A CASE OF ADRENOCORTICAL HYPERFUNCTION
NORMALIZED DURING THE SECOND AND THIRD TRIMESTERS
OF THREE PREGNANCIES

By

P. I. Jørgensen and V. Sele

ABSTRACT

Detailed hormonal studies were performed before, during and after three pregnancies in an untreated patient with adrenocortical hyperfunction due to hyperplasia. The patient was clinically characterized by oligomenorrhoea and moderate hirsutism, but showed no signs of virilization or of Cushing's disease. In the non-pregnant state her 17-ketosteroid excretion was elevated to twice the normal value, the androsterone fraction being moderately and the aetiocholanolone fraction greatly elevated, whereas the excretion of dehydroepiandrosterone was essentially normal. In the non-pregnant state the excretion of 17-ketogenic steroids, tetrahydrocortisol, tetrahydrocortisone, cortisone and tetrahydrocorticosterone was also considerably elevated. On high doses of dexamethasone (8 mg daily) or cortisone (100 mg daily) all fractions of 17-ketosteroids as well as the cortisol metabolites were suppressed to about one-half.

Without preceding or simultaneous steroid treatment the patient conceived three times. During all three pregnancies every sign of excessive hormone production ceased. The excretion of 17-ketosteroids in all fractions fell to 20–30%/o, that of 17-ketogenic steroids to between 30%/o and 35%/o, and that of cortisol metabolites to between 5%/o and 46%/o of the levels found before and after the pregnancies. The considerable endocrine activity of the foeto-placental unit may have "normalized" the maternal hypothalamic-pituitary-adrenocortical feedback mechanism, either by suppressing or by altering the sensitivity of the feed-back system. An alternative theory might be an accelerated rate
of cortisol metabolism by the liver in the non-pregnant state which is normalized during the last two trimesters of the pregnancies. The findings are being published as a contribution to the elucidation of the endocrinology of pregnancy.

Adrenocortical hyperfunction due to hyperplasia with increased production of androgens, virilization and menstrual irregularities is nearly always accompanied by sub- or infertility, if untreated.

Wilkins et al. (1952) observed that cortisone therapy in these cases resulted in normalization of 17-ketosteroid excretion, a regular menstrual cycle and other signs of normal ovarian function. During the subsequent years further publications reported pregnancy in corticosteroid-treated patients with adrenogenital syndrome or other forms of adrenocortical hyperfunction (Speroff 1965). As already mentioned, ovulation very rarely occurs in patients with adrenocortical hyperfunction, and accordingly there have been only a few reports on pregnancy in untreated cases (Southren et al. 1961).

METHODS

The urinary hormone excretion was determined by the following methods:

17-Ketosteroids: Johnsen (1956).
Pregnanediol, pregnanetriol: Klopper et al. (1955).

Complete 24-hour urine collections without preservative were used. The 17-ketosteroids and oestriol were analysed by the Hormone Department, Statens Seruminstitut, Copenhagen, the corticosteroids by the Department of Clinical Physiology, Glostrup Hospital, Denmark, and the other steroids by Medicinsk Laboratorium, Copenhagen. Plasma corticosteroids were determined, by the method of Buus (1968), at Medicinsk Laboratorium, Copenhagen.

CASE REPORT

At the end of the study the patient was 26 years of age and in her third pregnancy. During childhood she had shown a tendency to obesity which, however, subsided spontaneously during the subsequent years. Menarche at 16. The patient had normal periods for one year, but thereafter the vaginal bleeding became more scanty, and the intervals were 3–8 months. At the same time she developed moderate hirsutism with a virile demarcation of the pubic hair and some facial hair. The breasts developed normally. During repeated admissions around the age of 18 and 19 (1961–1963) gynaecological examination showed no abnormalities apart from the hirsutism. In particular, there was no hypertrophy of the clitoris. Intravenous pyelography was normal. The basal metabolic rate, glucose tolerance and blood pressure were within
the normal range. Weight 56.5 kg, height 162 cm. The spontaneous urinary excretion of hormones indicated adrenocortical hyperfunction that could be suppressed by cortisone and by dexamethasone (cf. Results). Aortography showed no signs of adrenal tumour, and X-rays of the sella turcica were normal.

During the next four years (1965–1968) the patient conceived three times despite persisting oligomenorrhea and without therapy:

First pregnancy

The pregnancy continued in a normal manner. Owing to the normal hormone excretion (Table 1) no steroid therapy was given. In the 39th week of gestation the patient was admitted because of contractions. There was pronounced tension of the uterus, and the heart sounds were inaudible. On the same day the patient was delivered of a stillborn girl, birth weight 2600 g. Autopsy did not reveal any definite cause of death (grade I–II maceration, pleural petecchiae and intracranial congestion), but on the placenta there was a large, adherent clot, indicating premature separation of the placenta.

Although signs of adrenocortical hyperfunction returned after delivery (Table 1) the patient conceived again in 1966, after a period of oligomenorrhea without treatment.

Second pregnancy

The pregnancy ran a normal course. Because of a normalized hormone excretion no steroid therapy was given. Vaginal delivery took place in the 41st week. A short time before delivery the heart sounds were affected, so that episiotomy was done. Immediately afterwards, a living, normal boy of 3150 g was delivered. The placenta was normal.

After this pregnancy the untreated patient continued to exhibit signs of hypercorticism (cf. Table 1). Nevertheless, she conceived again in 1968 during a period of spontaneously regular menstruation (4/30 – 35 days).

Third pregnancy

During this pregnancy the patient showed a tendency to moderate oedema, but the blood pressure was normal and the pregnancy ran a normal course. Due to a suspicion of too large a baby, labour was induced by medication in the 41st week. After two hours' contractions, the heart sounds were poor, and Caesarian section was performed. The infant, a boy weighing 3950 g, exhibited no abnormalities.

RESULTS

Spontaneous excretion in the urine in the non-pregnant state

17-Ketogenic steroids (Table 1). – The mean excretion was 32.8 mg/24 h, range 28–38 mg/24 h, i.e. above normal (7–20 mg/24 h). The highest values were found in the period between the second and the third pregnancy.

Cortisol metabolites (Table 3). – The analysis was performed between the second and the third pregnancy. The total excretion was 17.4 mg/24 h, i.e.
Table 1.

The excretion of steroids in urine before, during and after the pregnancies.

<table>
<thead>
<tr>
<th>Year</th>
<th>Week of pregnancy</th>
<th>17-KGS mg/24 h (7-20)</th>
<th>17-KS mg/24 h (4-18)</th>
<th>DHA mg/24 h (0.5-4.5)</th>
<th>A mg/24 h (0.6-6.5)</th>
<th>Ae mg/24 h (1.2-6.0)</th>
<th>R mg/24 h (0.1-0.9)</th>
<th>U mg/24 h (0.1-2.2)</th>
<th>P3 mg/24 h</th>
<th>P2 mg/24 h</th>
<th>Oc3 mg/24 h</th>
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</thead>
<tbody>
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<td>1961</td>
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<td>26.2</td>
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<tr>
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<td>13.0</td>
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<td>3.4</td>
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<td>-</td>
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</tr>
</tbody>
</table>

First pregnancy

Second pregnancy
The values in brackets are non-pregnant normal limits. According to the pregnanediol and oestriol normal limits see "methods" (references). 

**Abbreviations:** 17-KGS = 17-ketogenic steroids (total 11-oxy and 11-deoxy compounds). 17-KS = 17-ketosteroids, DHA = dehydroepiandrosterone = 3β-hydroxy-androst-5-en-17-one, A = androsterone = 3α-hydroxy-5α-androstan-17-one, Ae = aetiocholanolone = 3α-hydroxy-5β-androstan-17-one, R = rest fraction = mainly corticosteroids, U = unknown steroids, P3 = pregnanetriol = 5β-pregnane-3α,17,20α-triol, P2 = pregnanediol = 5β-pregnane-3α,20α-diol, Oe3 = oestriol = oestra-1,3,5(10)-triene-3,16β,17β-triol.
Table 2.
The excretion of steroids in non-pregnant state, before and after treatment with corticosteroids.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Dose (day)</th>
<th>17-KGS</th>
<th>17-KS</th>
<th>U</th>
<th>DHA</th>
<th>A</th>
<th>Ae</th>
<th>R</th>
<th>P3</th>
<th>P2</th>
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<tbody>
<tr>
<td>Control</td>
<td></td>
<td>32.8</td>
<td>1.4</td>
<td>2.6</td>
<td>6.2</td>
<td>9.3</td>
<td>13.3</td>
<td></td>
<td></td>
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<tr>
<td>Cortisone</td>
<td>100 mg</td>
<td>19.5</td>
<td>0.5</td>
<td>1.6</td>
<td>3.2</td>
<td>4.2</td>
<td>9.9</td>
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</tr>
<tr>
<td>Control</td>
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<td>33.7</td>
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<td>0.9</td>
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<td>18.1</td>
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<td>Control</td>
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<td>34.8</td>
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<td>–</td>
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<tr>
<td>Dexa-methasone</td>
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<td>8.3</td>
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<tr>
<td></td>
<td>2 mg</td>
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<td>–</td>
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<td>–</td>
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<td>0.7</td>
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</tr>
<tr>
<td></td>
<td>8 mg</td>
<td>10.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 mg</td>
<td>8.0</td>
<td>21.5</td>
<td>1.3</td>
<td>2.8</td>
<td>3.2</td>
<td>8.7</td>
<td>5.6</td>
<td>0.6</td>
<td>0.8</td>
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<tr>
<td>Control</td>
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<td>62.4</td>
<td>3.4</td>
<td>6.6</td>
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<td>21.5</td>
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<td>1.8</td>
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<tr>
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<td>37.8</td>
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<td>–</td>
<td>–</td>
<td>2.2</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations and normal limits of excretion: see Table 1.

above the normal range (1.3–10 mg/24 h). The fractions tetrahydrocortisol, tetrahydrocortisone and cortisol were excreted in increased quantities, whereas the excretion of the other metabolites was normal.

Corticosterone metabolites (Table 3). – The investigation was carried out between the second and third pregnancy. Total excretion 0.99 mg/24 h, i.e. at the upper end of the normal range (0.12–1.00 mg/24 h). There was a slightly increased excretion of tetrahydrocorticosterone and tetrahydro-11-dehydrocorticosterone, whereas the excretion of the other metabolites was normal.

Pregnanetriol (Table 1). – The analysis was done before the first and between the second and third pregnancy. The mean excretion was 1.4 mg/24 h, i.e. within the range of normal (0.1–2.2 mg/24 h). The highest values were found between the second and third pregnancy.

17-Ketosteroids (Table 1). – The total excretion averaged 34.2 mg/24 h, ranging from 25.4 to 51.2 mg/24 h, i.e. above the normal range (4–18 mg/24 h). The highest values were observed between the second and third pregnancy. The mean excretion of androsterone, and especially of aetiocholanolone, was increased, whereas the values for dehydroepiandrosterone were normal before
the first pregnancy, but elevated between the second and the third. The rest fraction averaged 10.9 mg/24 h (normal range 1.2–6.0 mg), highest between the second and third pregnancy. Elevated values were also found for the “U” fraction, mean 1.7 mg/24 h, as compared with the normal range of 0.1–0.9 mg/24 h.

Excretion in the urine during corticosteroid suppression in the non-pregnant state (Tables 2 and 3)

17-Ketogenic steroids. – After dexamethasone therapy, 0.5 mg 4 times daily, the excretion fell to 63 % (1967) and after 2 mg 4 times daily it fell to 24 % (1962) and 22 % (1967) of the initial values.

Cortisol metabolites (Table 3). – After treatment with dexamethasone, 2 mg 4 times daily (1967), the total excretion fell to 43 % of the initial values. The decrease was evenly distributed between the individual fractions: tetrahydrocortisol 36 %, allotetrahydrocortisol 38 %, tetrahydrocortisone 50 % and cortisol 54 %.

Corticosterone metabolites (Table 3). – After treatment with dexamethasone, 2 mg 4 times daily, there was no major change in total excretion or in the excretion of the individual fractions.

Pregnanetriol (Table 2). – After treatment with dexamethasone, 0.5 mg 4 times daily, the excretion fell to 58 %, and after 2 mg 4 times daily to 22 % of the initial value.

17-Ketosteroids (Table 2). – After treatment with cortisone 100 mg daily in the form of suppositories for 4 days (1962) the excretion of 17-ketosteroids fell to 59 % of the initial values. The decrease in all essentials was evenly distributed in all fractions: dehydroepiandrosterone 60 %, androsterone 50 %, aetiocholanolone 45 %, rest fraction 74 % and “U” fraction 36 %. After treatment with dexamethasone 2 mg 4 times daily for 3 days (1962) a fall in the total excretion to 59 % of the initial level was observed. The fall was evenly distributed in the individual fractions (53–64 %). After treatment with dexamethasone 0.5 mg 4 times daily for two days (1967) there was no fall in the excretion. Thereafter, the dose was altered to 2 mg 4 times daily, and two days later the total excretion was 42 % of the initial values, the fall for the individual fractions being: dehydroepiandrosterone 26 %, androsterone 34 %, aetiocholanolone 60 %, rest fraction 44 % and “U” fraction 35 % of the initial values.

Spontaneous excretion in the urine during the pregnancies (Tables 1 and 3)

17-Ketogenic steroids (Table 1). – During the first pregnancy the excretion
Table 3.
The excretion in urine of metabolites of corticosteroids in the untreated, non-pregnant state, in the non-pregnant state treated with dexamethasone and in the untreated pregnant state.

<table>
<thead>
<tr>
<th></th>
<th>THF mg/24 h (0.3–2.8)</th>
<th>A-THF mg/24 h (0.1–2.4)</th>
<th>THE mg/24 h (0.8–4.9)</th>
<th>U mg/24 h (0.0–0.05)</th>
<th>F mg/24 h (0.01–0.10)</th>
<th>E mg/24 h (0.02–0.13)</th>
<th>Total F mg/24 h (1.3–10.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant</td>
<td>7.7</td>
<td>1.6</td>
<td>7.8</td>
<td>0.04</td>
<td>0.24</td>
<td>0.06</td>
<td>17.44</td>
</tr>
<tr>
<td>control</td>
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<td></td>
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</tr>
<tr>
<td>Non-pregnant</td>
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<td>0.6</td>
<td>3.9</td>
<td>0.09</td>
<td>0.13</td>
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<tr>
<td>Dexamethasone</td>
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<td></td>
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<tr>
<td>Pregnant state</td>
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<td>0.08</td>
<td>3.2</td>
<td>0.20</td>
<td>0.11</td>
<td>0.14</td>
<td>4.53</td>
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</tbody>
</table>

Abbreviations: THF = tetrahydrocortisol = 3α,11β,17,21-tetrahydroxy-5β-pregn-20-one, A-THF = allotetrahydrocortisol = 3α,11β,17,21-tetrahydroxy-5α-pregn-20-one, THE = tetrahydrocortisone = 3α,17,21-trihydroxy-5β-pregnan-11,20-dione, U = Reichtstein U = 17α,20β,21-trihydroxy-preg-4-ene-3,11-dione, F = cortisol = 11β,17,21-trihydroxy-pregn-4-ene-3,20-dione, E = cortisone = 17,21-dihydroxy-pregn-4-ene-3,11,20-trione, Total F = total cortisol metabolites, THS = tetrahydro-11-deoxycortisol = 3α,17,21-trihydroxy-5β-pregnan-20-one, THB = tetrahydrocorticosterone = 3α,11β,21-trihydroxy-

was determined only once. It proved to be within the normal range, making up 36% of the mean excretion before pregnancy. During the second pregnancy, when numerous analyses were performed, the excretion was still very high in the 8th week. After the 13th week it fell to levels within the normal range, the mean excretion from the 18th to the 34th week of pregnancy being only 39% of those determined after the pregnancy. In the third pregnancy the excretion of ketogenic steroids was not determined.

Cortisol metabolites (Table 3). – These were determined only during the second pregnancy. The total excretion was within the range of normal (1.3–10 mg/24 h), but was only 26% of that measured after the pregnancy. The corresponding relations for the individual fractions were: tetrahydrocortisol 10%, allotetrahydrocortisol 5%, tetrahydrocortisone 41% and cortisol 46%.

Corticosterone metabolites (Table 3). – These were tested only during the second pregnancy. The total excretion and the excretion of the individual fractions did not show much difference either during or after pregnancy.

Pregnanetriol (Table 1). – The excretion in the second pregnancy was not essentially different from that after this pregnancy.

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Table 3.
The excretion in urine of metabolites of corticosteroids in the untreated, non-pregnant state, in the non-pregnant state treated with dexamethasone and in the untreated pregnant state.

<table>
<thead>
<tr>
<th>THS mg/24 h</th>
<th>THB mg/24 h</th>
<th>A-THB mg/24 h</th>
<th>THA mg/24 h</th>
<th>B mg/24 h</th>
<th>A mg/24 h</th>
<th>Total B mg/24 h</th>
<th>P3 mg/24 h</th>
<th>Δ5-P3 mg/24 h</th>
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<tr>
<td>(0.0–0.09)</td>
<td>(0.02–0.22)</td>
<td>(0.05–0.53)</td>
<td>(0.0–0.04)</td>
<td>(0.0–0.02)</td>
<td>(0.12–1.00)</td>
<td>(0.2–1.7)</td>
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<td>0.31</td>
<td>0.08</td>
<td>0.05</td>
<td>0.88</td>
<td>1.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>


17-Ketosteroids (Table 1). – The excretion was recorded during all the pregnancies. During the first pregnancy, in the 20th–34th week, the excretion was within the normal range (4–18 mg/24 h). This applied to the total excretion as well as to the individual fractions. During the second pregnancy there was, in the 8th and 13th weeks an excretion, total and for all fractions, which was above the normal range. Thereafter all the values were within the normal range. In the third pregnancy analyses were performed during the 34th and the 37th week. The values were within the normal range for all fractions.

The mean excretion of 17-ketosteroids during the pregnancies was calculated in per cent of the mean excretion before and after the pregnancies, as follows for the first, second and third pregnancy respectively: total 17-ketosteroids 41 %, 33 % and 26 %, dehydroepiandrosterone 65 %, 37 % and 22 %, androsterone 43 %, 45 % and 25 %, aetiocholanolone 25 %, 21 % and 14 %, “U” fraction 25 %, 38 % and 19 % and the “rest fraction” 50 %, 34 % and 45 %.

Pregnanediol (Table 1). – The excretion was found to be normal during the second pregnancy.
Oestriol (Table 1). — The excretion was recorded during the second and the third pregnancy and proved to be increasing within the normal range.

**Plasma cortisol**

The cortisol concentration in the plasma was 14.6 μg/100 ml at 8 a.m. and 9.0 μg/100 ml at 8 p.m. during the 37th week of the second pregnancy and after delivery at 8 a.m. 12.6 μg/100 ml.

**DISCUSSION**

The state of adrenocortical hyperfunction during the period before the first pregnancy and in the periods between the pregnancies may be characterized as follows according to the results of the analyses:

*Increased production of androgens.* — The excretion of 17-ketosteroids was elevated to twice the normal. The androsterone fraction was moderately and the etiocholanolone fraction greatly elevated, whereas the excretion of dehydroepiandrosterone was normal in most of the analyses. The production was not affected by dexamethasone 2 mg daily, but after the administration of dexamethasone 2 mg 4 times daily or cortisone 100 mg daily as suppositories the excretion in all the fractions fell to about 50% of the control values. Thus, hyperplasia of the adrenal cortex occurred as manifested clinically by moderate hirsutism, but without virilization, and by oligomenorrhea with ovulation.

*Increased production of cortisol.* — The excretion of 17-ketogenic steroids was elevated to twice the upper limit of normal. The same applied to the excretion of tetrahydrocortisol, tetrahydrocortisone and cortisol, whereas the pregnanetriol excretion was normal. After treatment with dexamethasone 2 mg 4 times daily the excretion of all the fractions fell to 50% or less of the control values. Thus, there was an excessive production of cortisol. Clinically, the patient exhibited no signs of Cushing’s disease.

*Increased production of corticosterone.* — The total excretion of corticosterone metabolites was normal, but the excretion of tetrahydrocorticosterone was increased more than two-fold. Dexamethasone therapy did not essentially alter this condition. In other words, there was a slightly increased production of corticosterone, not manifest clinically: There were no electrolyte disturbances, and the blood pressure was normal.

During the *pregnancies* all these signs of excessive hormone production disappeared. Thus, during the second and third trimesters the excretion of 17-ketosteroids in all the fractions fell to between 20% and 50%, 17-ketogenic steroids to between 30% and 35% and cortisol metabolites to between 5% and 46% of the values observed before and after the pregnancies.
In the present results there is nothing to indicate that the patient's hyperandrogenism was conditioned by a congenital enzyme defect in the synthesis of cortisol or of corticosterone (normal excretion of pregnanetriol, increased excretion of cortisol and corticosterone metabolites). The results of the suppression experiments rule out the presence of a tumour and make it reasonable to assume that apart from the pregnancies there has been hyperfunction of the adrenal cortex, either due to increased ACTH production or to an altered feed-back level in the interaction between the hypothalamus, pituitary and the adrenal cortex.

The normalization during the pregnancies may have been due to interference with the maternal feed-back mechanism. This may have been caused by a pregnancy-conditioned increase in the plasma level of cortisol. In normal pregnant women the concentration of cortisol increases with advancing gestation, so that during the last trimester the level is appreciably higher than in normal non-pregnant women (Bro-Rasmussen et al. 1962). A suggested explanation is a reduced glucuronide conjugation of cortisol metabolites as well as an increased binding of cortisol to the plasma globulin transcortin which increases towards the termination of pregnancy, due to the high oestrogen level at this time (Jailer et al. 1959; Booth et al. 1961). Another explanation of the high plasma concentration of corticosteroids during pregnancy might be an increased production in the foetal adrenal cortex which, even at an early stage of gestation, is able to form cortisol and corticosterone (MacNaughton 1969), but quantitatively this can hardly play any major role. In our patient only one determination of plasma cortisol was carried out, during the 37th week of the second pregnancy. The concentration was 14.6 µg/100 ml at 8 a.m. and 9.0 µg/100 ml at 8 p.m. on the same day. These values are lower than expected at this stage of gestation (Bro-Rasmussen et al. 1962). Furthermore, the total excretion of cortisol metabolites in the same pregnancy was very low as compared with the excretion during the period after the pregnancy and even lower than the level found after the administration of 8 mg dexamethasone daily to the non-pregnant patient. These findings directly militate against a pregnancy-conditioned cortisol suppression by the maternal ACTH production, unless very special conditions exist with regard to conjugation and plasma protein binding.

It is difficult to assess the present case on the basis of the literature, as nearly all published cases of adrenocortical hyperfunction have been treated with corticosteroids before and during the pregnancies (Speroff 1965). In these cases the excretion of 17-ketosteroids has been unchanged or slightly increasing during the pregnancies. However, Southren et al. (1961) have described a patient with congenital adrenal hyperplasia who conceived without any treatment. In this case the excretion of 17-ketosteroids was found to rise, within the first four weeks of the pregnancy, to a maximum of 55 mg/24 h,
but thereafter fell gradually to 27 mg/24 h in the 14th week. Two weeks later spontaneous abortion occurred. These findings agree with those described here, the steroid pattern in our patient being still abnormal during the first trimester and thereafter becoming normal for the remainder of the pregnancy.

It is well-known that during pregnancy there is considerable endocrine activity in the foeto-placental unit (Klopper & Diczfalusy 1969). In the present case this activity has possibly “normalized” the hypothalamic-pituitary-adrenocortical feed-back mechanism by suppression or by altering the sensitivity in the feed-back system. An alternative theory could be an altered cortisol metabolism by the liver. If so the normal plasma cortisol concentration combined with the increased excretion of 17-ketogenic steroids and corticosteroid metabolites in the non-pregnant state and at the beginning of pregnancy may be explained by an accelerated rate of cortisol metabolism while the condition in the last two trimesters of pregnancy might be the result of an alteration in metabolism during the pregnancies with a normal production-rate of cortisol.

The findings are being published as a contribution to the further elucidation of the endocrinology of pregnancy.

REFERENCES


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