THE EXCRETION OF HORMONES IN CASES OF HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA

By
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ABSTRACT

The urinary excretion of gonadotrophin, oestrogens and pregnanediol has been estimated in ten patients with hydatidiform mole and in three female patients with chorionepithelioma. In all 13 cases an increased excretion of gonadotrophin was found. The excretion of pregnanediol (investigated in seven patients only) was of the same magnitude as in non-pregnant women except in one case, where a slightly increased excretion was found. The excretion of oestrogens was low; one case of mole and two of chorionepithelioma excreted amounts at the non-pregnant level, whereas most of the remainders excreted amounts much lower than in normal pregnancies of a corresponding gestational length. Two patients, however, excreted amounts comparable to those of a normal pregnancy. As the ratio oestriol: oestrone + oestradiol was at the non-pregnant level, the oestrogens excreted by patients with hydatidiform mole and chorionepithelioma are assumed to have been produced by the ovaries of the woman strongly stimulated by the enormous amounts of gonadotrophin present.

Although it is well known (Hamburger 1944 and others) that the urine of patients with hydatidiform mole or chorionepithelioma contains large amounts of chorionic gonadotrophin, there are only few data on the excretion of other hormones.

Pigeaud & Burthiault (1951) found that some patients with hydatidiform mole excreted increased amounts of pregnanediol, some normal and some diminished amounts. Zander & Müntermann (1956) reported that mole tissue had almost the same concentration of progesterone as normal placental tissue.

Payne (1941) found a normal excretion (i.e. the same as in a normal pregnancy of the same gestational length) of oestrogens in two cases of hydatidiform mole and Hinglais & Hinglais (1949 a) reported a similar finding in

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16 cases. In both these investigations biological assay was used. In contrast Smith & Smith (1935) in five cases, found excretions of oestrogens corresponding only to non-pregnant levels. Lately Erb et al. (1961) have reported on two cases of hydatidiform mole. One patient excreted normal amounts of oestrone + oestradiol and oestriol, but rather low amounts of pregnanediol, while the other patient excreted rather small amounts of oestrogens (although within the normal range), but normal amounts of pregnanediol.

De Snoo (1928) found by biological assay an excretion of 320-1000 IU of oestrogen in a case of chorionepithelioma of the tube; bilateral oophorectomy had previously been performed.

METHODS AND MATERIAL

Hormone analyses

Oestrone and oestradiol: Method of Brown (1955)
Pregnanediol: Method of Klopper et al. (1955).
Gonadotrophin: Increase of uterine weight in the immature rat.

The excretion of oestrone, oestradiol, oestriol, pregnanediol and gonadotrophin has been investigated in 10 cases of hydatidiform mole. Since three cases were admitted to hospital for symptoms of threatened abortion (case KK, GB and IM), the urine specimens were only analysed for oestriol and had been discarded when the diagnosis of mole was obtained. In two cases (AO and KJ) the urines were only investigated for oestriol and gonadotrophin as the presence of a mole was only realized later.

The hormone excretion of three cases of chorionepithelioma was also investigated. Case reports will be presented later.

In all 13 cases the diagnosis of hydatidiform mole or of chorionepithelioma was confirmed by histological examination.

RESULTS

Hydatidiform mole

The results of the hormone analyses in cases of hydatidiform mole are shown in Table 1. In Fig. 1 the excretion of oestriol in the mole cases is plotted together with the excretion of oestriol in normal pregnancies (Frandsen & Stakemann 1963 a).

In all the 7 cases in which the excretion of gonadotrophin was estimated the excretion was found to be higher than that found in normal pregnancies (Loraine 1950).

The pregnanediol excretion was estimated in 5 cases. Only one case (LB) had an excretion of the same magnitude as in a normal pregnancy, the others were lower, actually at the normal, non-pregnant level (Klopper 1957).

The figures in Table 1 show that the excretion of oestriol was elevated as compared to the non-pregnancy level in all cases except in case IN. In this and 7 other cases, however, the amounts excreted were much lower than in normal pregnancies of the same gestational length. Only two cases (KJ and GB) excreted amounts comparable to those in a normal pregnancy.
Table 1.
Excretion of oestrogens, gonadotrophin and pregnanediol in cases of hydatidiform mole.

<table>
<thead>
<tr>
<th>Case</th>
<th>Weeks of amenorrhoea</th>
<th>$OE_1$ $\mu g/24$ h</th>
<th>$OE_2$ $\mu g/24$ h</th>
<th>$OE_3$ $\mu g/24$ h</th>
<th>$OE_3/\text{OE}_1 + \text{OE}_2$</th>
<th>$G$ IU/24 h</th>
<th>$P$ mg/24 h</th>
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<tbody>
<tr>
<td>KK</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>85</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>210</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IN</td>
<td>25</td>
<td>21</td>
<td>12</td>
<td>104</td>
<td>3.1</td>
<td>132 000</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>26</td>
<td>12</td>
<td>138</td>
<td>3.1</td>
<td>650 000</td>
<td>3.2</td>
</tr>
<tr>
<td>AO</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>269</td>
<td>–</td>
<td>700 000</td>
<td>–</td>
</tr>
<tr>
<td>BA</td>
<td>16</td>
<td>106</td>
<td>45</td>
<td>219</td>
<td>1.9</td>
<td>600 000</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>280</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GB</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>525</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>1100</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>KJ</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>1100</td>
<td>24 000</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LM</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>43</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LB</td>
<td>12</td>
<td>117</td>
<td>29</td>
<td>125</td>
<td>0.9</td>
<td>854 000</td>
<td>7.6</td>
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<tr>
<td></td>
<td>13</td>
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<td>–</td>
<td>132</td>
<td>–</td>
<td>2470 000</td>
<td>–</td>
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<tr>
<td></td>
<td>14</td>
<td>77</td>
<td>55</td>
<td>130</td>
<td>1.0</td>
<td>2500 000</td>
<td>7.7</td>
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<td></td>
<td>15</td>
<td>252</td>
<td>187</td>
<td>240</td>
<td>0.5</td>
<td>2540 000</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>194</td>
<td>–</td>
<td>5700 000</td>
<td>–</td>
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<tr>
<td></td>
<td>17</td>
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<td>–</td>
<td>425</td>
<td>–</td>
<td>8400 000</td>
<td>–</td>
</tr>
<tr>
<td>BH</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>184</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>62</td>
<td>19</td>
<td>102</td>
<td>1.3</td>
<td>240 000</td>
<td>1.9</td>
</tr>
<tr>
<td>IE</td>
<td>32(?)</td>
<td>94</td>
<td>58</td>
<td>335</td>
<td>2.2</td>
<td>46 000</td>
<td>3.4</td>
</tr>
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</table>

$OE_1$ = oestrone.
$OE_2$ = oestradiol.
$OE_3$ = oestriol.
$G$ = gonadotrophin.
$P$ = pregnanediol.

Case KJ: A 17-year-old primagravida. Last period July 17th, 1959. She had had transitory vaginal bleeding in October 1959, and since the bleeding had re-occurred she was admitted to hospital on November 16th. The next day she delivered 600 g of mole tissue. Urine for assay of oestriol and gonadotrophin had been collected before the delivery. In the following weeks the excretion of HCG showed no tendency to decline and consequently a curette was performed with the removal of mole tissue. As the high excretion of HCG
The excretion of oestriol in cases of hydatidiform mole.

continued and large ovarian cysts developed, a hysterectomy had to be carried out and a destructive mole was found in the uterine wall. Since the operation she has done well and there have been no signs of recurrence. By mistake no urine specimens were analysed for oestrogens during the recurrences.

The second patient (GB) with a rather high excretion of oestriol has shown no sign of recurrence, and, on the other hand, a low excretion was found in the only other patient with ovarian cysts (LB).

The excretion of oestrone and oestradiol was investigated in only 5 cases. With the exception of case IN the excretion was higher than the non-pregnant levels, but lower than the values found in normal pregnancy.

Case IN: A 56-year-old woman who had had two normal pregnancies 30 and 28 years ago. Her periods had in the two years prior to the present admission been irregular with intervals of approximately two months. Present pregnancy: Last period September 1961. She was admitted to hospital on March 5th, 1962 complaining of dyspepsia. On examination a mass was found
in her lower abdomen reaching up to the umbilicus. A frog test was positive. Because of her age a mole was suspected (Eastman 1956). This diagnosis was confirmed by the finding of a high urinary excretion of gonadotrophin and an excretion of oestrogens so low that it fell within the range found in the non-pregnant state. On March 12th a hysterectomy was carried out and an enlarged uterus with 500 g of mole tissue was removed.

**Chorionepithelioma**

The hormone excretion was investigated in three female patients with chorionepithelioma. The results are presented in Table 2.

The excretion of gonadotrophin was elevated in all three cases. The excretion of pregnanediol and the three oestrogens was at the non-pregnant level or slightly higher, but always much lower than the excretion in a normal pregnancy.

*Case AN*: The patient was admitted to hospital 10 months after a normal delivery because a tumour had been found in the lung. The tumour was extirpated and found to be a chorionepithelioma. One week after the operation a urine specimen was collected for hormone assay. After another two weeks the patient died from metastases in the brain.

*Case GH*: A 33-year-old woman had a hydatidiform mole removed in 1961.

<table>
<thead>
<tr>
<th>Case</th>
<th>OE1/24 h</th>
<th>OE2/24 h</th>
<th>OE3/24 h</th>
<th>OE3/OE1 + OE2/24 h</th>
<th>G IU/24 h</th>
<th>P mg/24 h</th>
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</thead>
<tbody>
<tr>
<td>AN</td>
<td>–</td>
<td>–</td>
<td>72</td>
<td>2.0</td>
<td>180 000</td>
<td>–</td>
</tr>
<tr>
<td>GH</td>
<td>13</td>
<td>9</td>
<td>44</td>
<td>2.0</td>
<td>60 000</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>7</td>
<td>43</td>
<td>1.4</td>
<td>45 000</td>
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</tr>
<tr>
<td></td>
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<td>60</td>
<td>1.1</td>
<td>279 000</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>13</td>
<td>70</td>
<td>2.1</td>
<td>62 000</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>30</td>
<td>185</td>
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<td>122 000</td>
<td>1.8</td>
</tr>
<tr>
<td>AH</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>&lt; 20</td>
<td>9 000</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>&lt; 20</td>
<td>7 000</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.**

Excretion of oestrogens, gonadotrophin and pregnanediol in cases of chorionepithelioma.

OE1 = oestrone.
OE2 = oestradiol.
OE3 = oestriol.
G = gonadotrophin.
P = pregnanediol.
Following the removal the excretion of HCG declined, but one year later elevated amounts were excreted once more. A search was made for the trophoblastic tissue. The uterus and tubes were extirpated, but no abnormal tissue was found. However, in April 1963 a chest X-ray disclosed a tumour in the the lung, and this was found after operation to be a chorionepithelioma. The excretion of hormones had been estimated at intervals all through 1962 and 1963. She died from widespread metastases in October 1963.

**Case AH:** A 22-year-old woman who had previously had two normal deliveries. Present disease: At the calculated term she delivered a dead baby in her home on February 26th, 1963; foetal movements had stopped for unknown reasons a few days previously. After the delivery she had continuous slight vaginal bleeding, but she did not see her doctor until April 1st. Treatment with ergotamine was tried but without effect. She was admitted to hospital on June 6th. On examination a uterus enlarged, as in a pregnancy of 3 months' duration, was found. A curettage was carried out, but the vaginal bleeding continued. On a further examination it was found that the bleeding came from a little tumour at the top of the vagina. Both a biopsy from this tumour and the tissue removed at curettage were found on histological examination to be chorionepithelioma. She was operated on June 16th and the uterus, tubes and top of vagina were extirpated. Ten days later, new metastases were demonstrated in the vagina and the patient was therefore referred to the Radiumstationen in Copenhagen. She is now under treatment with vaginal applied radium and Methotraxate®. On July 15th a chest X-ray disclosed metastases in the lungs.

**DISCUSSION**

It must be considered as established that the gonadotrophin of pregnancy is produced by the placenta, since such a production can be demonstrated in cultures of placental tissue (*Jones et al. 1943; Stewart et al. 1948*). The placenta also seems to produce progesterone, since this was demonstrated in perfusion experiments by *Goerke et al.* (1961). It has also been assumed that the oestrogens of pregnancy are produced by the placenta, and the evidence in favour of this theory has been summed up by *Diczfalusy* (1960). However, recently results have been reported which indicate that the foetal adrenal is also involved in this production (*Frandsen & Stakemann 1961* and 1963 b).

Because of the possible role of the foetus in the production of oestrogens, the urinary excretion in cases of hydatidiform mole and chorionepithelioma is of particular interest.

In our 13 cases investigated, one case of mole (IN) and all three cases of chorionepithelioma excreted amounts of oestrone, oestradiol and oestriol, which were within the maximal output found outside pregnancy. The remainder of
the patients excreted higher amounts, but only two (GB and KJ) reached amounts of almost the same magnitude as in a normal pregnancy.

It seems reasonable to assume that the slight increase of oestrogen excretion found in most of the cases is due to an increased production from the ovaries of the patients because of the enormously elevated amounts of gonadotrophin present. Even the amounts of 1100 µg oestriol found in two cases might be produced by the ovaries, since Hamburger (pers. comm.) and Diczfalusy (1963) found an excretion of this magnitude in non-pregnant patients after treatment with gonadotrophins.

In this connection it is worth mentioning that Hinglais & Hinglais (1949 b) found that ovarian cysts in a woman with a hydatidiform mole contained large amounts of oestrogen.

Only the above-mentioned findings of de Snoo (1928) are in disagreement with this assumption. However, the method of assay was unfortunately not described, and it is possible that the specificity was inadequate for the exclusion of a gonadotrophin effect.

With regard to the ratio oestriol/oestrone + oestradiol, values of 1–3 were found. This corresponds to the values found in non-pregnant women. In normal pregnancies of 15–25 weeks’ duration, the ratio is higher; based on the data given by Cassmer (1959) values of more than 10 are found at this stage of pregnancy. The oestrogen metabolism in cases of mole and chorionepithelioma thus seems more comparable with that in non-pregnant women than with that present during pregnancy.

The difference in oestrogen metabolism between the normal and abnormal pregnancies can be explained by 1) absence of a foetal contribution to the production of oestrogens, 2) absence of a foetal contribution to the metabolism of a placental production of oestrogens, or 3) different production rates of the various oestrogens by normal and abnormal placental tissue.

The results reported here on the excretion of oestrogen in cases of hydatidiform mole and chorionepithelioma are not incompatible with our theory that the foetal adrenal takes part in the production of oestrogens during pregnancy.

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