THE RELATIONSHIP OF SEX STEROIDS TO URIC ACID LEVELS IN PLASMA AND URINE

By

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ABSTRACT

The effect of endogenous and exogenously administered oestrogens, androgens and progesterone on plasma and urinary uric acid and uric acid clearance was studied in a total of 65 healthy volunteers, including normal menstruating and post-menopausal women, girls with primary amenorrhoea and adult male subjects. A serial study throughout a full cycle in 3 women showed an inverse relationship between plasma uric acid levels and endogenous oestrogens. Administration of conjugated and synthetic oestrogens produced a fall in plasma uric acid concentration through a uricosuric effect in most subjects of both sexes. Testosterone propionate caused a definite increase in plasma uric acid levels in post-menopausal women while endogenous testosterone changes due to Leydig cell stimulation produced no definite effect in male subjects. Administration of a progesterone preparation produced an effect similar to that of oestrogens in post-menopausal women. The evidence presented here supports the view that sex steroids play a significant part in uric acid regulation in biological fluids of both sexes.

It has been well established that uric acid (UA) concentration in the plasma of healthy subjects is related to age and sex and that in women of reproductive age plasma uric acid (PUA) levels are markedly lower than those of adult men of comparable age (Mikkelsen et al. 1965). The underlying cause for these

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differences has up to the present not been clarified but most of the evidence accumulated from clinical observations as well as from experimental studies indicates that PUA is closely related to endocrine factors and particularly to sex steroid hormones (Wolfson et al. 1949; Mikkelsen et al. 1965; Scott & Pollard 1970; Nicholls et al. 1973). The present study was designed to examine the effect of endogenous as well as exogenously administered sex steroids on PUA, urinary uric acid (UUA) and uric acid clearance (UAC) in healthy subjects of both sexes.

MATERIAL AND METHODS

Subjects

A total of 65 properly informed volunteers were included in this study and allocated to each of the following groups:

A. Female subjects (34).
   1. Normally menstruating women, aged 23–26 (3).
   2. Post-menopausal women, aged 42–56 (28).
      a) Group treated with conjugated oestrogens (COe) (Premarin®, Ayerst)
         1.25 mg per day orally for 4 days (13).
      b) Group treated with testosterone propionate (TP) (Testoviron®, Schering AG.)
         intramuscularly for 3 days (7).
      c) Group treated with oestradiol monobenzoate (OeB) (Ovocyclin M®, Ciba)
         10 mg as a single intramuscular injection (4).
      d) Group treated with progesterone in oily solution (P) (Lutocyclin®, Ciba)
         10 mg/day intramuscularly for 4 days (4).
   3. Girls with primary amenorrhoea treated with COe 2.5 mg/day orally (3).

B. Male subjects (31).
   1. Group of 5 men, aged 17–51, who had a Leydig cell stimulation test.
   2. Group of 24 men treated with various oestrogens:
      a) Group treated with COe 1.25 mg/day orally for 4 days (14).
      b) Group treated with OeB 2 mg/day intramuscularly for 3 days (6).
      c) Group treated with ethinyl oestradiol (EOe) (Progynon C®, Schering AG.)
         60 mg orally for 3 days (4).
   3. Group of 2 men treated with P 10 mg/day intramuscularly for 4 days.

UUA and UAC determination was performed in 11 post-menopausal women (7 treated with COe and 4 with P) and in 8 men (6 treated with COe and 2 with P). Furthermore, plasma creatinine estimations were carried out in 11 post-menopausal women treated with COe (6) or TP (5).

All the subjects studied were healthy with no history or condition currently related to UA imbalance. An alcohol free diet with less than 200 mg of purine per day was introduced 2–3 days before the study and was followed throughout the period of investigation, during which no medication was allowed. Fasting blood samples were taken on 2 successive days before medication, on the last day of medication and on the first day after withdrawal of treatment. Twenty-four hour urine collections were made before and on the last day of medication. The relationship of endogenous sex
steroids and PUA, UUA and UAC was examined in two groups. In the first, serial assays were performed throughout a menstrual cycle, during which basal body temperature (BBT) was recorded and pregnanediol (P_2) was estimated on days 20–21. In the second, 5 men received intramuscular injections of 1500 IU of human chorionic gonadotrophin (HCG) every other day for 3 days and plasma testosterone (PT) and UA were estimated in 4 and 5 of them, respectively.

The effect of exogenously administered sex steroids on PUA, UUA and UAC was studied in 57 subjects. Dosage has been arbitrarily determined, in some cases the preparation available being the decisive factor. The duration of treatment was again arbitrarily chosen, the important consideration being to keep that period as short as possible and thus to minimize any possible biological effects.

Methods

PUA and UUA were measured using the colorimetric technique of Brown (1945) as modified by Caraway (1960b), and plasma creatinine (PC) by the method of Folin & Wu (1919) as modified by Caraway (1960a). PT was estimated using the competitive protein binding technique of Lawrence & Swyer (1973) while P_2 was determined by the method of Klopper et al. (1955).

Results are graphically illustrated in Figs. 1–4 while numerical values are presented in Tables 1 and 2.

A. Endogenous sex steroids and uric acid

1. Marked variations throughout the menstrual cycle studied were observed in all three subjects (Fig. 1). These cycles were considered according to such

![Fig. 1.](image)

Plasma uric acid (PUA) variations throughout three ovulatory menstrual cycles. The mean value (X) of the first part is significantly higher than that of the second and third ones. [Menstrual bleeding. PUA. Basal body temperature (BBT).]
Table 1.
PUA, UUA, UAC and PC in post-menopausal women before and during sex steroid treatment.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Before treatment</th>
<th>During treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± sd</td>
<td>Range</td>
<td>No. obs.</td>
</tr>
<tr>
<td>PUA</td>
<td>COe 5.01 ± 0.89</td>
<td>2.73-6.52</td>
<td>25</td>
</tr>
<tr>
<td>mg/100 ml TP 5.34 ± 1.40</td>
<td>3.40-7.80</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>P   3.90 ± 0.90</td>
<td>2.40-4.70</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>UUA</td>
<td>COe 428.9 ± 116.5</td>
<td>252.4-598.2</td>
<td>7</td>
</tr>
<tr>
<td>mg/d</td>
<td>P 313.2 ± 218.7</td>
<td>53.2-575.8</td>
<td>4</td>
</tr>
<tr>
<td>UAC</td>
<td>COe 7.8 ± 0.9</td>
<td>6.8-9.2</td>
<td>7</td>
</tr>
<tr>
<td>ml/min</td>
<td>P 6.6 ± 2.3</td>
<td>4.0-10.4</td>
<td>4</td>
</tr>
<tr>
<td>PC</td>
<td>COe 0.72 ± 0.17</td>
<td>0.54-0.90</td>
<td>6</td>
</tr>
<tr>
<td>mg/100 ml TP 0.60 ± 0.15</td>
<td>0.45-0.90</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

indices as the BBT pattern and $P_2$ values as being ovulatory in character. A distinct fall of PUA levels was noted at the mid part of the three cycles. When readings for days 0–9, 10–17 and 18 to end of the three cycles were added, the mean value for the first part of the cycle was significantly higher than that of the second or third part ($P < 0.005$ and 0.05, respectively) whereas no difference was found between the second and third parts.

2. PUA showed no uniform change as a result of endogenous T changes after Leydig cell stimulation (Fig. 4 enclosure). Indeed a satisfactory T response was seen in subjects a (80 %) and b (101 %) while subnormal responses were noted in subjects c (18 %) and d (25 %). In subjects a, b and d there were no marked PUA changes from the control situation, while an increase as well as a decrease was noted in subjects c and e, respectively.

B. Exogenously administered sex steroids

1. Post-menopausal women. The results obtained in this group of women is shown in Table 1 and Figs. 2 and 3.

Oestrogens. – COe administration caused a variable decrease in PUA in 9 women while in the remaining 4 an upward trend was noted (Fig. 2). The

![Fig. 2.](image)

The effect of conjugated oestrogens (COe) testosterone propionate (TP) and progesterone (P) on plasma uric acid (PUA) urinary uric acid (UUA), uric acid clearance (UAC) and plasma creatinine (PC) in post-menopausal women. —— Individual cases. ——— Mean of the group.
mean on treatment PUA value was significantly lower than the control value, 
\( P < 0.025 \), t-test for paired differences, (Bradford-Hill, 1967)). UUA showed 
a rise following COe treatment in 6 out of 7 women \( (P < 0.05) \) and this was 
reflected in the UAC increase noted in these subjects \( (P < 0.005) \).

In contrast to their effect on UA, COe produced no significant change in 
the mean PC value in 6 women, the individual responses varying widely 
(Fig. 2). The effect of oestradiol \((\text{Oe}_2)\) monobenzoate given as a single injection 
on PUA was not consistent (Fig. 3). A definite lowering effect was observed immediately or after 30 min in subjects 3 and 4 whereas an upward 
trend was noted in the remaining 2 women (1 and 2).

**Testosterone propionate.** - This androgen produced an increase of PUA 
levels in all but one of the subjects studied (Fig. 2) and the mean on treatment PUA value of the group was significantly higher than the mean control value (Table 1). A significant effect of this androgen on the PC concentration 
was not seen.

**Progesterone.** - This steroid produced a variable PUA change in the women 
of this group. However, a marked rise in UUA and UAC was noted in all 
4 subjects but was significantly only in the case of UAC \( (P < 0.01) \).

2. Male subjects. The results obtained in this group are presented on 
Table 2 and Fig. 4.

**Oestrogens.** - COe administration had a lowering effect on PUA in 11 sub¬
jects of the group \( (P < 0.005) \), and produced a rise in the mean UUA and 
UAC values in 6 men \( (P < 0.05) \). Similarly, OeB had a lowering effect on 
PUA levels in all the subjects studied \( (P < 0.025) \) while E02 had no definite 
effect, although a downward tendency was evident (Fig. 4).

![Graph](image)

*Fig. 3.*

The acute effect of oestradiol \((\text{Oe}_2)\) monobenzoate on plasma uric acid (PUA)

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Table 2.
PUA, UUA and UAC in adult men before and during sex steroid treatment.

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Before treatment</th>
<th>During treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± sd</td>
<td>Range</td>
<td>No. obs.</td>
</tr>
<tr>
<td>PUA</td>
<td>COc</td>
<td>6.16 ± 1.11</td>
<td>4.15-7.68</td>
</tr>
<tr>
<td>mg/100 ml</td>
<td>OeB</td>
<td>6.83 ± 0.50</td>
<td>6.00-7.30</td>
</tr>
<tr>
<td></td>
<td>EOe</td>
<td>7.81 ± 1.84</td>
<td>5.83-10.16</td>
</tr>
<tr>
<td>P</td>
<td>5.40 ± 0.90</td>
<td>4.50-6.00</td>
<td>4</td>
</tr>
<tr>
<td>UUA</td>
<td>COc</td>
<td>409.8 ± 101.4</td>
<td>290.7-585.0</td>
</tr>
<tr>
<td>mg/d</td>
<td>P</td>
<td>572.5</td>
<td>536.0-609.9</td>
</tr>
<tr>
<td>UAC</td>
<td>COc</td>
<td>6.9 ± 1.3</td>
<td>4.9-8.5</td>
</tr>
<tr>
<td>ml/min</td>
<td>P</td>
<td>10.1</td>
<td>9.5-10.7</td>
</tr>
</tbody>
</table>

Progesterone. – This steroid was given to only 2 subjects and produced diametrically opposed results on UUA and UAC (UUA: 42.8 to 92.8 and 64.2 to 48.8 mg/day. UAC: 9.5 to 17.2 and 10.7 to 7.6 ml/min).

3. Patients with primary amenorrhoea. In 3 girls with idiopathic primary amenorrhoea treated on a long-term basis with COe 2.5 mg per day, a definite decrease in PUA was noted in all 3 cases after variable periods of time (28 to 80 days) on treatment (5.3 ± 0.70 to 4.1 ± 0.6 mg/100 ml).

Miscellaneous observations

The mean ± sd control PUA value of the post-menopausal group studied was 5.5 ± 0.4 mg/100 ml, the corresponding value of a group of menstruating women (follicular phase) being 4.2 ± 0.50 mg/100 ml and significantly lower than the former group (P < 0.025). The mean ± sd control value for the group of men (6.4 ± 0.5) was significantly higher than that of both groups of women (P < 0.001 and P < 0.001, respectively).

When the control readings of the post-menopausal subjects were plotted against time (years) after the menopause no correlation was found between the two variables (r = 0.123, n = 36).

Fig. 4.
The effect of conjugated oestrogens (COe), progesterone (P), oestradiol benzoate (OeB) and ethinyl oestradiol (EOe) on plasma uric acid (PUA), urinary uric acid (UUA) and uric acid clearance (UAC) in men.
Enclosure. The effect of Leydig cell stimulation on plasma testosterone (PT) and PUA levels in 4 and 5 men, respectively. —— Individual cases. ——— Mean of the group.
DISCUSSION

The present study was designed to examine the possible effect of sex steroids on UA in healthy subjects of both sexes and to this end physiological studies, dynamic tests and exogenous administration of naturally occurring or synthetic sex steroids were employed.

The results obtained have clearly demonstrated that sex steroids have a definite effect on UA concentration in either of the biological fluids examined. Thus, conjugated or synthetic oestrogens produced a marked PUA decrease in most of the women and men studied and this effect was associated with an increase of UUA and UAC in the subjects treated with COe.

Furthermore, marked variations in the PUA concentration throughout ovulatory menstrual cycles were observed in a manner inverse to that of plasma or urinary oestrogens during the normal cycle. In quantitative terms, higher mean PUA values were found at the early part of the cycle as compared with the middle and last third which are usually associated with higher levels of oestrogens. Surprisingly, EO₃, a most potent synthetic oestrogen, produced only a slight fall in the PUA levels, but this was noted in all 4 subjects included in the group. A more notable decrease might have been seen, had the number of the subjects and the duration of treatment, or both, been greater. It is equally possible that conjugated oestrogens, with oestrone sulphate as their principal ingredient differ in their metabolic effects from EOe. One should also bear in mind that the various regimes of oestrogen treatment used were not similar in terms of the dosage given and this may account for the lack of consistent effect on UA.

Of interest was the lack of a definite pattern of PUA change following the intramuscular injection of oestradiol monobenzoate; this probably indicates that the steroid used had not an immediate effect on UA. Ideally such an effect should have been evaluated only in terms of free oestradiol appearance rate after the injection, but unfortunately estimations of this steroid were not performed. A definite rise in PUA concentration has been demonstrated in the post-menopausal women studied as an effect of treatment with TP. Confirmatory evidence for our findings comes from the clinical observations of Graber-Duvernay & Graber-Duvernay (1957) who reported that acute attacks of gout appeared in 3 women after androgen therapy. Unfortunately, clearance studies were not performed in our group of cases and therefore no satisfactory explanation as to the possible mechanism of TP's action can be offered. The situation was less clear-cut in the case of endogenous testosterone changes after Leydig cell stimulation and their effect on PUA. This was probably due to the small number of men studied and the lack of sufficient T response to HCG stimulation in 2 of the subjects. The possibility also exists that treatment with HCG affects PUA in a more complex way since Leydig cell stimu-
lation results not only in a rise in T secretion but also in a considerable increase in oestradiol output from the testis. Naturally, the PUA changes might have been different after administration of synthetic testosterone at higher dose-levels.

The observations made in this study with respect to the effect of P on PUA, UUA and UAC in women were based on limited number of cases and therefore should be accepted with reservation. However, in all 4 cases a marked rise in UUA and UAC was evident and it appears that P at the dose given produced a uricosuric effect through an increase of UAC. The situation as far as the 2 men was concerned was far from clear.

Plasma creatinine was not affected by either COe or TP in post-menopausal women. This observation is in accord with that of other investigators (Nicholls et al. 1973) who found no changes in the plasma or in the urinary creatinine levels in a series of men given pharmacological doses of synthetic oestrogens.

Of interest was the lack of any relationship between years elapsing since the menopause and PUA levels. Longitudinal studies will obviously reflect more closely the true relationship between the two parameters, although it appears unlikely that such a correlation exists. In practical terms this means that the adjustment of PUA concentration to post-menopausal levels is probably reached before and during menopause, in a manner resembling the progressive ovarian failure occurring some years before the menopause (Adamopoulos et al. 1971). The finding of no significantly different PUA, UUA and UAC mean control values between groups of men and post-menopausal women is in agreement with the results of Mikkelsen et al. (1965) who reported that a gradual rise in PUA values to almost male adult levels occurred in women after the menopause. The mechanism through which oestrogens affect UA metabolism has not yet been elucidated. It is possible that these steroids exert their action at one or more steps of the UA metabolic pathway, thus affecting the rate of endogenous UA production, degradation or excretion and/or the rate of exogenous UA metabolism. The present study has clearly demonstrated that conjugated oestrogens produced their effect on PUA through an increase of its renal clearance in both sexes, although other pathways cannot be excluded. Since similar observations have been made by other investigators (Nicholls et al. 1973) in men treated with the synthetic oestrogen stilboestrol, it appears reasonable to assume that both conjugated as well as synthetic oestrogens share the same uricosuric property, through a mechanism related to an alteration of renal tubular activity (Gutman & Yü 1961).

Other endocrine factors such as e.g. thyroid hormones are known to play a part in UA regulation (Leeper et al. 1960) but their contribution particularly in the present study is a matter of speculation. Undoubtedly, sex steroids affect thyroid hormone kinetics mainly through their effect on thyroxine binding.
globulin. Furthermore, thyroxine treatment of hypothyroid patients has been shown to produce a uricosuric effect through an increase of renal blood flow (Leeper et al. 1960). However, in view of the known effect of sex steroids on thyroxine binding globulins, it is difficult to establish whether a synergistic, antagonistic or no interrelated action exists between thyroid hormones and the different kinds of sex steroids on their effect on UA.

In conclusion, it appears that sex steroids do affect UA metabolism in the manner shown in this study and therefore sex and age related differences between healthy subjects are probably due to differences in their endocrine profile. Furthermore, it appears that oestrogens exert their action through a uricosuric effect in both sexes whereas the situation is not clear as far as androgenic steroids are concerned since their effect on PUA in women has not been confirmed in men. Finally, evidence is presented to the effect that progesterone exerts an action on PUA similar to that of oestrogens in women.

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