTH), progesterone and androgen production.
- ▶ Elevated progesterone levels lay an important role in inhibiting leutinising hormone pulsatility and therefore can affect ovulation, menstruation and fertility. An optimised glucocorticoid and mineralocorticoid regimen should target suppression of serum progesterone concentrations during the follicular phase of the menstrual cycle.
- ▶ In pregnancies with an unaffected fetus, the placenta serves as a metabolic barrier to reduce fetal exposure to circulating maternal androgens. Dexamethasone has been used to reduce fetal androgen production in an affected fetus. However, as the outcome of prenatal treatment with dexamethasone is not clear it is not recommended as a routine approach.
- ▶ The complexity of care in women with CAH highlights the need for multidisciplinary team comprising a paediatrician, geneticist, endocrinologist, gynaecologist and psychologist.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Mulaikal RM, Migeon CJ, Rock JA. Fertility rates in female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med* 1987;316:178–82.
- 2 Krone N, Wachter I, Stefanidou M, *et al.* Mothers with congenital adrenal hyperplasia and their children: outcome of pregnancy, birth and childhood. *Clin Endocrinol (Oxf)* 2001;55:523–9.
- 3 Jääskeläinen J, Hippeläinen M, Kiekara O, *et al.* Child rate, pregnancy outcome and ovarian function in females with classical 21-hydroxylase deficiency. *Acta Obstet Gynecol Scand* 2000;79:687–92.
- 4 Casteras A, De Silva P, Rumsby G, *et al.* Reassessing fecundity in women with classical congenital adrenal hyperplasia (CAH): normal pregnancy rate but reduced fertility rate. *Clin Endocrinol (Oxf)* 2009;70:833–7.
- 5 Hagenfeldt K, Janson PO, Holmdahl G, *et al.* Fertility and pregnancy outcome in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Hum Reprod* 2008;23:1607–13.
- 6 Speroff L, Glass RH, Kase NG, eds. *Clinical gynecologic endocrinology and infertility*, 6th edn. Maryland, USA: Lippincott Williams & Wilkins, 1999.
- 7 Stikkelbroeck NM, Hermus AR, Braat DD, *et al.* Fertility in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Obstet Gynecol Surv* 2003;58:275–84.
- 8 Arlt W, Willis DS, Wild SH, *et al.* Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. *J Clin Endocrinol Metab* 2010;95:5110–21.
- 9 Witche SF. Management of CAH during pregnancy: optimizing outcomes. *Curr Opin Endocrinol Diabetes Obes* 2012;19:489–96.
- 10 Bachelot A, Chakhtoura Z, Plu-Bureau G, *et al.* Influence of hormonal control on LH pulsatility and secretion in women with classical congenital adrenal hyperplasia. *Eur J Endocrinol* 2012;167:499–505.
- 11 Stikkelbroeck NM, Sweep CG, Braat DD. Monitoring of menstrual cycles, ovulation, and adrenal suppression by saliva sampling in female patients with 21-hydroxylase deficiency. *Fertil Steril* 2003;80:1030–6.
- 12 Reisch N, Arlt W, Krone N. Health problems in congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Horm Res Paediatr* 2011;76:73–85.
- 13 Gastaud F, Bouvattier C, Duranteau L, *et al.* Impaired sexual and reproductive outcomes in women with classical forms of congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2007;92:1391–6.
- 14 Poulain M, Frydman N, Duquenne C, *et al.* Dexamethasone induces germ cell apoptosis in the human fetal ovary. *J Clin Endocrinol Metab* 2012;97:E1890–7.
- 15 Ogilvie CM, Rumsby G, Kurzwinski T, *et al.* Outcome of bilateral adrenalectomy in congenital adrenal hyperplasia: one unit's experience. *Eur J Endocrinol* 2006;154:405–8.
- 16 Speiser PW, Azziz R, Baskin LS, *et al.* Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:4133–60.
- 17 Altieri A, Franceschi S, Ferlay J, *et al.* Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol* 2003;4:670–8.
- 18 Smith HO. Gestational trophoblastic disease epidemiology and trends. *Clin Obstet Gynecol* 2003;46:541–56.
- 19 Tham BW, Everard JE, Tidy JA, *et al.* Gestational trophoblastic disease in the Asian population of Northern England and North Wales. *BJOG* 2003;110:555–9.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow