Pathological mechanisms in polycystic ovary syndrome: modulation of LH pulsatility by progesterone

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Summary. The pulsatile discharge of luteinizing hormone (LH) in nine patients with polycystic ovary syndrome (PCO) and nine patients with amenorrhoea but without PCO, who exhibited LH discharge in response to oestrogen provocation, were studied by 4-h measurement of gonadotrophin pulsatility before and after a course of progesterone injections. No significant differences were found in the gonadotrophin pulsatility patterns of the two groups, although the LH/FSH ratio rose significantly in the patients without PCO after progesterone but not in the patients with PCO, suggesting an abnormality of FSH storage. The ability to discharge gonadotrophins in response to oestrogen provocation has been reported to be present in patients with ≥1 LH pulses in a 4-h study period. This, however, was not demonstrated in five of the nine PCO patients despite the presence of 'normal' gonadotrophin pulsatility patterns.

It is still uncertain what the primary lesion is in patients with the polycystic ovary syndrome (PCO). It is not clear whether the cyclical modulation of gonadotrophin releasing hormone pulsatility is disturbed secondary to an alteration in central nervous system rhythms—probably mediated by dopamine (Quigley et al. 1981), or whether primary production of excess androgens by the ovary or adrenal may lead to abnormalities in gonadotrophin synthesis and/or release (Yen et al. 1976).

Attempts to characterize patients with PCO endocrinologically by the investigation of hypothalamic-pituitary-ovarian function have proved difficult. While basal luteinizing hormone (LH) levels are elevated in only one-third of patients (Yen et al. 1976; Givens et al. 1976) an exaggerated response to LH releasing hormone (LHRH) is found in two-thirds (Duignan 1976; Patten et al. 1975; Rebar et al. 1976). Duignan et al. (1975) suggested that the normal cyclical release of LH was being suppressed by elevated levels of circulating free androgens acting at either the pituitary gland or the hypothalamus. Normal gonadotrophin responses to oestrogen provocation were found in the majority of patients with PCO by Shaw et al. (1975) and Kandell et al. (1978) showed that these patients could be divided into two groups on the basis of their response to an oestrogen amplification test.

Recently we have reported that two patients with PCO showed absence of LH pulsatility over a 4-h period with 10 min sampling of blood. After 5 days of progesterone treatment, however, pulsatile LH discharge, similar to that seen in other patients before progesterone treatment, was reversed (El Sheikh et al. 1984). We therefore studied nine patients with documented PCO syndrome and nine other patients with amenorrhoea and oligoamenorrhoea to investigate

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whether there was a specific disorder in the hypo-
thalamic control of gonadotrophin release peculiar to the PCO syndrome.

Patients and methods

The study included 18 patients in nine of whom the PCO syndrome had been diagnosed. The diagnosis was based on the endoscopic finding of bilaterally enlarged smooth featureless ovaries and a thickened capsule in eight patients. The ninth was considered unsuitable for endoscopic evaluation due to her gross obesity: however, bilateral polycystic ovaries of twice normal size were found on ultrasonography.

Five of the patients were hirsute, three had amenorrhoea of >12 months duration and six had oligomenorrhoea. Seven complained of infertility, one did not desire to become pregnant and one had one child (Table I). The other nine patients had been diagnosed as suffering from idiopathic hypothalamic amenorrhoea and had a normal response to oestrogen provocation. Laparoscopy: Assessment showed no evidence of polycystic ovaries.

All patients gave their informed consent. Basal plasma levels of oestradiol-17β, progesterone, testosterone, gonadotrophin and prolactin were determined and thyroid function was assessed. An X-ray of the pelvis/lower was carried out on all subjects. A combined 100-μg LHRH/200-
μg TRH (thyrotrophin releasing hormone) test was performed on each patient and an oestrogen provocation test (Shaw et al. 1975) using 1 mg of intramuscular oestradiol benzoate.

An increase in plasma LH concentration of ≥ 10 μU/ml above baseline levels indicated the presence of positive oestrogen-gonadotrophin feedback. Intact negative feedback, which was present in all of the patients, was defined as a fall in LH and/or follicle stimulating hormone (FSH) below the baseline concentration after oestrogen administration.

All patients had an initial 4-h morning pubertal thyrocyte study; samples were collected at 10-min intervals as described previously (El Sheik et al. 1983) in 14 patients and at 5-min intervals in four of the PCO group. Progesterone, 50 μg, was then given intramuscularly daily for 5 days and a pubertal study was repeated on the sixth day. All patients were sampled at 10-min intervals during the second study.

The blood samples were centrifuged and the plasma was separated immediately after each pubertal study and stored at −20°C. All samples from each patient were analysed in the same assay batch for FSH and LH; oestradiol-
17β and progesterone were measured in the 0 min sample only. The in vivo immunoassays have been described previously (El Sheik et al. 1983). The mean in vitro coefficients of variation for the usable portions of the standard curves were 3.1% for LH and 2.1% for FSH. The mean interassay coefficients of variation were 4.5% for LH and 3.3% for FSH.

An LH pulse was defined as: an increase in concentration of ≥200% of the value at the nadir followed by a continuous decline in concentra-
tion in the subsequent two samples (Einhut et al. 1975; West et al. 1975). The pulse amplitude was expressed as the percentage increase in LH concentration from the nadir to the subsequent peak. The results obtained were compared using Student's t-test and Kendall's rank correlation test.

### Table 1. Summary of clinical data and baseline investigation in nine patients with polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Parity</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Mean±SEM LH Basal (μU/ml)</th>
<th>FSH (μU/ml)</th>
<th>LH:FSH ratio</th>
<th>Testosterone (nmol/l)</th>
<th>Oestradiol (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>0-0</td>
<td>50</td>
<td>150</td>
<td>18±5</td>
<td>3.5±2</td>
<td>5.8±3</td>
<td>2.0±1</td>
<td>430</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>0-0</td>
<td>78</td>
<td>165</td>
<td>12±3</td>
<td>3.9±1</td>
<td>2.3±1</td>
<td>3.8±1</td>
<td>262</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>0-2</td>
<td>55</td>
<td>152</td>
<td>7.4±3</td>
<td>1.8±1</td>
<td>2.5±1</td>
<td>1.5±1</td>
<td>145</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>0-0</td>
<td>48</td>
<td>167</td>
<td>2.7±6</td>
<td>4.1±2</td>
<td>3.2±2</td>
<td>2.2±1</td>
<td>220</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>1-0</td>
<td>110</td>
<td>159</td>
<td>4.7±3</td>
<td>1.3±1</td>
<td>2.7±1</td>
<td>2.0±1</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>0-0</td>
<td>64</td>
<td>151</td>
<td>2.0±3</td>
<td>8.0±1</td>
<td>1.3±1</td>
<td>1.5±1</td>
<td>182</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>0-0</td>
<td>71</td>
<td>176</td>
<td>9.5±4</td>
<td>6.8±1</td>
<td>2.1±1</td>
<td>3.5±1</td>
<td>249</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>0-4</td>
<td>106</td>
<td>158</td>
<td>11±4</td>
<td>2.3±1</td>
<td>4.5±1</td>
<td>1.5±1</td>
<td>170</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>0-0</td>
<td>60</td>
<td>159</td>
<td>21±3</td>
<td>5.7±1</td>
<td>4.7±1</td>
<td>9.0±1</td>
<td>390</td>
</tr>
</tbody>
</table>

Notes: A, Amenorrhoea; O, oligomenorrhoea.
Results
The complete data are presented in Table 2 and 3 and Figs 1 and 2. Eight of the nine PCO patients showed a pulsatile pattern of LH release, according to the definition above, with a frequency ranging from 3-5 pulses in the 4-h study period (mean 3.6) and a mean amplitude of 42 (SEM 10.3%). After progesterone treatment the mean pulse frequency was reduced to 2.1 pulses in the 4-h study period (P<0.05) and the mean amplitude was increased to 72 (SEM 14.2%) (P<0.05). All nine patients in the non-PCO group showed pulsatile LH release before progesterone treatment with a frequency of 3-5 pulses in the 4-h study period (mean 4.1) and a mean amplitude of 42.2 (SEM 2.4%). After progesterone treatment the pulse frequency was reduced to a mean of 2.2 pulses in the 4-h study period (P<0.001) and the mean amplitude increased to 73.8 (SEM 19.9%) (P<0.001).

There were no significant differences in the plasma concentrations of oestradiol before or after progesterone treatment in either group nor between PCO patients with intact positive feedback and those without. Simultaneous luteal phase plasma concentrations of progesterone were achieved on the treatment regimen at the time of the second pulsatility study (mean 52 (SEM 6.4) nmol/l) in the PCO group and 27 (SEM 6.5) nmol/l in the non-PCO group. The mean concentrations rose in five of the non-PCO patients after progesterone treatment and fell in five; there was a significant fall in mean FSH concentra-tions (P<0.001) and a consequent rise in the L/H:FSH ratio in all nine patients (P<0.001). In the PCO patients mean LH concentrations rose in five and fell in four patients and although the mean FSH concentrations fell significantly (P<0.05), the falls were not enough to alter the L/H:FSH ratio to a statistically significant degree. The increase in LH pulse amplitude produced by progesterone treatment was significantly greater in the non-PCO than in the PCO patients. There was no difference noted in the GnRH analogue responses to progesterone between those PCO patients with intact positive feedback and those without.

Discussion
In the present study it has been shown that progesterone modulates LH pulsatile release in patients with PCO as it has previously been shown to do in amenorrheic women with intact oestrogen-progesterone feedback (El Sheikh et al. 1984) and some of these patients have been used as controls in this study. Eight of the nine patients with PCO demonstrated 3-5 LH pulses in the 4-h study period although four had absence of positive feedback as judged by a 1-mg oestrogen provocation test. This is in contrast to our recent studies (El Sheikh et al. 1985) which showed that in the presence of LH pulsatility LH was discharged in response to oestrogen provocation.

It has been suggested (Rebar et al. 1976) that the high LH concentrations found in patients with PCO appear to be the result of greater amplitude or increased frequency of pulsatile LH release. In this study, however, no correlation was found between the amplitude of LH pulses and the basal LH.

Indeed, patient no. 7 with the highest basal LH level had no pulses by our definition of a pulse. Backstrom et al. (1942) used a different definition of a gonadotrophin pulse based on the concept of a rise greater than the coefficient of variation of the assay. Although this is attractive, as it allows unexplained fluctuations less than our required 20% increment over the basal value to be considered as pulses, it has the disadvantage that it allows pulses to be defined on two samples barely 20 min apart. Nevertheless patient no. 7 still fails to show any pulses even by their definition. We would postulate that as this patient exhibits 3 pulses after progesterone treatment her pre-treatment pulses may be being masked by the very high basal value of LH. The frequency of LH pulses was 3-4 in the 4 h study period similar to that in the non-PCO patients with intact oestrogen-progesterone feedback.

After the initial study of four patients with PCO with a 5-min sampling interval it was noted that no more LH pulses were demonstrated than were found by 10-min sampling. It had been thought that the frequency of LH discharge might be greater in patients with PCO and that more frequent sampling would avoid failure to demonstrate peaks. This was not the case as the pulsatility studies after the initial four were carried out with a 10-min sampling frequency.

No correlation was found between the clinical features of the patients with PCO and the pattern of absolute values of their gonadotrophins either before or after progesterone treatment. In particular no differences could be found between the amenorrheic patients with PCO and those with oligomenorrhea to explain their failure to initiate cycles.
Table 2: Luteinizing hormone (LH) pulsatile release over 4 h in nine patients with polycystic ovary

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>LH (iu/l)</th>
<th>FSH (iu/l)</th>
<th>LH/FSH ratio</th>
<th>Basal E2 (pmol/l)</th>
<th>Basal P (nmol/l)</th>
<th>LH pulse frequency</th>
<th>Peak amplitude (% increase)</th>
<th>Intact positive feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24 ± 0.05</td>
<td>3 ± 0.07</td>
<td>4.6</td>
<td>325</td>
<td>&lt;2</td>
<td>3</td>
<td>46</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>30 ± 0.32</td>
<td>2.5 ± 0.06</td>
<td>3.9</td>
<td>315</td>
<td>&lt;2</td>
<td>4</td>
<td>31</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>6 ± 1.35</td>
<td>3 ± 0.02</td>
<td>1.8</td>
<td>175</td>
<td>&lt;2</td>
<td>4</td>
<td>115</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>26 ± 0.73</td>
<td>5 ± 0.04</td>
<td>4.6</td>
<td>360</td>
<td>&lt;2</td>
<td>4</td>
<td>65</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>3 ± 0.08</td>
<td>2.9 ± 0.01</td>
<td>1.8</td>
<td>390</td>
<td>&lt;2</td>
<td>3</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>22 ± 0.34</td>
<td>7 ± 0.05</td>
<td>2.9</td>
<td>150</td>
<td>&lt;2</td>
<td>4</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>10 ± 1.96</td>
<td>4 ± 0.04</td>
<td>4.9</td>
<td>&lt;30</td>
<td>&lt;2</td>
<td>0</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>10 ± 1.12</td>
<td>4 ± 0.02</td>
<td>3.3</td>
<td>130</td>
<td>&lt;2</td>
<td>5</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>17 ± 0.37</td>
<td>3 ± 0.01</td>
<td>5.3</td>
<td>455</td>
<td>&lt;2</td>
<td>5</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>24 ± 0.5</td>
<td>5 ± 0.17</td>
<td>3.8</td>
<td>231 ± 45</td>
<td>—</td>
<td>5.6</td>
<td>42 ± 10.1</td>
<td>-</td>
</tr>
</tbody>
</table>

Values before progesterone administration

Values after progesterone administration

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>LH (iu/l)</th>
<th>FSH (iu/l)</th>
<th>LH/FSH ratio</th>
<th>Basal E2 (pmol/l)</th>
<th>Basal P (nmol/l)</th>
<th>LH pulse frequency</th>
<th>Peak amplitude (% increase)</th>
<th>Intact positive feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 ± 0.54</td>
<td>3 ± 0.05</td>
<td>4.4</td>
<td>&lt;0.01</td>
<td>&gt;80</td>
<td>2</td>
<td>106</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>10 ± 0.36</td>
<td>2 ± 0.05</td>
<td>2.9</td>
<td>210</td>
<td>41</td>
<td>2</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1 ± 0.38</td>
<td>2.4 ± 0.02</td>
<td>2.4</td>
<td>50</td>
<td>37</td>
<td>2</td>
<td>149</td>
<td>2</td>
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<td>1 ± 0.43</td>
<td>5 ± 0.03</td>
<td>5.2</td>
<td>390</td>
<td>67</td>
<td>2</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1 ± 0.36</td>
<td>2.6 ± 0.01</td>
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<td>350</td>
<td>25</td>
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<td>107</td>
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<td>1 ± 0.57</td>
<td>4 ± 0.05</td>
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<td>100</td>
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<td>3</td>
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</tr>
<tr>
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<td>1 ± 0.87</td>
<td>3 ± 0.05</td>
<td>3.3</td>
<td>145</td>
<td>42</td>
<td>3</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>10 ± 0.54</td>
<td>5 ± 0.05</td>
<td>5.0</td>
<td>160</td>
<td>45</td>
<td>2</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>2 ± 0.11</td>
<td>2 ± 0.01</td>
<td>1.1</td>
<td>295</td>
<td>&gt;80</td>
<td>1</td>
<td>1</td>
<td>90</td>
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<tr>
<td>Mean ± SEM</td>
<td>1 ± 0.70</td>
<td>3 ± 0.07</td>
<td>3.0</td>
<td>200 ± 38</td>
<td>72 ± 6.4</td>
<td>2.1</td>
<td>72 ± 14.2</td>
<td>-</td>
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</table>

*Results shown are the 4 h means ± SEM LH and FSH plasma concentrations, the basal (time 0 sample) estradiol (E2) and progesterone (P) plasma concentrations, the LH pulse frequency and mean amplitude (% increase of LH from nadir) in subsequent peak.*
Table 3. Luteinizing hormone (LH) pulsatile release over 4 h in nine patients without polycystic ovary syndrome and with intact gonadotrophin pituitary feedback.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>LH (u/l)</th>
<th>FSH (u/l)</th>
<th>LH/FSH ratio</th>
<th>Basal E₂ (pmol/l)</th>
<th>Basal P (nmol/l)</th>
<th>LH pulse frequency</th>
<th>Pulse amplitude (% increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>12 3±1 30</td>
<td>3±0 04</td>
<td>5±4</td>
<td>350 &lt; 2</td>
<td>4 ±2 29</td>
<td>10</td>
<td>4 ±2 29</td>
</tr>
<tr>
<td>11</td>
<td>19 9±1 54</td>
<td>4±0 06</td>
<td>4±6</td>
<td>250 &lt; 2</td>
<td>4 ±2 41</td>
<td>11</td>
<td>4 ±2 41</td>
</tr>
<tr>
<td>12</td>
<td>16 1±0 42</td>
<td>4±0 06</td>
<td>3±3</td>
<td>355 &lt; 2</td>
<td>4 ±2 49</td>
<td>12</td>
<td>4 ±2 49</td>
</tr>
<tr>
<td>13</td>
<td>9 8±0 50</td>
<td>3±0 04</td>
<td>2±7</td>
<td>240 &lt; 2</td>
<td>3 ±2 48</td>
<td>13</td>
<td>3 ±2 48</td>
</tr>
<tr>
<td>14</td>
<td>17 3±0 36</td>
<td>5±0 08</td>
<td>3±2</td>
<td>690 &lt; 2</td>
<td>4 ±2 38</td>
<td>14</td>
<td>4 ±2 38</td>
</tr>
<tr>
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<td>3±0 06</td>
<td>1±6</td>
<td>395 &lt; 2</td>
<td>5 ±2 49</td>
<td>15</td>
<td>5 ±2 49</td>
</tr>
<tr>
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<td>12 6±0 40</td>
<td>5±1 06</td>
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<td>110 &lt; 2</td>
<td>4 ±2 47</td>
<td>16</td>
<td>4 ±2 47</td>
</tr>
<tr>
<td>17</td>
<td>15 3±0 34</td>
<td>3±0 04</td>
<td>4±4</td>
<td>195 &lt; 2</td>
<td>4 ±2 34</td>
<td>17</td>
<td>4 ±2 34</td>
</tr>
<tr>
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<td>10 6±0 34</td>
<td>3±0 04</td>
<td>2±8</td>
<td>320 &lt; 2</td>
<td>5 ±2 45</td>
<td>18</td>
<td>5 ±2 45</td>
</tr>
<tr>
<td>Mean±SEM 10</td>
<td>12 3±1 45</td>
<td>4±2 02</td>
<td>3±2</td>
<td>315±6 ±2</td>
<td>4 ±1 42 2 ±2 4</td>
<td>10</td>
<td>4 ±1 42 2 ±2 4</td>
</tr>
</tbody>
</table>

+ Values before progesterone administration

+ Values after progesterone administration

+ Results shown are the 4-h mean±SEM LH and FSH plasma concentrations, the basal (zero sample) oestradiol (E₂) and progesterone (P) plasma concentrations, the LH pulse frequency and mean amplitude (expressed as the % increase of LH from nadir to subsequent peak).
Fig. 2. Luteinizing hormone pulsatility studies before (●) and after (○) progesterone treatment in nine patients (nos 10-18) without polycystic ovary syndrome.
There was no significant difference found between the oestradiol levels of the two groups of patients before or after progesterone treatment and this may explain the failure to demonstrate a difference in the pulsatile levels of gonadotrophin release between the SCO and non-SCO patients as elevated oestradiol levels have been shown to augment the efficacy sensitivity to LH/H by a direct pituitary action (Yen et al. 1975). Although four of the PCO patients had testosterone levels above the normal female range of up to 5.8 nmol/l, there were no abnormalities of the presence of hirsutism and there was no correlation between gonadotrophin, oestradiol and testosterone levels.

In five of the PCO patients and four non-PCO patients mean LH values rose after progesterone, but there was no significant change in the mean values for the groups as a whole. Taking all the 18 patients together it is possible to divide them into two groups of nine on the basis of their mean LH response to progesterone administration (Table 4). Nine patients showed deviation of mean LH after progesterone administration (PCO 0.5) and nine showed reduction (P<0.05). This difference in response to progesterone treatment was significant; but no classical features could be identified to differentiate the groups. SCO and non-PCO patients were equally distributed as were those exhibiting positive oestradiol–gonadotrophin feedback; there was no correlation between body-weight or basal cortisol concentrations and the patient groupings. There was no difference in the number of pulses nor their amplitude between the two groups.

It has recently been demonstrated (El Sheikh et al. 1985) that the presence of LH discharge in response to oestradiol provocation is associated with the presence of LH pulses in a 4-h study period. Although eight of the nine patients with PCO had 3-5 LH pulses in the 4-h study period, five of them had no positive feedback as demonstrated by the 1 mg oestradiol provocation test. The rise in the LH/FSH ratio in the non-PCO group in response to progesterone may mirror the reduction in secretion of FSH by the pituitary in the luteal phase of the menstrual cycle allowing storage in preparation for initiation of the next cycle. This phenomenon was not demonstrated in the PCO patients suggesting a failure of FSH storage possibly as a result of the abnormal feedback effects of endogenous adrenal or ovarian steroids.

Berger et al. (1975) divided patients with PCO into two groups, ‘typical’ and ‘atypical’. Type 1 were characterized by higher levels of LH and were labelled ‘typical’ being considered to be comparable to the original patients described by Stein & Leventhal (1935). We could identify no difference in gonadotrophin pulsatility between these two groups of patients on applying the criteria of these workers to our subjects.

The PCO syndrome would seem more likely to be an end stage of many different abnormalities of folliculogenesis and ovulation than a single disease entity. In the patients studied here no specific abnormality in the pulsatile pattern of gonadotrophin release could be demonstrated before or after its modulation by progesterone.

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