Polycystic ovaries and recurrent miscarriage—a reappraisal

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The prevalence of polycystic ovaries (PCO) was established amongst 2199 consecutive women (median age 33 years; range 19–46) with a history of recurrent miscarriage (median 3; 3–14). A diagnosis of PCO was made if the ovarian volume was enlarged (>9 ml), there were ≥10 cysts of 2–8 mm in diameter in one plane and there was increased density of the stroma. In a cohort study, the prospective pregnancy outcome of 486 of the women scanned who were antiphospholipid antibody negative and who received no pharmacological treatment during their next pregnancy was studied. The prevalence of PCO was 40.7% (895/2199). The livebirth rate was similar amongst women with PCO (60.9%; 142/233) compared to that amongst women with normal ovarian morphology (58.5%; 148/253; not significant). Neither an elevated serum luteinizing hormone concentration (>10 IU/l) nor an elevated serum testosterone concentration (>3 nmol/l) was associated with an increased miscarriage rate. Polycystic ovarian morphology is not predictive of pregnancy loss amongst ovulatory women with recurrent miscarriage conceiving spontaneously. The search for a specific endocrine abnormality that can divide women with PCO into those with a good and those with a poorer prognosis for a future successful pregnancy continues.

Key words: polycystic ovaries/pregnancy outcome/prevalence/recurrent miscarriage

Introduction

Recurrent miscarriage, the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive. Since this is significantly higher than that expected by chance alone (0.34%), a proportion of couples is likely to have a persistent underlying abnormality to account for their repeated pregnancy losses. Polycystic ovaries (PCO) are the most commonly identified ultrasound abnormality amongst women with recurrent miscarriage (Sagle et al., 1988; Clifford et al., 1994).

Women with PCO form a heterogeneous group. At one end of the spectrum are those with chronic anovulation and hyperandrogenism and at the other end are the much larger number who have PCO morphology on ultrasound scan but no menstrual or biochemical abnormality (Franks, 1995). Previous studies have reported that women who either hypersecrete luteinizing hormone (LH) or who are hyperandrogenaemic, two classical endocrinopathies associated with PCO, are at increased risk of miscarriage following either spontaneous or assisted conception (Stanger and Yovich, 1985; Howles et al., 1987; Homburg et al., 1988; Regan et al., 1990). However, a recent prospective randomized placebo controlled study reported that pre-pregnancy pituitary suppression of high endogenous LH does not improve the live birth rate of women with recurrent miscarriage and PCO who hypersecrete LH (Clifford et al., 1996).

We therefore addressed the question of whether PCO morphology itself was predictive of adverse pregnancy outcome amongst ovulatory women with a history of recurrent miscarriage conceiving spontaneously. Subsidiary aims were to establish (i) the prevalence of PCO amongst women with recurrent miscarriage and (ii) the biochemical profile of women with recurrent miscarriage and PCO.

Materials and methods

Subjects

Ovarian morphology was determined in 2199 consecutive women (median age 33 years; range 19–46) with a history of recurrent miscarriage (median 3; 3–14) seen in our specialist miscarriage clinic between 1991 and 1999. We have previously reported on the prevalence of PCO morphology amongst the first 500 of these women (Clifford et al., 1994). The prospective pregnancy outcome of 486 of these women who (i) conceived spontaneously, (ii) were antiphospholipid antibody negative and (iii) received no pharmacological treatment during their next pregnancy was studied. All women had a normal shaped uterine cavity on ultrasound scan and a normal peripheral blood karyotype, as did their partners.

Diagnosis of PCO

Pelvic ultrasound scanning was performed by trained pelvic ultrasonographers on an Ultramark 9 (Advanced Technology Laboratories, Bothel, Seattle, USA) using either a 3.5 MHz abdominal or a 5 MHz vaginal probe in the early to mid-follicular phase of the menstrual cycle. A diagnosis of PCO was made if the ovarian volume was enlarged (>9 ml), and there were ≥10 cysts of 2–8 mm in diameter in one plane and there was increased density of the stroma, which was subjectively quantified (Adams et al., 1986). These ultrasound criteria have been widely used in European studies to define polycystic ovarian morphology (reviewed by Kyei-Mensah et al., 1996).

Endocrine investigations

Serum LH and testosterone concentrations were measured in the follicular phase of the menstrual cycle, between days 5 and 8. LH
was measured with a heterogeneous sandwich magnetic separation assay and testosterone with a competitive magnetic separation assay on the Technicon Immuno 1 Immunoanalyser System (Bayer Corporation, Tarrytown, New York, USA). The coefficient of variation for the LH assay was <3% and for the testosterone assay 8%.

### Antiphospholipid assays

All women were screened for aPL on at least two occasions >6 weeks apart prior to pregnancy. Lupus anticoagulant (LA) was detected using the dilute Russell’s viper venom time (dRVVT) together with a platelet neutralization procedure. Patient samples with a dRVVT ratio (test/control) of ≥1.1 were re-tested with a platelet neutralization procedure. A decrease of ≥10% in the ratio was considered positive for LA (Lupus Anticoagulant Working Party on behalf of the BCSH Haemostasis and Thrombosis Taskforce, 1991). Anticardiolipin antibodies (aCL) were identified using a standardized enzyme linked immunosorbent assay (ELISA). An IgG anticardiolipin level ≥5 GPL units and an IgM anticardiolipin level ≥3 MPL units were considered to be positive (Khamashta and Hughes, 1993). Women with persistently positive tests for either LA or aCL were diagnosed as having the primary antiphospholipid syndrome and were treated with aspirin and heparin during pregnancy.

### Management during pregnancy

None of the 486 women received pharmacological treatment during their pregnancy, but all were encouraged to attend a dedicated early pregnancy clinic at which supportive care was offered and serial first trimester ultrasound scans were performed.

### Statistical analysis

Normally distributed continuous variables were analysed using the Student’s *t*-test; otherwise the Mann–Whitney *U*-test was used. Discrete variables were analysed using the χ² test.

### Results

The prevalence of polycystic ovarian morphology amongst women with recurrent miscarriage was 40.7% (895/2199). There were no cases of unilateral PCO. Although the mean follicular phase LH and testosterone concentrations were significantly higher amongst women with PCO compared to those with normal ovaries, the mean levels of these hormones remained within the normal range (Table I). There was no significant difference in the body mass index [weight (kg)/height (m)²] between the two patient groups (Table I).

The prospective pregnancy outcome of 233 women with PCO (median age 32 years; range 19–44) and a history of recurrent miscarriage (median 3; 3–14) was compared to that of 253 women (median age 33 years; 19–45) with a history of recurrent miscarriage (median 3; 3–13) who had normal ovarian morphology (Figure 1). Amongst women who did not report a pregnancy, the prevalence of PCO (40.3%; 405/1004) was similar to that of the population prevalence of PCO in this study (40.7%). There was no significant difference in either the age nor the number of previous miscarriages between the two groups (Table II). All women had persistently negative tests for aPL and no woman received pharmacological treatment during pregnancy, except for folic acid as prophylaxis against neural tube defects.

The overall live birth rate was apparently higher amongst women with PCO (60.9%; 142/233) compared to that amongst women with normal ovaries (58.5%; 148/253; not significant). There was no significant difference in either the mean gestation at delivery or the mean birthweight between women with successful pregnancies who had PCO and those who had normal ovarian morphology (Table III). The majority of miscarriages amongst both groups of women occurred in the first trimester of pregnancy (Table III). There was no significant difference in the future live birth rate between women with PCO and those with normal ovarian morphology irrespective of the number of previous miscarriages (Figure 2).

The live birth rate was apparently higher amongst women with an elevated LH concentration (>10 IU/l) compared to that amongst women with a lower LH concentration [38/53 (72%) versus 252/433 (58%); not significant (*P* = 0.06)]. This difference, however, failed to reach significance. Women with an elevated testosterone concentration (>3 nmol/l) had a
similar live birth rate (69.2%) compared to those with a lower testosterone concentration (66%; not significant). The live birth rate was also similar amongst women with a cycle length of >35 days compared to those with a shorter cycle [10/13 (77%) versus 280/473 (59%; not significant)].

Discussion

Our own unit has reported that the prevalence of PCO amongst an unselected cohort of 257 women is 23% (Polson et al., 1988). This is in broad agreement with prevalence data subsequently published by others (Farquhar et al., 1994; Koivunen et al., 1999). Compared with our historic cohort, the prevalence of PCO (40.7%) is significantly higher amongst women with recurrent miscarriage compared to that in the general population. In a much smaller study we have previously reported the prevalence of PCO amongst women with recurrent miscarriage to be 56% (Clifford et al., 1994). This difference may be accounted for by the current much larger study being a more accurate reflection of the true population prevalence of PCO amongst women with recurrent miscarriage. However, amongst ovulatory women with a history of recurrent miscarriage conceiving spontaneously, PCO morphology per se does not predict an increased risk of future pregnancy loss. Furthermore, there was no significant difference in the prospective livebirth rate between those women with either an elevated serum follicular phase LH concentration (>10 IU/l) or an elevated testosterone level (>3 nmol/l) compared to those with normal concentrations. We were unable to confirm previous reports that women with a menstrual cycle of >35 days were at increased risk of miscarriage compared to those with a shorter cycle (Quenby and Farquharson, 1993).

These results are at variance with earlier studies which reported that women with a raised follicular phase serum LH concentration were at increased risk of miscarriage following either spontaneous conception (Regan et al., 1990) or assisted conception (Howles et al., 1987; Homburg et al., 1988; Hamilton-Fairley et al., 1991). These apparently deleterious effects of high LH were reversed by LH suppression using gonadotrophin-releasing hormone (GnRH) analogues (Balen et al., 1993b; Homburg et al., 1993).

More recent studies have not confirmed these original reports and have questioned the relationship between an elevated LH concentration and recurrent miscarriage. There was no significant difference in the future pregnancy outcome of women with an elevated serum LH concentration compared to those with a normal LH concentration (Tulppala et al., 1993). A similar result was reported later (Liddell et al., 1997). Both these studies included only women with three or more consecutive pregnancy losses.

Measurement of LH remains a controversial area. Earlier studies assayed LH concentrations using a classical radioimmunoassay, whilst more recent studies have used immuno-metric methods. Even when the same reference standard is used, radioimmunoassays in general give higher LH readings than immuno-metric methods (Balen et al., 1993a). More recently, a genetic variant of LH (vLH) has been discovered (Tapanainen et al., 1999). The biological activity of vLH is greater than that of wild-type LH in vitro, but its half-life in the circulation is shorter and the overall effect on in-vivo bioactivity is unclear. The presence of variant vLH is not associated with any clear effect on endocrine variables such as endometrial maturation or mid-luteal phase oestradiol and progesterone concentrations and does not affect miscarriage rates (Tulppala et al., 1998). As LH is secreted in a pulsatile manner we have previously addressed the possibility that tonic hypersecretion of LH, assayed in early morning urine samples collected throughout the menstrual cycle, was predictive of miscarriage. In a prospective randomized placebo-controlled study we reported that suppression of high endogenous LH secretion with a GnRH analogue did not improve the live birth rate (Clifford et al., 1996).

Apart from hypersecretion of LH, hyperandrogenemia is a feature of the polycystic ovarian syndrome. We found that in women with recurrent miscarriage, although the mean testosterone concentration was significantly higher amongst those with PCO compared to those with normal ovaries, it was still within the normal range (<3 nmol/l). Women with an elevated testosterone concentration had a similar prospective live birth rate compared to those with a normal testosterone concentration. Other investigators have reported a similar relationship between free testosterone concentrations and future pregnancy outcome (Liddell et al., 1997). However, this is not a universal finding. Increased concentrations of androgens have been reported amongst women with recurrent miscarriage and that these increased concentrations are (i) associated with

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Table III. Details of the prospective pregnancy outcome of women with polycystic ovaries and those with normal ovarian morphology. SD = standard deviation. There were no significant differences between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Normal ovaries n = 253</th>
<th>Polycystic ovaries n = 233</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of live births</td>
<td>148</td>
<td>142</td>
</tr>
<tr>
<td>Mean (SD) of gestation at delivery (weeks)</td>
<td>37.6 (2.1)</td>
<td>37.3 (2.3)</td>
</tr>
<tr>
<td>Mean (SD) of birth weight (kg)</td>
<td>3.25 (0.72)</td>
<td>3.36 (0.62)</td>
</tr>
<tr>
<td>No. of miscarriages</td>
<td>105</td>
<td>91</td>
</tr>
<tr>
<td>First trimester</td>
<td>101</td>
<td>86</td>
</tr>
<tr>
<td>Second trimester</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 2. Prospective pregnancy outcome amongst women with recurrent miscarriage. PCO = polycystic ovaries.
retardation of endometrial development in the luteal phase (Okon et al., 1998) and (ii) future miscarriage (Tulppala et al., 1993). However, the results of the latter study are based on fewer than 10 pregnancies. Further studies are warranted to explore the effect of androgens, both ovarian and adrenal, on the endometrium and their relationship to adverse pregnancy outcome.

This large data set has allowed us to examine the relationship between polycystic ovarian morphology and recurrent miscarriage. Although PCO are found significantly more often amongst women with recurrent miscarriage than in the normal population, ovarian morphology itself is not a risk factor for future pregnancy loss amongst women with recurrent miscarriage conceiving spontaneously. The search for a specific endocrine abnormality that can divide women with PCO into those with a good and those with a poorer prognosis for a future successful pregnancy continues.

References


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