BRIEF COMMUNICATION

THE EFFECT OF AN ORAL CONTRACEPTIVE ON
URINARY GONADOTROPHIN IN WOMEN
AT MID-CYCLE

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In a previous study of the effect of an oral contraceptive (Brown, Wells &
Cunningham, 1964), urinary gonadotrophin was measured by its ability to
This method of assay, though not specific for luteinizing hormone, was con-
sidered appropriate for investigating the action of drugs which prevent ovula-
tion. The study of two women, one through two complete menstrual cycles and
the other through three, showed that treatment with a combination of nor-
ethenodrel and mestranol abolished the mid-cycle peak of gonadotrophin
excretion. Before further study of the mode of action of oral contraceptives,
more experience was gained with the pattern of excretion of gonadotrophin
during the normal menstrual cycle measured with this assay (Wells, Brown &
Cunningham, 1965). In thirteen cycles from eight subjects, the highest excre-
tion (apart from values obtained during menstruation) occurred near mid-
cycle. Although assays were done on 48-hr collections of urine, for descriptive
purposes the peak has been assigned to the first or second 24 hr of the collection
according to whether the preceding or the following 48-hr collection gave the
higher value. The mid-cycle peak, defined in this way, occurred 13±2 days
before the onset of the next period. A limited study of urinary gonadotrophin
levels at this stage of the cycle has now been made (a) before, and (b) during
the use of an oral contraceptive. The object was to test the hypothesis that an
oral contraceptive abolishes the mid-cycle peak of gonadotrophin excretion.

Healthy women aged 20 to 39 years with regular menstrual cycles were
selected from those attending a clinic which provided advice on contraception.
All were parous, the most recently pregnant having been delivered 6 months
previously: she had not breast-fed and had had four periods at regular intervals
before starting the trial. It was essential that the subjects were intelligent and
willing to co-operate in the accurate collection of urine specimens.

In the cycle before medication, urine was collected over four consecutive 24-
hr intervals, beginning 15 days before the expected start of the next period.

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Experience of the normal cycle (Wells et al., 1965) was the basis for expecting that this collection would include the mid-cycle peak in most subjects. In the next cycle, a tablet containing ethynodiol diacetate 1 mg and mestranol 0.1 mg (Ovu: Searle) was taken daily for 20 days starting on Day 5, and a further 4-day collection of urine was made. This collection was timed to follow the first day of the preceding period by the same interval as the collection in the control cycle. The hypothesis that the oral contraceptive would abolish the peak during the second collection implied that the mean daily excretion of gonadotrophin would be lower during this collection. If the treatment did not influence the pattern of gonadotrophin excretion it would be a matter of chance whether the gonadotrophin level would be higher or lower during the second collection.

The gonadotrophin was extracted from each 24-hr specimen by the kaolin-acetone method used previously (Brown et al., 1964). Later, the four extracts corresponding to a 4-day collection were pooled by dissolving in saline and precipitating with acetone. The pooled extracts were assayed by the method of Cunningham (1962) under the conditions of Wells et al. (1964) and the results expressed as the mean daily excretion in terms of the first international reference preparation for human menopausal gonadotrophin (IRP). In three assays the highest dose of extract produced no ovulation and the results are shown as less than a certain value. In all other assays, except one, the extract was assayed at two or more levels against standard at three dose-levels. In one subject, the extract obtained during the use of the oral contraceptive, when tested at four dose-levels, gave an uncharacteristic dose–response line which was significantly different in slope from that of the standard. No explanation can be offered for this alteration in slope.

The results for the eight women studied (Table 1) support the hypothesis being tested. In all seven in whom assay before and during treatment was possible, the mean gonadotrophin excretion fell while the oral contraceptive was being taken. In the eighth case, comparison was not possible; but seven out of

### Table 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Parity</th>
<th>Mean daily excretion of gonadotrophin (95% fiducial limits) in mg equivalents of IRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Control cycle</strong></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>1</td>
<td>16 (12–21)</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>2</td>
<td>28 (21–37)</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>1</td>
<td>22 (16–32)</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>2</td>
<td>17 (13–23)</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>4</td>
<td>48 (36–63)</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>3</td>
<td>44 (33–60)</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>3</td>
<td>24 (20–31)</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>2</td>
<td>43 (31–61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th><strong>During treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>1</td>
<td>12 (9–16)</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>2</td>
<td>&lt;9.6</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>1</td>
<td>&lt;7.5</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>2</td>
<td>7.5 (5–11)</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>4</td>
<td>&lt;12</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>3</td>
<td>(Non-parallelism)</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>3</td>
<td>9.7 (7–12)</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>2</td>
<td>23 (16–33)</td>
</tr>
</tbody>
</table>

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eight changes in the postulated direction is significantly different from random expectation ($P<0.05$). The arithmetic mean fall in the seven women was of more than 16.8 mg IRP/day. This is significantly greater than zero on a $t$-test ($P<0.01$). If the fall in the logarithm of the mean daily excretion in the seven women is tested, this is seen to be even less likely to be due to chance ($P<0.001$). The latter is probably the better way to test the significance as the initial gonadotrophin level varies considerably among subjects. It rises with age and parity, though correlation of level and age is just short of statistical significance.

Although this investigation was strictly limited, we see no obvious ways in which the circumstances of the experiment would give a systematic bias towards lower levels of gonadotrophin excretion in the second cycle. The results therefore lend strong support to the suggestion that this oral contraceptive abolishes the mid-cycle peak of gonadotrophin excretion found in normal menstrual cycles.

We are grateful to the subjects for their co-operation and to Dr I. A. G. MacQueen for permission to study them. We are also grateful to Mrs Dorothy Brown for organizing the urine collections and to Miss Margaret Scorgie for technical assistance.

REFERENCES


