UROPEPSIN EXCRETION IN NORMAL PREGNANCY AND IN TOXAEMIA OF LATE PREGNANCY

By K. Soiva, O. Castrén and P. Koskinen

In previous investigations (Parviainen et al., 1949, 1950, Soiva, 1953, Soiva & Parviainen, 1955) attempts were made to elucidate the significance of hormonal factors, especially of corticosteroids, in the aetiology of toxaemia of late pregnancy, particularly in relation to the theory of adaptation diseases of Selye (1946, 1950). Similar conclusions on the function of the adrenal cortex during pregnancy and in toxaemia of pregnancy have been presented by several other authors (e.g. Gemzell, 1953, 1956, Venning et al., 1954, Elert, 1954, Mastboom, 1955, Raab et al., 1956), but it has not always been possible to demonstrate any differences in adrenocortical function between normal pregnant and toxaemia patients (e.g. Martin & Mills, 1956). In this connection mechanical factors have been held to be more important than hormonal factors (Dieckmann & Pottinger, 1955).

When studying the function of the adrenal cortex both direct hormone determinations and indirect methods have been employed. The hormone determinations, i.e. those involving the determination of the hormone concentration in the blood or the excretion of hormones in the urine by chemical and biological methods, are influenced by many unknown factors such as the transfer of hormones from the adrenal gland to the tissues, the metabolism of the hormones, the amounts of hormone taken up by the tissues and the secretion of hormones into the urine. For this reason, the indirect method, i.e. the determination of the effect of the hormone on the function of the organism, may frequently yield more reliable results. One possibility of assessing the activity of the adrenal cortex is provided by the determination of uropepsin (Gray et al., 1950, 1953, 1956). The studies of Gray et al. (1956) show that the pepsin secretion of the stomach is determined not only by stimulation via the
vagus nerve system and by the gastrin secreted by the mucosa of the gastric antrum, but also by the hormonal effect of the hypothalamus-anterior pituitary-adrenal axis. Under normal conditions the gastric function is semiautomatic with regard to the third influence and only requires a normal adrenocortical function. In conditions of stress, however, the secretion of pepsin is more directly controlled by the adrenocortical activity. Hence since normal pregnancy may be considered as a prolonged, although physiological, condition of stress, it was thought of interest to carry out an investigation on the excretion of uropepsin in normal pregnancy and in cases of toxaemia of pregnancy.

MATERIAL AND METHODS

The material comprised 81 women who were in the second to tenth month of pregnancy. In 59 of these, no symptoms of toxaemia were observed during pregnancy or labour, and hence these subjects formed the group of «normal» pregnancies. In the remaining 22, symptoms of toxaemia (proteinuria, blood pressure exceeding 140 mm. Hg and oedema) were evident during gestation. Ten of the pregnant women of the first group were under treatment at the Women's Hospital of the University of Turku for minor disorders (erosion of the cervix, hyperemesis, suspected prolongation of pregnancy) as were also 10 women of the toxaemia group. The other pregnant women were visitors at local Maternity Centres. A third group of 11 normal non-pregnant women was also examined for purposes of comparison. None of the women were known to have had ulcers or other serious diseases of the stomach.

Collection of urine. When the urine specimens were collected, particular attention was paid to secure complete 24-hour urine collections from all the patients. Those subjects who were not under treatment in the hospital were given, in addition to verbal instructions, detailed printed instructions to be followed in the collection of urine.

The determination of uropepsin in the 24-hour urine samples was performed by the method of West, Ellis & Scott (1952), which is a modification of the method described by Sylvest (1949). In order to avoid variations, an emulsion prepared from homogenized milk powder was substituted for fresh whole homogenized milk. The standard employed was pure pepsin powder (Pepsin. Union Chim. Belge) and the amounts of uropepsin in mg. excreted during 24 hours were evaluated in terms of this standard. In a few of the cases, the determinations were repeated after varying intervals during pregnancy.

The results were analysed statistically by the variance and factorial techniques.

RESULTS

For the normal non-pregnant women (11 cases) the mean uropepsin excretion was 1.51 mg./24 hours (range: 0.1–3.50 mg.).

To determine the effect of corticotrophin, the uropepsin excretion was measured before and after the intramuscular administration of 20 I. U. of a
long-acting corticotrophin preparation to four pregnant women under hospital
treatment for hyperemesis. In all four cases an increased uropepsin excretion
was found after the administration. The mean increase was 134 per cent.

The excretion of uropepsin during normal pregnancy (Table 1). The mean
uropepsin excretion in primigravidae was 1.68 mg./24 hours during the first
trimester, 2.95 mg./24 hours during the second, and 2.42 mg./24 hours during
the third. The figure for the first trimester did not differ significantly from
the mean value for normal non-pregnant women. During late pregnancy (fifth
to tenth month) the mean uropepsin excretion in 49 normal pregnant women
was 2.60 mg./24 hours which was significantly higher than the excretion ob¬
tained in non-pregnant and in pregnant women during the first trimester (27
cases; mean excretion 1.60 mg./24 hours). The confidence level of the dif¬
ference is 96 per cent.

In order to test the possible influence of gastric disorders on the uropepsin
excretion, the occurrence of heartburn, nausea and vomiting was followed
during the late period of pregnancy in normal pregnant women. For five
women in whom these symptoms were frequently observed, the mean uropepsin
excretion was 3.49 mg./24 hours, while for 12 pregnant women with no symp¬
toms of this kind the mean excretion was 4.08 mg./24 hours. The difference
between the mean excretions is not statistically significant.

Uropepsin excretion in toxaemia of late pregnancy (Table 2). In this group
of patients the mean excretion of uropepsin for the primigravidae was 5.27

Table 1.
Uropepsin excretion in mg. per 24 hours in normal pregnancy.

<table>
<thead>
<tr>
<th>Months</th>
<th>Primigravidae</th>
<th></th>
<th></th>
<th>Multigravidae</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean</td>
<td>Range</td>
<td>No.</td>
<td>Mean</td>
<td>Range</td>
<td>No.</td>
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<tr>
<td>2-4</td>
<td>7</td>
<td>2.13</td>
<td>0.50-4.90</td>
<td>9</td>
<td>1.33</td>
<td>0.18-5.31</td>
<td>16</td>
</tr>
<tr>
<td>5-7</td>
<td>8</td>
<td>3.15</td>
<td>0.72-9.47</td>
<td>9</td>
<td>2.76</td>
<td>0.41-6.41</td>
<td>17</td>
</tr>
<tr>
<td>8-10</td>
<td>9</td>
<td>2.81</td>
<td>0.35-4.30</td>
<td>23</td>
<td>2.27</td>
<td>0.40-6.46</td>
<td>32</td>
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</tbody>
</table>

Table 2.
Uropepsin excretion in mg. per 24 hours in toxaemia of late pregnancy.

<table>
<thead>
<tr>
<th>Months</th>
<th>Primigravidae</th>
<th></th>
<th></th>
<th>Multigravidae</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean</td>
<td>Range</td>
<td>No.</td>
<td>Mean</td>
<td>Range</td>
<td>No.</td>
</tr>
<tr>
<td>5-7</td>
<td>3</td>
<td>5.27</td>
<td>0.50-9.71</td>
<td>3</td>
<td>3.38</td>
<td>1.75-4.25</td>
<td>6</td>
</tr>
<tr>
<td>8-10</td>
<td>9</td>
<td>2.60</td>
<td>0.31-4.62</td>
<td>9</td>
<td>3.98</td>
<td>0.78-10.76</td>
<td>18</td>
</tr>
</tbody>
</table>
mg./24 hours during the second trimester and 2.60 mg./24 hours during the third trimester, and the corresponding excretions for multigravidae 3.38 mg./24 hours and 3.98 mg./24 hours, respectively. The difference between the mean values for the primigravidae and multigravidae is not significant.

The investigated urine specimens of seven of the 18 toxaemic patients during the third trimester of pregnancy were collected during treatment at home and those of the remaining 11 during hospital treatment of several days' duration. The mean uropepsin excretion for the patients treated at home was 4.34 mg./24 hours (range: 1.12–10.76 mg./24 hours) and for the hospitalized patients 2.62 mg./24 hours (range: 0.78–6.39 mg./24 hours). The mean figure for the patients treated at home seems to be higher than for those treated in the hospital in whom the toxaemia symptoms were generally diminishing in intensity, but the difference was not found to be statistically significant.

For the 24 toxaemia patients examined during the late period of pregnancy (5–10 months), the mean uropepsin excretion was 3.55 mg./24 hours, which is significantly higher than the mean excretion for normal pregnant women during the corresponding period.

The mean uropepsin excretion of the non-pregnant and pregnant women during the first trimester of pregnancy was 1.60 mg./24 hours. The uropepsin excretion was clearly higher during the later stages of normal pregnancy (2.60 mg./24 hours), and even higher in the toxaemia patients (3.55 mg./24 hours). (The confidence level of the difference is 99.7%). For those patients in whom the determinations were repeated during pregnancy, a similar increase was also noted.

**DISCUSSION**

Hyperfunction of the adrenal cortex is accompanied by an increased activity of gastric glands, which is manifested by an increased excretion of uropepsin (Gray et al., 1956). A higher than normal uropepsin excretion has been established not only in gastric ulcer and Cushing's disease but also in various conditions of physical and emotional stress. The uropepsin excretion is increased by the so-called glucocorticoids such as cortisone, cortisol, corticosterone and metacorten, but not by desoxycorticosterone, androgens, progesterone or oestrogens. Of the hormones of the anterior lobe of the pituitary gland, only corticotrophin promotes the excretion of uropepsin. Somatotrophin, thyrotrophin and gonadotrophins are inactive in this respect. The pepsinogen content of the plasma has not been found to be increased by therapeutic doses of corticotrophin, cortisone and cortisol (Hoard & Browning, 1956).

The uropepsin excretion during the early period of normal pregnancy gives no indication of an increased function of the adrenal cortex. Elsner & Feiks (1954) established a lower than normal uropepsin excretion in patients with
hyperemesis and considered this an indication of temporary hypofunction of the adrenal cortex. A high increased uropepsin excretion has been observed during the late period of pregnancy, especially in primigravidae. An increased activity of the adrenal cortex during late pregnancy is also indicated by the increased excretion of glucocorticoids observed by Venning (1946) and Gemzell's demonstration (1956) of an increased concentration of 17-hydroxycorticosteroids in the blood.

The uropepsin excretion in toxaemia of late pregnancy is more than twice that of non-pregnant women and of women in early pregnancy. The excretion in toxaemia is of the same magnitude as in Cushing's disease, but not as high as that brought about by acute stress resulting from an operation, burns or electric shock (Gray et al., 1956). According to several previous studies the excretion of the adrenal salt-regulating hormone is enhanced in toxaemia (e.g. Venning et al., 1954, Soiva & Parviainen, 1955, Raab et al., 1956). Martin & Mills (1956) did not, however, observe the aldosterone excretion to be higher in toxaemia than in normal pregnancy and considered that toxaemia may result from a disturbance in the equilibrium between the sodium-retaining and sodium-excreting factors. Venning et al. (1957) found a high aldosterone excretion during late normal pregnancy, but the excretion was no higher in 8 toxaemic patients than in normal pregnant women. Ingle (1956), however, assumed that the cortical hormones play a supporting role in the manifestation of certain diseases but are only rarely the primary causative agents.

The individual variations in uropepsin excretion are relatively large and hence a single determination is of little prognostic value in pregnancy.

SUMMARY

The uropepsin excretion in 11 normal non-pregnant women, 59 women at various stages of pregnancy and 22 women with toxaemia of late pregnancy has been measured by the method of West, Ellis & Scott (1952). Repeated determinations were made in some of the cases.

The mean daily excretion of uropepsin was 1.51 mg. in non-pregnant women, 1.68 mg. during early pregnancy, 2.60 mg. during late pregnancy and 3.55 mg. in toxaemia of late pregnancy.

No significant difference was observed between the mean excretions of primigravidae and multigravidae. Corticotrophin promoted the uropepsin excretion of hyperemesis patients. Gastric disorders were not found to influence the uropepsin excretion during pregnancy. The uropepsin excretion of toxaemia patients treated at home was no greater than of those under hospital treatment.

The increased uropepsin excretion during late pregnancy indicates a high activity of the adrenal cortex, but the adrenocortical hyperfunction is even more pronounced in toxaemia of late pregnancy.
ACKNOWLEDGMENTS

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REFERENCES