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DETAILED HORMONAL STUDIES DURING 
AND AFTER PREGNANCY IN A 
PREVIOUSLY HYPOPHYSECTOMIZED PATIENT 

By 
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ABSTRACT 

This is a report on detailed hormonal studies before, during, and after pregnancy in a hypophysectomized patient who conceived after treatment with human gonadotrophins. 
On the basis of the results the following conclusions were drawn: 
(1) In a patient who, judging by numerous investigations, no longer had any production of pituitary gonadotrophic hormones, it was possible 
(a) by treatment with human gonadotrophic hormones to induce ovulation, 
(b) without further stimulation to attain conception and preserve the conceptus, 
(c) to carry through a normal pregnancy, ending at term in vaginal delivery of a normal infant. 
(2) In this patient, whose pituitary corticotrophin production had totally ceased or had been negligible before the pregnancy, the endocrine state appeared to be completely normalized during pregnancy; thus: 
(a) on unchanged corticosteroid medication the mean plasma corticoid concentration as well as the urinary excretion of corticoid metabolites, 17-ketogenic steroids, and 17-ketosteroids were considerably higher during than after the pregnancy, 
(b) the urinary excretion of pregnanediol, oestriol and chorionic gonadotrophin was normal during the pregnancy. 
Moreover, the results of metyrapone tests before, during and after the pregnancy, ACTH stimulation test after delivery, and measurements of diurnal fluctuations in the concentration of plasma cortisol during the pregnancy are reported.

117
The increased steroid production during pregnancy may be partially explained as a consequence of the activity in the foeto-placental unit which, however, can hardly have been quantitatively decisive. It must be presumed, therefore, that as a result of the pregnancy ACTH or an ACTH-like factor has been secreted, stimulating the maternal adrenal. It is assumed that the corticotrophin has been produced in the placenta and that it has passed to the maternal circulation.

The role of the pituitary gland in the female hormone cycle is well substantiated, but it is not known to what extent the maternal hypophysis influences the conceptus at the time of its nidation and after the foeto-placental unit has been established. Pregnant hypophysectomized patients are well-suited objects for a further elucidation of this problem and have been described by Little et al. (1958) and Kaplan (1961), but in both cases hypophysectomy was performed during pregnancy. However, recent advances in stimulation therapy by human gonadotrophins have made it possible to attain ovulation and conception in previously hypophysectomized patients (Gemzell & Kjessler 1964; Vande Wiele et al. 1970; Luukkainen et al. 1970; Corral et al. 1972).

In this paper a detailed report is given of hormonal studies before, during, and after pregnancy in a hypophysectomized patient who conceived after treatment with human gonadotrophins.

METHODS

The hormones were measured by the following methods:

17-Ketosteroids: Johnsen (1956).
Oestrogen (total): Brown et al. (1968).

Complete 24-h urine collections without preservative were used. The specimens analysed for corticosteroid metabolites were quick-frozen and assayed at the same time in the Department of Clinical Physiology of the Glostrup Hospital, Copenhagen. The other steroids were determined at Statens Seruminstitut, Copenhagen. Plasma corticosteroids were determined at Medicinsk Laboratorium, Copenhagen.

The following abbreviations and trivial names will be used:

17-KGS: 17-ketogenic steroids.
17-KS: 17-ketosteroids.
Oøg: oestriol, oestra-1,3,5(10)-triene-3,16α,17β-triol.
Pø: pregnanediol; 5β-pregnane-3α,20α-diol.
P₃: pregnanetriol; 5β-pregnane-3a,17,20α-triol.
Total Oe: total oestrogens.
THF: tetrahydrocortisol; 3α,11β,17,21-tetrahydroxy-5β-pregn-20-one.
Allo-THF: allo-tetrahydrocortisol; 3α,11β,17,21-tetrahydroxy-5α-pregn-20-one.
THE: tetrahydrocortisone; 3α,17,21-trihydroxy-5β-pregnane-11,20-dione.
Compound U: 17α,20α,21-trihydroxy-pregn-4-env-3,11-dione.
F: cortisol; 11β,17,21-trihydroxy-pregn-4-ene-3,20-dione.
E: cortisone; 17,21-dihydroxy-preg-4-ene-3,11,20-trione.
THS: tetrahydro-11-desoxy cortisol; 3α,17,21-trihydroxy-5β-pregn-20-one.
11-deoxycortisol; 17,21-dihydroxy-preg-4-ene-3,20-dione.
THB: tetrahydrocorticosterone; 3α,11β,21-trihydroxy-5β-pregn-20-one.
Allo-THB: allo-tetrahydrocorticosterone; 3α,11β,21-trihydroxy-5α-pregn-20-one.
THA: tetrahydro-11-dehydrocorticosterone; 3α,21-dihydroxy-5β-pregnane-11,20-dione.
B: corticosterone; 11β,21-dihydroxy-pregn-4-ene-3,20-dione.
ACTH: corticotrophin.
HCG: human chorionic gonadotrophin.
HMG: human menopausal gonadotrophin.
PBI: protein-bound iodine.
TSH: thyrotrophin.
Prednisolone: 11β,17α,21-trihydroxy-pregna-1,4-diene,3,20-dione.
Dexamethasone: 9α-fluoro-16α-methyl-11β,17,21-trihydroxy-pregna-1,4-diene-3,20-dione.

Metrapone test. – During the first 48 h the 24-h urine was collected, and blood samples were drawn at 9 a.m. on the third day a 24-h urine sample was collected, and from noon onwards Metopiron® (metrapone tartrate) tablets were administered, 500 mg every other hour until noon the next day, i.e. a total of 6000 mg. On the fourth day the 24-h urine was collected, and blood samples were drawn at noon. On the fifth and sixth days the 24-h urine was collected. The test was performed in hospital the patient receiving an unchanged dose of prednisolone, 10 mg daily.

ACTH stimulation test. – After blood sampling at 9 a.m. a 4-h intravenous drip infusion of Synacthen® (tetracosactide INN) was started, 0.25 mg in 500 ml physiological saline. Blood samples were drawn at 10 a.m. (I), 11 a.m. (II), at 12 noon (III), and at 1 p.m. (IV) for cortisol determination.

CASE REPORT

The patient was 27-year-old primigravida. Her development during childhood had been normal. At the age of 11 spontaneous, scanty and rare vaginal bleeding appeared, but ceased entirely one year later. Since then, bleeding occurred only after hormone therapy. The breasts were well-developed at the age of 12, whereas pubic hair was very sparse. Owing to increasing obesity and persistent amenorrhoea the patient was started, at the age of 16, on thyroid, oestrogen and progesterone medication which resulted in slight vaginal bleedings.

At the age of 18 she was admitted because of visual disturbances, fatigue and dizziness during the past year. She did not exhibit acromegalic features, but axillary and pubic hairing was scanty. Ophthalmoscopy and carotid angiography disclosed
signs of a pituitary tumour. At this juncture there was a normal excretion of pituitary gonadotrophins, 19 MUU/24 h, and a normal urinary excretion of 17-KS. The basal metabolic rate, measured on two occasions, was +3 and +7.8%/o. On 26-9-1962 cranietomy was done with intracapsular excision of a cherry-sized chromophobe pituitary adenoma. The post-operative course was uneventful. In October 1963 the patient received X-ray therapy for 3 weeks.

During the next year she began to suffer again from increasing fatigue and visual disturbances. In February, 1964, a recurrence was suspected, and exploratory craniotomy was done, but failed to show any signs of recurrence. The patient was discharged on thyroid, 200 IU daily, and cortisone, 25 mg daily. On this medication she felt better. In 1965, on unchanged treatment, she was found to have a urinary excretion of 17-KS of 1.5 mg/24 h, 17-KGS 9.4 mg/24 h. The pituitary gonadotrophins were not demonstrable in the urine (<3 MUU/24 h). In 1966 the patient was investigated in more detail because of weight gain. She was found to be hypothyroid, the BMR being -17.9%/o. The PBI and T₃ tests were normal. The ¹³¹I uptake was normal (14.3 and 13.9 µg before and 49.7 µg after stimulation with thyrotrophin). The excretion of 17-KGS was 17.6 mg/24 h, of 17-KS 2.5 mg/24 h, and pituitary gonadotrophins were still not detectable in the urine. With the metyrapone test a fall in plasma cortisol of from 3.3 µg/100 ml to 0.8 µg/100 ml and an increase in 11-deoxycorticisol of from 0.18 µg/100 ml to 0.53 µg/100 ml were found. At the first blood sampling, the cortisone medication had been withheld for 48 h. The patient was discharged on cortisone, 30 mg daily, and Eltroxin® (levo-thyroxine sodium) 0.3 mg daily.

In 1967, the patient then aged 24, was admitted here for the first time, as she wanted to become pregnant. She was obese (weight 83 kg, height 167 cm). Axillary hairing was normal, but pubic hair was sparse. The breasts were large, with well-developed glandular tissue. The uterus felt normal; the ovaries were not palpable. On curettage, no tissue could be removed from the 7 cm deep uterine cavity. Pyelography and glucose tolerance test showed normal findings. The EEG was severely abnormal. Chromosomal analysis showed a normal female. With a view to later stimulation therapy, the patient was put on oestrogen.

Stimulation therapy. - In October 1969 the patient was admitted and treated continuously with gonadotrophins in the form of injections as follows: HMG (Humantex® LEO Copenhagen) 150 IU for 4 days, 225 IU for 6 days and 150 IU for 5 days, and thereafter with HCG (Physex® LEO Copenhagen), 3000 IU for 5 days, i.e. 18 days of treatment in all. This treatment caused an increase in the excretion of total oestrogen of from 0 µg/24 h to 230 µg/24 h and in the pregnanediol excretion of from 0.16 mg/24 h to 4.17 mg/24 h. Thus, it seemed very likely that ovulation had been induced. Menstruation occurred 27 days after the institution of the treatment.

In September 1970 HMG-HCG treatment was again administered in hospital as outlined above. Menstruation did not occur, and 37 days after the institution of the treatment, 19 days after its termination, there was still a high excretion of oestrogen (189.6 µg/24 h) and pregnanediol (2.4 mg/24 h). 10 days later the output of pregnanediol was 18.6 mg/24 h, and the HCG pregnancy test was positive.

The pregnancy

Time of conception: Early October 1970. Foetal movements: first on 15-1-1971. Delivery: 22-6-1971. During the first half of pregnancy the patient was supervised by a specialist in her home town, but thereafter and until delivery she was in the Obstetrical Department A, Rigshospitalet, except for the period May 1st-24th, 1971.
Complications: Moderate vomiting during the first trimester, a tendency to mild oedema, and in the 39th week one day with pyuria and significant bacteriuria accompanied by low-grade fever. Non-hormonal investigations: Blood pressure ranging from 120/70 to 130/70 mmHg. No proteinuria or glycosuria. Haematocrit 31–39%. Blood group A, Rhesus positive, no antibodies. Urinary output usually between 1600 and 2000 ml/24 h, maximum 2200/24 h. Specific gravity of urine usually between 1010 and 1015, ranging between 1003 and 1020. Serum urea as a rule between 20 and 25 mg/100 ml (maximum 40 mg/100 ml). Serum sodium 136–142 meq./l, serum potassium 2.7–3.5 meq./l. Standard bicarbonate in the serum: 22.2–26.2 meq./l. Amniocentesis a total of five times and ultrasonic scanning: No abnormality. Ophthalmological examination: Incomplete bitemporal hemianopsia (unchanged from before). Treatment: Cortisone 30 mg/24 h from before the pregnancy until March 1, 1971, prednisolone 10 mg/24 h from 2nd March to 24th May, 1971, dexamethasone 1.5 mg/24 h from 25th May until after delivery. Furthermore, throughout the pregnancy Eltroxin® 0.3 mg/24 h, and Adurix® (clopamide) 20 mg/24 h. During the period 14th June until delivery Pyelol® (calcium chloride 0.6 g + phenyl salicylate, 0.3 g per tablet) 6 tablets/24 h. Moreover, periodically Pyridoxin® (pyridoxine chloride) 20 mg/24 h. In addition, iron, calcium and vitamins throughout the pregnancy.

Delivery

Course: During the last two weeks before delivery the patient had noticed daily, irregular uterine contractions. On 21-6-1971 at 8 p.m. she began to have spontaneous, regular contractions which during the subsequent hours increased only slightly in strength and frequency. For this reason, she was given a sedative by mouth (acetyl glycinamide chloral hydrate = Ansopal®) 1 g, and thereafter slept fitfully. On 22-6 at 11 a.m. she still had only minor contractions, and because of decreasing contractions an intravenous drip was established containing: 500 ml glucose solution, Syntocinon® (oxytocin) 10 IU and Efosin® (phenpiprani chloridum). Thereafter, the contractions increased, and labour progressed satisfactorily. On 22-6 at 5.30 p.m. the membranes were ruptured, and moderate quantities of clear, unstained amniotic fluid were emptied out. On 22-6 at 6.10 p.m. the cervix was fully dilated, and satisfactory bearing-down pains were recorded. At this juncture trichlorethylene was being given on a mask and a pudendal block was set up with lidocaine 200 mg. Owing to the history of hydropyseotomy, vacuum extraction was employed, and without any difficulty a live boy was delivered at 7 p.m. in the first regular cephalic presentation. On delivery of the first shoulder Methergin® (methyl ergometrine maleate) 0.2 mg was injected intravenously. The placenta was spontaneously delivered 15 min later. Puerperal period: Due to a tendency to moderate bleeding and anaemia, a blood transfusion was given, and the patient received Methergin tablets for three days. Otherwise, the puerperium was uneventful.

Steroid therapy: From 22nd to 26th June cortisol was injected in decreasing doses: 200, 100, 75, 50 and 50 mg. From 26–6 dexamethasone 1.5 mg daily until 28–7 when prednisolone, 10 mg daily, was started. Lactation: The patient did not notice any tension of the breasts or secretion of milk, and this too was not observed objectively, not even on attempts at milking. Placenta: Weight 780 g, macroscopically normal, cord normal. Infant: Was intensively supervised, but did not at any time exhibit abnormalities. Birth weight: 4010 g, length 52 cm. Out-patient follow-up 2 and 4 weeks after birth showed no abnormalities. Steroid excretion in the 1st week of life: 17-KGS 0.6, 0.6, 0.5 mg/24 h, 17-KS: 0.5, 0.6, 0.5 mg/24 h, P2: 0.7 mg/24 h.

121
Table 1.

The excretion of steroids and the plasma level of corticosteroids during pregnancy and during the first 7 weeks after delivery.

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<tr>
<th>Steroid dose per day</th>
<th>Week</th>
<th>17-KGS mg/24 h</th>
<th>17-KS mg/24 h</th>
<th>P₂ mg/24 h</th>
<th>Oe₃ µg/24 h</th>
<th>Total Oe µg/24 h</th>
<th>HCG IU/24 h</th>
<th>F µg/100 ml plasma</th>
<th>E µg/100 ml plasma</th>
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<td>0.7</td>
<td>0.1</td>
<td>0.15</td>
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RESULTS

Corticosteroids in plasma (Table 1)

Cortisol (F). – The cortisol values were within the range of normal for non-pregnant patients (6.8–30 µg/100 ml) (Buus 1968) but below the level for normal pregnant women (Bro-Rasmussen et al. 1962). The concentration did not show any definite tendency to increase, and no major fluctuations occurred on alteration of the steroid medication. The highest value was measured four days ante partum. The relatively high concentrations during the first week post partum must be related to the cortisol therapy which was given at that time (cf. Case report). Thereafter, the values decreased. Thus, a comparison of the periods 37th–40th week of gestation with 3rd–5th week post partum, in which the patient received unchanged dexamethasone (Decadron®) therapy, shows that the mean plasma cortisol level was 14.5 µg/100 ml during pregnancy and 1.9 µg/100 ml after delivery.

Cortisone (E). – During the pregnancy the concentration of cortisone was within or at the upper limit of normal for non-pregnant women (0.7–1.6 µg/100 ml) (Buus 1968). After delivery there was a gradual fall to very low levels. As expected, the cortisol/cortisone ratio was essentially the same during and after pregnancy.

11-Deoxycortisol (S). – The levels were within the normal range for non-pregnant subjects (<0.5 µg/100 ml) (Buus 1968) during as well as after the pregnancy.

Corticosterone (B). – The levels were in or above the range of normal for non-pregnant subjects (0.2–1.0 µg/100 ml) (Buus 1968), whereas after delivery they were mainly below 0.2 µg/100 ml.

Diurnal variations. – From Table 2 it is apparent that during the pregnancy the afternoon values of cortisol were 36–62% of the morning values and those of corticosterone 56–93% of the morning values. Corresponding determinations after delivery disclosed such low levels that a calculation of the difference would have been of no significance.

Table 2.
Diurnal variations in the concentrations in plasma (µg/100 ml) of cortisol (F) and corticosterone (B) during the 25th–28th week of pregnancy and 8 weeks after delivery.

<table>
<thead>
<tr>
<th>Week</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>8</th>
<th>Week</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>900</td>
<td>6.0</td>
<td>15.6</td>
<td>8.1</td>
<td>19.1</td>
<td>0.76</td>
<td>900</td>
<td>0.6</td>
<td>0.9</td>
<td>1.3</td>
<td>1.2</td>
<td>0.09</td>
</tr>
<tr>
<td>F</td>
<td>1500</td>
<td>3.0</td>
<td>9.7</td>
<td>2.9</td>
<td>9.7</td>
<td>0.07</td>
<td>B</td>
<td>1500</td>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

124
Urinary hormone excretion (Tables 1 and 3)

17-KGS. – The excretion of 17-KGS during the pregnancy was in the upper half of or above the normal range for non-pregnant subjects (4.4–13.2 mg/24 h) (Wilson & Lipsett 1963). The excretion remained essentially constant until the 36th week when, on changing the medication to dexamethasone, a fairly abrupt decrease occurred, followed by a new, gradual increase. After delivery the excretion rapidly decreased. Thus, a comparison of the periods 37th–40th week of gestation and 3rd–5th week post partum shows an average excretion of 12.4 mg/24 h during pregnancy and of 1.9 mg/24 h after delivery.

17-KS. – This excretion was within the range of normal for non-pregnant subjects (4–18 mg/24 h) (Johnsen 1956) during pregnancy, whereas post partum, it fell to considerably lower levels. Comparison of the periods 37th–40th week of gestation with the 3rd–5th week post partum showed an average excretion of 11.0 mg/24 h during and 2.1 mg/24 h after the pregnancy.

Corticoid metabolites (Table 3). – Determination of metabolites was carried out from the 25th to the 40th week of gestation and on one urine sample 5 weeks post partum (Table 3). Table 3 gives the ranges for excretion in 5 normal pregnant women in the second trimester. In our patient there was a gradually increasing excretion of total cortisol metabolites. The determinations in the 25th and 32nd week showed excretions in conformity with those in pregnant controls. The distribution of tetrahydro-metabolites of cortisol was normal during the pregnancy. There was a low or negligible excretion of Allo-THF during three of the tested days. Such a fall in all compounds was also observed in the 5 pregnant controls (Damkjær Nielsen et al. 1969). As for corticosterone metabolites there was no increase from the 32nd to the 40th week, and the excretions were in keeping with those found in pregnant controls. After delivery one 24 h-urine was analysed. This showed an excretion of about 5% of the excretions during the 40th week of gestation.

Pregnanediol. – The excretion during pregnancy was normal (Trolle 1955), but fell to very low values immediately after delivery.

Oestriol. – The excretion was within the range of normal during the pregnancy (Frandsen 1963). When dexamethasone therapy was instituted, there was a fairly abrupt fall, followed by a new, gradual increase. After delivery the excretion of total oestrogen fell to immeasurable values.

HCG. – During the pregnancy a normal excretion of this hormone was observed.

Metyrapone test

32nd week of pregnancy (Table 4). – The response to metyrapone must be considered as slight. Despite a fall in plasma cortisol, there was but little increase in 11-deoxycortisol. The excretion of 17-KGS and 17-KS was essentially
Table 3.
The excretion of corticosteroid-metabolites in mg per day during and after pregnancy and control values

<table>
<thead>
<tr>
<th>Steroid dose per day</th>
<th>Week of pregnancy</th>
<th>25</th>
<th>32</th>
<th>39</th>
<th>40</th>
<th>5 weeks after</th>
<th>5 pregnant women 2. trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisolone 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>0.3</td>
<td>0.6</td>
<td>0.6</td>
<td>0.9</td>
<td>0.7</td>
<td>0.4 -1.1</td>
<td></td>
</tr>
<tr>
<td>Allo THF</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.04-0.44</td>
<td></td>
</tr>
<tr>
<td>THE</td>
<td>0.9</td>
<td>1.9</td>
<td>2.1</td>
<td>3.1</td>
<td>0.13</td>
<td>1.2 -3.5</td>
<td></td>
</tr>
<tr>
<td>Comp. U</td>
<td>0.02</td>
<td>0.04</td>
<td>0.03</td>
<td>0.05</td>
<td>0</td>
<td>0.07-0.14</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.01</td>
<td>0.03</td>
<td>0.04</td>
<td>0.14</td>
<td>0.02</td>
<td>0.09-0.14</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td>0.05</td>
<td>0.04</td>
<td>0.08</td>
<td>0</td>
<td>0.02-0.24</td>
<td></td>
</tr>
<tr>
<td><strong>Total F</strong></td>
<td><strong>1.83</strong></td>
<td><strong>2.62</strong></td>
<td><strong>2.81</strong></td>
<td><strong>4.27</strong></td>
<td><strong>0.22</strong></td>
<td><strong>2.01-5.06</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisolone 10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THS</td>
<td>0.08</td>
<td>0.14</td>
<td>0.25</td>
<td>0.38</td>
<td>0.01</td>
<td>0.01-0.12</td>
<td></td>
</tr>
<tr>
<td>THB</td>
<td>0.05</td>
<td>0.20</td>
<td>0.15</td>
<td>0.03</td>
<td>0.01</td>
<td>0.03-0.20</td>
<td></td>
</tr>
<tr>
<td>Allo THB</td>
<td>0.05</td>
<td>0.08</td>
<td>0.06</td>
<td>0.04</td>
<td>0</td>
<td>0.03-0.20</td>
<td></td>
</tr>
<tr>
<td>THA</td>
<td>0.13</td>
<td>0.28</td>
<td>0.25</td>
<td>0.32</td>
<td>0</td>
<td>0.05-0.46</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.04</td>
<td>0</td>
<td>0.07</td>
<td>0</td>
<td>0</td>
<td>0 -0.11</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>0.02</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.01-0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Total B</strong></td>
<td><strong>0.27</strong></td>
<td><strong>0.58</strong></td>
<td><strong>0.53</strong></td>
<td><strong>0.39</strong></td>
<td><strong>0.01</strong></td>
<td><strong>0.22-0.93</strong></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.
The concentration of cortisol (F) and 11-desoxycortisol (S) in plasma and the excretion of hormones in the urine before, during and after the metyrapone test in the 32nd week of pregnancy and 8 weeks after delivery.

<table>
<thead>
<tr>
<th>Week</th>
<th>F µg/100 ml plasma</th>
<th>S µg/100 ml plasma</th>
<th>17-KGS mg/24 h</th>
<th>17-KS mg/24 h</th>
<th>Oe₃ mg/24 h</th>
<th>P₂ mg/24 h</th>
<th>HCG IU/24 h</th>
<th>P₃ mg/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>7.9</td>
<td>0.7</td>
<td>0.2</td>
<td>0.2</td>
<td>13.1</td>
<td>5.4</td>
<td>11.2</td>
</tr>
<tr>
<td>2</td>
<td>5.7</td>
<td>0.8</td>
<td>0.2</td>
<td>0.2</td>
<td>13.9</td>
<td>5.3</td>
<td>10.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Metyrapone</td>
<td>1</td>
<td>1.8</td>
<td>0.3</td>
<td>1.0</td>
<td>0.2</td>
<td>15.3</td>
<td>4.5</td>
<td>11.0</td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13.4</td>
<td>5.3</td>
<td>12.5</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>18.5</td>
<td>5.3</td>
<td>10.7</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>18.4</td>
<td>–</td>
<td>12.3</td>
<td>–</td>
</tr>
</tbody>
</table>
unchanged, whereas the excretion of pregnanetriol and oestriol was higher during the 24 hours of the test than the average excretion before and after (P3: 2.5 as compared with 1.5 mg/24 h and Oe3: 15.8 as compared with 10.9 mg/24 h).

8 weeks post partum (Table 4). – Minor shifts were observed, but all the values were so low that any calculation of difference is of no significance.

**ACTH stimulation test**

In an ACTH test 13 weeks after delivery a distinct response was obtained (Table 5).

<table>
<thead>
<tr>
<th></th>
<th>Control I</th>
<th>Stimulation II</th>
<th>Stimulation III</th>
<th>Stimulation IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol in plasma µg/100 ml</td>
<td>2.0</td>
<td>2.0</td>
<td>13.9</td>
<td>13.5</td>
</tr>
</tbody>
</table>

**DISCUSSION**

**Degree of pituitary insufficiency**

After intracapsular removal of a chromophobe pituitary adenoma, subsequent X-ray therapy, and repeated craniotomy which did not show signs of recurrence, the following conclusions may be drawn on the basis of the results:

**Gonadotrophins.** – After the hypophysectomy several determinations carried out before the pregnancy had shown the urinary excretion of pituitary gonadotrophins to be immeasurably low. Moreover, the oestrogen excretion was zero, and the pregnanediol excretion was extremely low, before as well as after the pregnancy. These findings, and the fact that after the operation the patient had constant amenorrhoea when untreated, must be taken to indicate an arrested production of gonadotrophic hormones after the craniotomy.

**TSH.** – In spite of thyroid medication the patient proved to be clinically hypothyroid after the hypophysectomy. The $^{131}$I uptake following thyrotrophin stimulation was normal, and the hypothyroidism must be interpreted as being of pituitary origin.

**ACTH.** – After the hypophysectomy a varying excretion of 17-KGS and 17-KS was found during the period before the pregnancy, but during this period the patient was on cortisone medication. The only plasma cortisol value measured before the pregnancy (control value before the metyrapone test) was
determined after cortisone had been withheld for 48 hours and was 3.3 μg/100 ml. This value, as well as the response, though slight, in the metyrapone test before pregnancy (cf. Case report) might indicate that at this juncture the patient had a slight endogenous cortisol synthesis which had been interfered with in the metyrapone test. These findings might be explained by slight autonomic function of the adrenal, but on the other hand it does not rule out a small production of ACTH. The low excretion of 17-KGS and of 17-KS as well as the negligible plasma concentration and excretion of corticosteroids might indicate an arrested adrenocortical function. However, it must be borne in mind that a production of ACTH, otherwise present, might have been suppressed by the steroid therapy, and that the adrenal cortex could very easily be activated by the post-partum ACTH test.

On this basis it must be concluded that during the period before and after delivery the maternal pituitary was presumably not producing any ACTH.

_Prolactin._ Post partum, there were no signs of mammary secretion or tension, and this appears to indicate an arrested production of prolactin.

The absence of diabetes insipidus as well as the spontaneous uterine contractions indicate that the production of the posterior lobe hormones vasopressin and oxytocin had been left largely intact by the hypophysectomy.

_Endocrine findings during the pregnancy_

In normal pregnant women the plasma level of cortisol has been found to increase with advancing gestational age, often being doubled during the last trimester as compared with the findings in non-pregnant subjects (Bro-Rasmussen et al. 1962), presumably due to the high oestrogen level during pregnancy (Jailer et al. 1959; Booth et al. 1961). This has no doubt also contributed to the high plasma corticosteroid level in our case, but has probably not been a decisive factor. The greatly increased urinary steroid excretion indicates rather a pregnancy-induced intensification of the production of cortisol, cortisone and corticosterone as well-defined steroid metabolites. Such a production might occur in:

1. the maternal adrenal,
2. the placenta,
3. the foetal adrenal.

_Maternal adrenal._ A presupposition for any essential function of the maternal adrenal must be the presence of ACTH or an ACTH-like principle in the maternal circulation. Apparently, the _foetal pituitary gland_ is able to synthesize ACTH. At least, this hormone has been identified in an extract from human foetal hypophyses (Taylor et al. 1953), and experience of intrauterine decapitation of rat and rabbit foetuses (Jost et al. 1962) indicates that in its development and function the foetal adrenal is dependent on a stimulating
principle from the foetal hypophysis. However, experience of pregnancies complicated by an anencephalic foetus (Frandsen & Stakemann 1963) makes it rather unlikely that ACTH does pass from the mother to the foetus, and indeed it has never been demonstrated that it is able to pass in a reverse direction (Gemzell 1953; Jørgensen & Lebech 1971). The placenta has also been suggested as the source of corticotrophin production. The findings of Little et al. (1958) in a pregnant, hypophysectomized patient have been adduced as an argument for no notable ACTH production in the placenta. Assali & Hamermesh (1954) found a greater ACTH activity in chorionic tissue than in intravillous blood, whereas Schwers et al. (1958) "maintained that all the ACTH activity was derived from the blood".

Placenta. – It has by now been substantiated (Younglai & Solomon 1969) that the placenta produces fairly large quantities of progesterone, pregnenolone and hydroxy compounds of these agents, whereas a formation of corticosteroids has never been definitely demonstrated. This agrees with clinical observations of pregnant patients with Addison's disease (Christy & Jailer 1958; Baulieu et al. 1956).

Foetal adrenal. – Many investigations (MacNaughton 1969) have indicated that from an early stage of foetal life this gland is very active in the production of numerous steroid metabolites, mainly oestrogen precursors, but also cortisol and corticosterone. It also seems beyond doubt that the foetal adrenal cortex is subject to superior regulation, and that the feed-back mechanism may be interfered with, partly by the administration of potent corticosteroids to the mother (Jørgensen 1969), by intra-amniotic injection of ACTH (Johannisson 1968; Jørgensen & Lebech 1971), and by metyrapone treatment of the mother (Dickey & Thompson 1969).

The results of the metyrapone test on the present patient during the pregnancy showed only a faint response, but yet of a sufficient magnitude so that the metyrapone apparently blocked cortisol synthesis at some site or other, possibly in the maternal adrenal, although a block in the foetal adrenal cortex cannot by any means be ruled out. Moreover, part of the explanation of the diurnal fluctuations in the plasma cortisol levels may have been caused by fluctuations in the foetal cortisol production.

The above considerations justify the conclusion that the "normalization" of the endocrine state during pregnancy in the present case may have been due to several factors:

(1) Steroid production in the foeto-placental unit. – The foetal adrenal cortex has no doubt played a role, also in corticoid synthesis, but this has probably not been decisive quantitatively. The placenta has presumably secreted part of the steroid metabolites found in the urine, but has not produced corticosteroids to any significant extent.
(2) Steroid production in the maternal adrenal. – The maternal adrenal may have been activated during the pregnancy. At any rate, after having been suppressed for 10 years, it was distinctly stimulated as shown by an ACTH test post partum. The stimulating principle during pregnancy might be derived from:

(A) The placenta. – Despite conflicting reports in the literature, it is considered likely that at some site or other in the placenta, possibly in the villi, an ACTH-like principle is formed, and that this principle may pass to the maternal circulation. If this is an essential cause, the diurnal fluctuations in plasma cortisol levels during the pregnancy are remarkable.

(B) A maternal pituitary remnant. – It cannot be ruled out entirely that a possible remnant of the pituitary gland has been activated to produce ACTH by the "pregnancy stress", and that after delivery this production has again been suppressed by continued steroid therapy.

(C) The foetal pituitary gland. – This explanation is not very likely, since judging by all previous findings ACTH is unable to pass from the foetus to the maternal circulation.

In our opinion, therefore, the most likely explanation is production and secretion of an ACTH-like principle in the placenta. With a view to elucidating these factors in more detail, we had planned further investigations of the patient (ACTH test followed by vasopressin and metyrapone test), but we refrained for various reasons, int. al. the risks attendant on temporary withdrawal of the steroid therapy. However, there is a possibility of another pregnancy in this patient, affording a new possibility of elucidating the problems concerning the endocrine functions of pregnancy.

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REFERENCES


131

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