CASE REPORT

Recurrent severe hyperandrogenism during pregnancy: a case report

H B Holt, S Medbak, D Kirk, R Guirgis, I Hughes, M H Cummings, D R Meeking


This report describes the case of a 28 year old woman with virilisation occurring in two successive pregnancies. Recurrent maternal virilisation is rare (seven previous reports) and this case is unique in its severity. Differential diagnoses include ovarian disease and fetal aromatase deficiency. New techniques to exclude a fetal cause were used in this case. This patient presented during the third trimester of her first pregnancy with rapid onset of hirsuitism, increased musculature, and deepening voice. A blood hormone profile revealed significant hyperandrogenism (testosterone, 72.4 nmol/litre; normal range, 0.5–3.0). She delivered a normal boy and maternal androgen concentrations returned rapidly to normal (testosterone, 0.8 nmol/litre). She presented two years later, during her second pregnancy, with similar symptoms and biochemistry (testosterone, 47.5 nmol/litre). Again, she delivered a healthy normal boy and androgens returned immediately to normal (serum testosterone, 2.0 nmol/litre). Ultrasonography revealed no evidence of ovarian (or adrenal) masses in either pregnancy. Umbilical cord venous blood sampling and placental assays revealed no evidence of fetal aromatase deficiency. Recurrent hyperandrogenism during pregnancy is rare. Ovarian luteoma rarely recurs and hyperreactio luteinalis does not lead to such pronounced androgen concentrations. Therefore, this patient has a unique ovarian condition that could be harmful to offspring and mother.

Virilisation during pregnancy is rare and there are few reported cases of recurrence in a subsequent pregnancy. Potential causes may be ovarian, fetal, or adrenal, although there are no reports of adrenal pathology being implicated in the aetiology of recurrent gestational virilisation. Ovarian causes of virilisation include primary malignancy, polycystic ovarian syndrome (PCOS), luteoma, and hyperreactio luteinalis (HL). The last two conditions are associated with large ovarian masses (with androgen production in proportion to the size of the ovarian mass), and rarely recur.1 Virilisation associated with PCOS is normally mild.2 Fetal aromatase deficiency (FAD) results from a genetic defect in the fetus, and can lead to maternal virilisation as a result of absent aromatase activity in the placenta. We have used novel techniques to exclude this diagnosis.

“Virilisation during pregnancy is rare and there are few reported cases of recurrence in a subsequent pregnancy”

There are seven previously reported cases of recurrent virilisation of pregnancy. This eighth case appears to be unique in its severity and perhaps its aetiology.

CASE REPORT

A 25 year old white woman presented at 37 weeks of gestation complaining of excess hair growth on her face and abdomen and a deepening voice of two months’ duration. The pregnancy was otherwise normal. She had no other past medical history and her only medication was folic acid. The pregnancy was planned and she became pregnant in her second menstrual cycle after discontinuation of the oral contraceptive pill. Her menstrual cycle had been regular before starting oral contraception. Examination revealed pronounced facial hair and acne (fig 1), with increased hair growth on her limbs and abdomen. Her voice was deep and she had increased upper body musculature. Blood investigations revealed a serum testosterone of 72.4 nmol/litre, sex hormone binding globulin (SHBG) of 570 nmol/litre, androstenedione of 156 nmol/litre, and dihydroepiandrosterone sulfate (DHEAS) of 2.8 μmol/litre. Labour was induced at 38 weeks and she delivered a healthy male infant vaginally. The baby had no signs of excess androgen exposure and possessed normal external genitalia.

A pelvic ultrasound scan was performed four weeks postpartum and showed moderately enlarged ovaries containing multiple small cysts but no discrete masses. Her androgen profile rapidly returned to normal (testosterone, 0.8 nmol/litre at three weeks postpartum). Her symptoms improved over the following weeks with dramatic resolution of her hirsuitism, although mild facial hair growth remained. Her deep voice resolved.

She remained asymptomatic with normal androgen profiles for two years until she re-presented while planning...
ANDROGEN ASSAYS

Testosterone in the first pregnancy was analysed on an ASC ANDROGEN ASSAYS, using a modified Lowry method. The interassay precision for DHEAS was 13% at 1.4 nmol/litre, 9.3% at 5.8 µmol/litre, and 7.9% at 17.9 µmol/litre. For SHBG the interassay precision was 4% at 4.7 nmol/litre, 5.2% at 63 nmol/litre, and 6.6% at 80 nmol/litre. The samples were diluted 1/10 before analysis with sample diluent supplied with the kit.

Oestradiol was analysed by fluorometric immunoassay on an AUTODELFA analyser (Perkin Elmer Life Sciences, Foster City, California, USA). This method has an interassay precision of 4.5% at 240 pmol/litre, 3.4% at 897 pmol/litre, and 4.7% at 2600 pmol/litre. The pregnancy samples were diluted within the working range of the kit with the zero calibrator.

As a guide to the concentrations that are found in normal pregnancy, DHEAS, androstenedione, testosterone, and SHBG were measured in 15 women at 16–20 weeks of gestation (table 4).

AROMATASE ASSAY

Previously frozen placental tissue was homogenised in four volumes of ice cold phosphate buffered saline. The resulting homogenate was centrifuged at 1000 g for 15 minutes at 4°C and the protein content of the supernatant measured using a modified Lowry method. Aromatase activity was determined using a tritiated water assay based on a method previously reported for genital skin fibroblasts. Briefly, 10 µl of supernatant was added to 1 ml phosphate buffered saline containing NAD, NADPH (1 mM) and progesterone (5 µM). Tritiated androstenedione (NET 926 250 Ci) was added as substrate to provide approximately 70 000 disintegrations/minute and incubated for two hours at 37°C. The reaction was stopped by the addition of unlabelled androstenedione and 2 ml of chloroform. Sealed tubes were gently agitated for two hours. A 200 µl sample of the aqueous layer was added to 3 ml scintillant and the tritiated water was counted on a Canberra Packard 2500TR. The analysis was performed in triplicate; results were expressed as fmol/mg protein/hour.

Results

Placental aromatase activity was in excess of 500 fmol/mg protein/hour. Mean (SD) values in genital skin fibroblasts were 215 (33.9) fmol/mg protein/hour (n = 20 (2)). This

Table 1: Androgen profiles during the second pregnancy

<table>
<thead>
<tr>
<th>Androgen</th>
<th>Pre-preg</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
<th>5 months</th>
<th>6 months</th>
<th>7 months</th>
<th>8 months</th>
<th>Postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (nmol/l)</td>
<td>1.4</td>
<td>4.5</td>
<td>12.2</td>
<td>21.8</td>
<td>22.8</td>
<td>20.5</td>
<td>32.7</td>
<td>37.2</td>
<td>47.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>1400</td>
<td>34900</td>
<td>48300</td>
<td>73900</td>
<td>108900</td>
<td>106600</td>
<td>220400</td>
<td>800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>18.1</td>
<td>32.5</td>
<td>50.0</td>
<td>72.0</td>
<td>59.4</td>
<td>60.0</td>
<td>121.0</td>
<td>115.0</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>4.3</td>
<td>3.2</td>
<td>5.1</td>
<td>3.1</td>
<td>2.9</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DHEAS, dihydroepiandrosterone sulfate; preg, pregnancy.
of 110.7 mg/24 hours (normal range, 6–15). 6 The second case sections associated with raised 17-ketosteroid concentrations bilateral ovarian masses noted at two consecutive caesarean androgenisation as a secondary finding, and three occurred concentrations. Two cases presented as ovarian masses with recurrent luteoma associated with raised androgen concentrations. One concentrations were moderate (18.3 nmol/litre). 2 Our reported case associated with recurrent virilisation testosterone concentrations did not quite return to normal (4.3 nmol/litre) between pregnancies, and the patient suffered with oligomenorrhoea and subfertility, suggestive of PCOS. 9

These diagnoses seem unlikely in our patient. She is white, slim, presented as a primigravida, and had no ovarian masses. In addition, her androgen concentrations were much higher than those previously reported.

HL is commonly a cystic, bilateral ovarian condition. It typically occurs in white primigravida women, and is associated with conditions that involve raised hCG values, such as multiple gestation and molar pregnancies. Ovarian hyperstimulation syndrome, which may occur after induction of ovulation with hCG, is thought to be an iatrogenic variant of this condition. HL can occasionally recur in subsequent pregnancies, but raised androgen values and androgenisation are only seen in 15% of cases. 7 There is only one case report of recurrent HL associated with raised androgen concentrations. 8 Where androgenisation does occur in this condition it typically occurs in white primigravida women and there is one case report of two affected siblings. 10 Androgenisation is a recently described cause of recurrent virilisation in pregnant women and there is one case report of two affected siblings. 11 Aromatase is a recently described cause of recurrent virilisation in pregnant women and there is one case report of two affected siblings. 10 Aromatase is a cytochrome p450 enzyme normally present in placenta, gonads, brain, adipose tissue, liver, muscle, and hair. It catalyses the conversion of androgens to oestrogens. During pregnancy, large quantities of DHEAS and 16α-DHEAS produced by the fetal and maternal adrenal glands are converted initially to androstenedione and 16α-androstenedione, and thereafter to oestrogens by placental aromatase. This enzyme activity may also protect a female fetus from virilisation in conditions of maternal androgen excess, such as congenital adrenal hyperplasia. 12 FAD is rare and results from point mutations in the CYP19 gene. 13, 14 Only about 1% enzyme activity appears necessary to prevent virilisation from increased androgen substrate. Consequently, the abundance of placental aromatase activity demonstrated during the second affected pregnancy suggests that a female infant would not have been virilised at birth. Affected individuals develop skeletal abnormalities related to oestrogen deficiency, and both male and female patients require oestrogen replacement. FAD was excluded in our patient by the normal cord androgens, the absence of low maternal oestrogen values, and the normal placental aromatase activity. 15

Table 3
Steroid profiles over the menstrual cycle

<table>
<thead>
<tr>
<th>Day of cycle</th>
<th>LH (IU/l)</th>
<th>FSH (IU/l)</th>
<th>Progesterone (nmol/l)</th>
<th>Oestradiol (pmol/l)</th>
<th>Testosterone (nmol/l)</th>
<th>Androstenedione (nmol/l)</th>
<th>DHEAS (µmol/l)</th>
<th>17-OHP (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.9</td>
<td>–</td>
<td>5.0</td>
<td>7.5</td>
<td>174</td>
<td>1.5</td>
<td>7.9</td>
<td>5.6</td>
</tr>
<tr>
<td>8</td>
<td>5.9</td>
<td>6.8</td>
<td>3.7</td>
<td>0.8</td>
<td>137</td>
<td>1.8</td>
<td>10.0</td>
<td>4.3</td>
</tr>
<tr>
<td>15</td>
<td>6.3</td>
<td>4.7</td>
<td>0.5</td>
<td>0.5</td>
<td>331</td>
<td>1.6</td>
<td>8.8</td>
<td>6.3</td>
</tr>
<tr>
<td>22</td>
<td>12.1</td>
<td>4.0</td>
<td>497</td>
<td>23.9</td>
<td>296</td>
<td>2.0</td>
<td>7.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

DHEAS, ditydroepiandrosterone sulfate; FSH, follicle stimulating hormone; LH, luteinising hormone; 17-OHP, 17-hydroxyprogesterone.

Table 4
Normal hormone concentrations at 16 to 20 weeks of gestation

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Normal concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEAS</td>
<td>0.8–5.8 µmol/l (2.30)</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>3.2–12.5 nmol/l (6.7)</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.8–3.3 nmol/l (1.7)</td>
</tr>
<tr>
<td>SHBG</td>
<td>97–476 nmol/l (305)</td>
</tr>
</tbody>
</table>

Values are range (mean).

DHEAS, dithyroepiandrosterone sulfate; SHBG, sex hormone binding globulin.
Take home messages

- We report a 28 year old woman with severe virilisation occurring in two successive pregnancies
- Recurrent maternal virilisation is rare—there are only seven previous reports—and this case is unique in its severity
- The differential diagnoses include ovarian disease and fetal aromatase deficiency (FAD)
- FAD was excluded and this case appears to be unique, with an ovarian origin that is not associated with an ovarian mass
- Although we were worried about the risk of fetal virilisation in a female baby, the normal placental aromatase activity and fetal androgen concentrations suggest that a female fetus would not have been affected.

acknowledgements

We thank R Ward for technical assistance with the aromatase assay.

authors’ affiliations

H B Holt, S Medbak, D Kirk, R Guirgis, M H Cummings, D R Meeking, Academic Department of Diabetes and Endocrinology, Portsmouth Hospitals NHS Trust, Portsmouth PO6 3LY, UK
I Hughes, Department of Paediatrics, Addenbrookes Hospital, Cambridge CB2 2QQ, UK

The patient gave her permission for this case report to be published

Correspondence to: Dr H Holt, Academic Department of Diabetes and Endocrinology, Portsmouth Hospitals NHS Trust, Portsmouth PO6 3LY, UK; hholt@doctors.net.uk

Accepted for publication 2 August 2004

REFERENCES

Recurrent severe hyperandrogenism during pregnancy: a case report

H B Holt, S Medbak, D Kirk, R Guirgis, I Hughes, M H Cummings and D R Meeking

*J Clin Pathol* 2005 58: 439-442
doi: 10.1136/jcp.2004.018382

Updated information and services can be found at:
http://jcp.bmj.com/content/58/4/439

These include:

**References**
This article cites 14 articles, 4 of which you can access for free at:
http://jcp.bmj.com/content/58/4/439#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections
Clinical diagnostic tests (805)

Notes