CASE REPORT

Fertility and pregnancy outcome in a woman with classic congenital adrenal hyperplasia

Deepti Jain

Department of Gynaecology,
Chotu Ram Hospital, Rohtak,
Haryana, India

Correspondence to

Dr Deepti Jain,
deeptijain62@gmail.com

SUMMARY

A 24-year-old woman with 21-hydroxylase deficient classic congenital adrenal hyperplasia, simple virilising form presented with secondary infertility. One year ago she had a spontaneous miscarriage in the second trimester of pregnancy. This time she conceived with prednisolone 5 mg and clomiphene citrate 100 mg. She was then continued with prednisolone during pregnancy. She had a spontaneous preterm delivery at 33 weeks. There was a marginal increase in the dose of prednisolone during pregnancy. There was no worsening of insulin resistance during pregnancy despite prednisolone administration. A normal healthy female infant was born and is being followed up on for ill-effects, if any, of maternal glucocorticoid administration during pregnancy. The baby girl has normal female external genitalia.

BACKGROUND

There are very few reports regarding the course of pregnancy, neonatal outcome and follow-up of children born to mothers with classical congenital hyperplasia, that is, the salt wasting and simple virilising form. The effects of maternal steroid administration on the physical and intellectual development of neonates are still not known. Fertility in women is decreased because of an excess of androgens and altered gonadotropin levels resulting in lesser pregnancies and hence the limited knowledge of the course of pregnancy.¹ The case is being reported so that it may be considered when a larger analytical case study of fertility outcome in women with classical congenital adrenal hyperplasia is carried out.

CASE PRESENTATION

A 24-year-old woman, a diagnosed case of 21-hydroxylase deficient simple virilising form of classic congenital adrenal hyperplasia presented for the treatment of infertility. Her diagnosis had been confirmed earlier with a very high testosterone level, raised 17-hydroxy progesterone level and an enlarged clitoris. She had earlier conceived with

prednisolone 5 mg and clomiphene citrate 50 mg, but aborted spontaneously around 22 weeks.²

This time she presented with secondary amenorrhoea and was put on prednisolone 5 mg with a calcium and folic acid supplement. After 2 months of prednisolone therapy, she reported on 8 August 2012 with a failure to conceive spontaneously. Since it was day two of her cycle, ovulation induction was performed with clomiphene citrate 100 mg. Her total testosterone level at this time was 99.24 ng/dL. She conceived in the same cycle and reported with a positive ELISA test for pregnancy on 18 September 2012. Routine investigations including thyroid stimulating hormone and glucose challenge test with 50 g glucose, O'Sullivan method, were performed and found to be normal. Her total testosterone level at 7 weeks of pregnancy was 365 ng/dL. She was prescribed folic acid 5 mg, metformin 500 mg once daily and was advised to increase the dose of prednisolone to 7.5 mg. She had bleeding per vaginum, diagnosed as threatened abortion on ultrasonography. However, she responded to micronised progesterone and bed rest.

An early anomaly scan at 14 weeks revealed no anomalies. Total serum testosterone level determined on 21 November 2012, that is, at 14 weeks pregnancy was 167 ng/dL and she was still on prednisolone 5 mg. The woman had not increased the dose as advised earlier. A dose increment of 1.25 mg was made. She was put on a weekly 100 mg intramuscular progesterone in view of the prior mid-trimester loss. Serial 4–5 weekly total testosterone estimations were performed and prednisolone dose was adjusted.

Reference values for normal total testosterone levels at different weeks of pregnancy were taken from an earlier study.³

The total increment in the dose of prednisolone was from 5 mg prior to pregnancy to 8.75 mg just before delivery.

A glucose challenge test conducted every month revealed blood glucose values in the normal range.

CrossMark

To cite: Jain D. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201298

Date	Duration of pregnancy (weeks)	Total serum testosterone (ng/dL)	Earlier prednisolone dose+dose increment (mg)
2 October 2012	7	365	5
21 November 2012	14+	167	5+1.25
14 December 2012	17+	187.24	6.25+1.25
29 January 2013	22+	138.02	7.50+0
21 February 2013	28+	167.0	7.50+1.25

Figure 1 Chart showing normal growth pattern using abdominal circumference as a growth parameter.

Haematinic, calcium and metformin 500 mg tablets were continued throughout pregnancy. She remained normotensive, blood pressure ranging from 100/70 in the first trimester to 124/70 at 33 weeks. Serial ultrasound scans showed normal growth pattern (figure 1). At 29 weeks the ultrasound scan showed estimated fetal weight to be 1439 g, that is, there was no evidence of intra-uterine growth retardation (figures 2 and 3).

The patient presented on 25 March 2013 at 32+weeks of pregnancy with pain on the lower abdomen. On examination, the cervix was 2 cm dilated and effaced with bulging membranes. Short course betamethasone was given considering the preciousness of the pregnancy and the fact that there is not much in literature about the benefit of prednisolone in the prevention of hyaline membrane disease. Tocolysis was performed with Ritodrine in drip, continued for 48 h.

However, she had premature rupture of membranes on 29 March 2013 that is, at 33 weeks and delivery followed rapidly. The total duration of labour was less than 3 h (figures 4 and 5).

A baby girl weighing 1.75 kg Apgar 1 min 8/10, 5 min 10/10 was born. The baby cried immediately after birth, was examined and found to have normal female external genitalia (figures 6 and 7).

FOLLOW-UP AND OUTCOME

The baby was put to the breast immediately after birth, but the badly retracted nipples made sucking very difficult. Milk secretion was abundant on the third day after delivery, and the baby was made to suck and also fed with expressed breast milk with a spoon. Eventually, one of the nipples could be pulled out with manual efforts and the baby started feeding from one breast.

One month after birth, the baby was examined. She weighed 2.8 kg, had crown-heel length 50 cm, occipito frontal circumference 34 cm and had normal neonatal reflexes. At 4 months of age, she weighed 5.2 kg, and had normal milestones.

DISCUSSION

There is a clear correlation between genotype and phenotype in women with classic congenital adrenal hyperplasia. The salt wasting forms of classical 21-hydroxylase deficiency exhibit large gene deletions or a mutation that affects splicing and hence no 21-hydroxylase enzyme activity. In women with simple virilising forms, 21-hydroxylase gene shows point mutations with low but detectable enzyme activity.

Classic congenital adrenal hyperplasia is an autosomal recessive disorder. In a woman with the classic form of the disease the probability of an infant being born with the disorder is 1:120⁴; hence hyperandrogenism will occur only in the child where the mutated gene manifests itself.

Literature is sparse regarding the pregnancy outcome and follow-up of infants born to mothers with classic congenital adrenal hyperplasia. The case was carefully monitored during

Figure 2 Scan showing fetus at 29 weeks.

Figure 3 Graph showing fetal weight in the normal range, that is, average for gestational age.

pregnancy and showed some strikingly different observations in comparison to those in earlier reports.

As recommended by authors, a glucocorticoid that is metabolised by placental 11- β -hydroxy steroid dehydrogenase such as hydrocortisone, cortisone acetate, prednisolone and methylprednisolone should be used.³ Although sex determination is illegal in India, but since this was a special circumstance it was asked for and allowed. On coming to know that it was a female fetus, prednisolone was continued during pregnancy. It was preferred over hydrocortisone because of the ease of oral administration. The dose of prednisolone was carefully adjusted so as to keep serum total testosterone in the upper normal range in order to protect the external genitalia of the fetus and at the same time to avoid cushingoid effects in the mother.

There is an increased propensity of female infants in women with classic congenital adrenal hyperplasia. In an earlier study reporting pregnancy outcome in four women with classic congenital adrenal hyperplasia, all infants were female.³ In a recent publication among children born to women with congenital adrenal hyperplasia, only 25% were boys as compared to 55% in the normal control population.⁴ This uneven sex ratio could be due to the feminine environment in these mothers at the time of implantation owing to steroid administration.

The serum testosterone values increased during pregnancy, however, the prednisolone dose increased by only 3.75 mg over and above the non-pregnant dose.

A very high incidence of worsening of insulin resistance and gestational diabetes has been reported in pregnant women with

Figure 4 Patient in the second stage of labour.

Figure 5 Episiotomy incision and crowning of fetal head.

Figure 6 Alert and active baby just after birth.

congenital adrenal hyperplasia.⁴ Metformin was given to our patient in view of these earlier reports, to prevent the development of glucose intolerance. However, in our patient with normal body mass index, the serial blood sugar values as determined by 50 g glucose challenge test were well within the normal range, that is, the woman remained normoglycaemic. Glucocorticoid use in these women has been found to be associated with an increased incidence of pre-eclampsia,⁵ however our patient was normotensive throughout pregnancy.

A very high incidence of caesarean section has been reported in women with congenital adrenal hyperplasia owing to two reasons; first, because of genital reconstructive surgery and

Figure 7 Normal female genitalia of the newborn.

second, due to cephalopelvic disproportion, because of the android nature of the pelvis as a result of an excess of androgens.⁴ However in this patient, a preterm delivery occurred preceded by a spontaneous mid-trimester abortion simulating cervical insufficiency. There could be a relation between cervical insufficiency and altered müllerian development in this case, which needs to be looked for in more number of women with classical congenital adrenal hyperplasia.

Short course betamethasone was given to this patient considering prematurity and preciousness of the baby. The baby exhibited normal Apgar and did not require oxygen or respiratory assistance. Hence the dilemma persists, whether betamethasone should be administered or steroids already being given to the mother for reducing androgen levels are sufficient to prevent hyaline membrane disease.

With serial scans, the growth of the fetus was studied and normal growth pattern was observed in this case. The baby was average for gestational age. There are conflicting reports in literature regarding the incidence of intrauterine growth retardation in these women. In one study, five infants small for gestational age were born in 31 term pregnancies.⁶ In a recent study all the children born to 14 women were in the normal average range for birth weight.⁴

A striking observation in this woman was poorly developed and badly inverted nipples; probably related to the hyperandrogenism and altered oestrogen/progesterone status in prepubertal age. Another point that needs to be highlighted is the adequate milk production, revealing a normal prolactin axis in these women.

A 4-month follow-up of the baby shows normal weight gain, growth pattern, milestones and even alertness as compared with other babies. Hence, maternal prednisolone resulted in hardly any ill effects on the baby of our patient, till 4 months of age.

CONCLUSION

In women with 21-hydroxylase deficient classic congenital adrenal hyperplasia, a glucocorticoid not metabolised by 11- β -hydroxysteroid dehydrogenase should be continued during pregnancy. The dose of the steroid should be carefully titrated with serum testosterone levels. The patient should be observed for complications such as gestational diabetes, pregnancy-induced hypertension and intrauterine growth retardation for a good neonatal outcome.

Learning points

- ▶ In a pregnant woman with classical congenital adrenal hyperplasia, serum testosterone levels should be measured every 4–6 weeks.
- ▶ A glucocorticoid, not metabolised by 11- β -hydroxysteroid dehydrogenase should be used in pregnancy.
- ▶ The dose of glucocorticoid should be closely titrated with the serum testosterone level.
- ▶ The infant should be examined for any evidence of virilisation immediately after delivery.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Otten BJ, Stikkelbroeck MMI, Claahsen-van der Grinten HJ, *et al.* Puberty and fertility in congenital adrenal hyperplasia. In: Delemarre-vander Wal HA. ed *Abnormalities in Puberty, Scientific and Clinical Advances*. Basel: Karger, 2005;8:54–66.
- 2 Jain D. An unusual case of secondary amenorrhoea. *BMJ Case Rep* 2013;2013:pii: bcr2012008053.
- 3 Lo JC, Schwitzgebel VM, Blake Tynell J, *et al.* Normal female infants born to mothers with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 1999;84:930–6.
- 4 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.
- 5 Dunic M, Janjanin N, Ille J, *et al.* Pregnancy outcome in women with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Pediatr Endocrinol Metab* 2005;887–95.
- 6 Krone N, Wachter I, Stephanidou M, *et al.* Mothers with congenital adrenal hyperplasia and their children outcome of pregnancy and childhood. *Clin Endocrinol* 2001;55:523–9.

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