Prevalence of polycystic ovaries in women with self-reported symptoms of oligomenorrhoea and/or hirsutism: Northern Finland Birth Cohort 1966 Study


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BACKGROUND: The aim of this study was to investigate the prevalence of polycystic ovaries (PCO) among women with self-reported oligomenorrhoea and/or hirsutism and to see whether women with symptoms and PCO have less favourable levels of biochemical markers than controls or women with symptoms and normal ovaries.

METHODS: The ultrasonographic ovarian morphology and the hormonal and metabolic profile of female cases with self-reported symptoms typical of polycystic ovary syndrome (PCOS) (n = 196) and asymptomatic controls (n = 67) at the age of 31 years were examined in a general population-based Northern Finland Birth Cohort 1966.

RESULTS: The prevalence of PCO (37.3 versus 18.2%; P = 0.004) was significantly higher in the cases (oligomenorrhoea and/or hirsutism) than in the controls. PCO morphology was detected in 18.4% of those who reported only hirsutism, in 47.9% of those reporting only oligomenorrhoea, and in 70.4% of those reporting both symptoms. In the cases with PCO compared to (i) the controls and (ii) the cases without PCO, body mass index (P = 0.026 and P = 0.011), ovarian volume [right P = 0.001, left P = 0.208 (non-significant) and right P < 0.001, left P = 0.022], mean follicle number (P < 0.001 and P < 0.001), testosterone (P = 0.063 and P = 0.029), free androgen index (P = 0.007 and P = 0.013) and insulin (P = 0.033 and P = 0.040) were higher, and sex hormone-binding globulin (P = 0.039 and P = 0.068) and glucose:insulin ratio (P = 0.060 and P = 0.054) lower. Cases with PCO also had higher waist:hip ratio (P = 0.011), infertility rate (P = 0.005) and glucose (P = 0.045) and lower insulin-like growth factor-binding protein-1 (P = 0.012) than controls. The clinical, hormonal and metabolic characteristics did not differ significantly between cases without PCO and controls with the exception of infertility rate, which was significantly higher in the cases without PCO (26.4 vs. 10.0%; P = 0.009).

CONCLUSIONS: In a general population, women with symptoms of oligomenorrhoea and/or hirsutism more often have PCO than asymptomatic women. Levels of biochemical and clinical markers in symptomatic women with PCO differed from and were less favourable than those in symptomatic women without PCO or asymptomatic women, implying an increased risk for health.

Key words: cohort/hirsutism/oligomenorrhoea/polycystic ovaries/ultrasound

Introduction

Polycystic ovary syndrome (PCOS) reflects multiple potential aetiologies and variable clinical presentations. In previous studies, polycystic ovaries (PCO) in ultrasonography have been seen in 92% of women with idiopathic hirsutism, 87% of women with oligomenorrhoea (Adams et al., 1986), 21–23% of randomly selected women (Clayton et al., 1992; Farquhar et al., 1994), 14–23% of regularly menstruating healthy women (Polson et al., 1988; Koivunen et al., 1999) and in 17% of women participating in routine Pap (Papanicolaou) smear
Materials and methods

Study population

The population derives from the Northern Finland Birth Cohort 1966 (NFBC 1966) followed since fetal period until the age of 31 years (Rantakallio, 1988; Figure 1). In 1966, 5889 females were born alive. In 1997–1998, 5687 of them were alive and traced for the 31 year follow-up study when a postal questionnaire including questions about hirsutism and oligomenorrhoea was sent to all women. The questions were: (1) Is your menstrual cycle often, over twice a year, more than 35 days? and (2) Do you have excessive growth of body hair? Of women who returned the questionnaire, with informed consent \( n = 4523 \), 24\% reported symptoms of hirsutism and/or oligomenorrhoea, 10.4\% reported hirsutism alone, and 3.4\% reported both symptoms. Women still living in the original target or capital city area \( n = 4074 \) were invited for a clinical examination. Of these, 3077 women filled in the postal questionnaire on PCOS-typical symptoms, and gave a blood sample \( n = 344 \). A total of 196 cases and 67 controls attended the ultrasound examination. Of these, pregnant women \( n = 12 \) were excluded. In the analyses of glucose and insulin, those who had not fasted before giving the blood sample \( n = 6 \) were excluded. Those who attended the ultrasound examination filled in an additional questionnaire with specific questions about reproductive health. This study has been approved by the ethical committee of the University of Oulu.

Clinical features

Body mass index (BMI) was calculated as the ratio of weight (kg) and height squared (m\(^2\)). Waist:hip ratio (WHR) was defined as the ratio between the circumference of the waist (at a level midway between the lowest rib margin and the iliac crest) and the hip (at the widest trochanters) using ongoing quality control (Laitinen et al., 2004). The questionnaire at the ultrasound examination included a question asking whether the attendee had ever had acne problems, and acne was also reported if it was observed at the examination. The postal questionnaire included the following questions about infertility, miscarriages and pregnancies: ‘Has infertility ever been a problem to you?’ (1) yes (earlier or at this moment), (2) no, (3) I do not know because I have not tried to get pregnant.’ ‘If you have been pregnant, how many times have you had (1) miscarriages, (2) abortions, (3) extrauterine pregnancies, (4) deliveries?’

Blood samples and laboratory methods

Blood samples were drawn in the morning (08:00–11:00) after an overnight fast. The samples could not be timed to the woman’s menstrual cycle for practical reasons. Blood glucose samples were stored at 4°C and analysed the same day. Serum insulin samples were
stored at −20°C and were analysed within 7 days of sampling. Testosterone, sex hormone-binding globulin (SHBG), insulin-like growth factor-binding protein-1 (IGFBP-1) and LH samples were stored at −80°C until analysed. Free androgen index (FAI) was calculated according to the equation testosterone×100/SHBG.

Concentrations of SHBG and LH were analysed by fluororimunoassay (Wallac Ltd, Finland), testosterone by automated chemiluminescence system (Ciba-Corning ACS-180; USA), insulin by radioimmunoassay (Pharmacia Diagnostics, Sweden), IGFBP-1 by immunoenzymometric assay (Medix Biochemica, Finland) and blood glucose by a glucose dehydrogenase method (Granutest 250; Diagnostica Merck, Germany). The intra- and inter-assay coefficients of variation were 1.3 and 5.1% for SHBG, 4.9 and 6.5% for LH, 4.0 and 5.6% for testosterone, 5.3 and 7.6% for insulin, 3.4 and 7.4 for IGFBP-1 and 1.5 and 2.3% for blood glucose.

Transvaginal ultrasound

Transvaginal ultrasonography of the ovaries was carried out to measure ovarian volumes and the number of follicles (Toshiba SSA-270A; Toshiba Co., Tokyo) using a 6 MHz curvilinear transvaginal probe, PVF-651VT, with a scanning angle of 120°. Ultrasound examinations were performed by two investigators (S.A. and R.K.) on period day 3–5, or if amenorrhoea was present, at any time. Polycystic ovaries were defined as ≥10 follicles 2–8 mm in diameter in one plane of either ovary in association with increased and/or hyperechogenic ovarian stroma, evaluated visually (Adams et al., 1986). Volume determinations were carried out using the formula for the volume of an ellipsoid: $\frac{4}{3}\pi\times\text{length}\times\text{width}\times\text{thickness}$.

Statistical analysis

Results are expressed as percentages for categorical variables and means and 95% confidence intervals or medians and interquartile ranges (where distribution persisted skewed after log-transformation) for continuous variables. Overall significance of differences between the three groups (cases with PCO, cases with normal ovaries, controls) by one-way ANOVA or Kruskal–Wallis test was analysed first. Because of our hypothesis and the many significant differences found, this was followed by paired tests between cases with PCO and controls, cases with normal ovaries and controls, and cases with PCO and cases with normal ovaries. Student’s two-tailed t-test was used to test the statistical significance of differences between groups of normally distributed variables. Log-transformation was used where needed to normalize the distribution. The Mann–Whitney U-test was used for variables with distributions that were skewed even after log-transformations. Statistical analysis of frequency differences between groups was evaluated by using Pearson’s $\chi^2$-test for independence. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 11.5 for Windows (Statistical Package for Social Science, Inc., USA). Positive and negative predictive values of symptoms of oligomenorrhoea and hirsutism were calculated. In this study, positive predictive value is the probability that an individual actually has PCO given that she has symptoms of PCOS (oligomenorrhoea and hirsutism). Negative predictive value is the probability that an individual truly has normal ovaries given that she has no symptoms of PCOS.

Results

Ultrasonographic findings

The prevalence of PCO was significantly higher among cases than controls (69/185, 37.3% versus 12/66, 18.2%; $P = 0.004$). Figure 2 shows the prevalence of PCO in ultrasonographic examination for all cases, controls, those who reported hirsutism only, oligomenorrhoea only, and both symptoms. Error bars represent 95% confidence intervals.

Clinical and biochemical characteristics

Clinical and biochemical characteristics of cases according to ultrasonographic finding of ovaries (PCO or normal) and controls are presented in Table I. BMI, WHR, infertility rate, ovarian volume (right), mean follicle number, FAI, insulin and glucose were significantly higher while SHBG and IGFBP-1 were lower among the cases with PCO as compared with controls. Testosterone tended to be higher ($P = 0.063$) and glucose/insulin lower ($P = 0.060$) in cases with PCO compared with controls. Rate of acne and miscarriages, LH and the number of pregnancies did not differ significantly between the groups. Cases with normal ovaries did not differ from the controls with the exception of infertility rate, which was significantly higher in cases with normal ovaries ($P = 0.009$). Cases with PCO had significantly higher BMI, ovarian volume, mean follicle number, testosterone, FAI and insulin, and tended to have lower SHBG ($P = 0.068$) and glucose/insulin ($P = 0.054$) than cases with normal ovaries. WHR, infertility, miscarriage or acne rate, number of pregnancies, LH, IGFBP-1 and glucose did not differ between cases with PCO and cases with normal ovaries.

Representativeness of study participants

The representativeness of study participants was checked both among the cases and the controls. There were no statistically significant differences in BMI, WHR, glucose, insulin, testosterone and IGFBP-1 values between the subjects who attended the gynaecological ultrasound examination and those who did not attend. Those who participated tended to have lower SHBG than non-participants, the result being borderline significant in controls (controls median 55.00 for participants versus 63.45 nmol/l for non-participants, Wilcoxon test $P = 0.051$; cases 53.10 for participants versus 55.25 nmol/l for non-participants, $P = 0.16$).

Figure 2. Polycystic ovaries (%) in controls, all cases, those who reported hirsutism only, oligomenorrhoea only, and both symptoms. Error bars represent 95% confidence intervals.
Discussion

Our previous study of this birth cohort (Taponen et al., 2003) showed that simple, symptom-based questions are useful in identifying women with an endocrine profile typical of PCOS and insulin resistance. In this study, we have demonstrated that the prevalence of PCO in ultrasonography among women with self-reported symptoms of hirsutism and/or oligomenorrhoea in the general population-based NFBC 1966 was significantly higher, double (37 versus 18%) compared with women who did not report these symptoms. The prevalence of PCO was even higher (70%) in women who reported both hirsutism and oligomenorrhoea.

To our knowledge, this is the first general population-based study on self-reported symptoms of PCOS and associated ultrasound findings and biochemical changes. The greatest strength of this study is the large and stable general female cohort followed longitudinally since the fetal period (Rantakallio, 1988). No notable differences were found in clinical or biochemical parameters between attendees and non-attendees of ultrasonographic examination. Therefore there seems to be no substantial outcome-related selection bias and the subjects who attended the gynaecological ultrasound examination represent well the entire case–control population in that sense.

The prevalence of PCOS is estimated to be 4–12% (Dunaif and Thomas, 2001). Among unselected women, the prevalence of PCOS defined histopathologically is 1.4–3.5% (Goldzieher, 1981), defined by biochemical parameters 2.5–7.5% (Futterweit and Mechanick, 1988; Polson et al., 1988), by the presence of oligomenorrhoea and biochemical hyperandrogenism 7% (Diamanti-Kandarakis et al., 1999) and by oligo-ovulation and clinical hyperandrogenism 4% (Knochenhauer et al., 1998).

In our study, the prevalence of PCO among women who reported symptoms of oligomenorrhoea and/or hirsutism (37%) was lower than reported previously in hospital-based studies among women with these symptoms (~70%) (Adams et al., 1986; Hull, 1987; Franks, 1989; O’Driscoll et al., 1994).

### Table I. Clinical and biochemical features in symptomatic cases with polycystic ovaries (PCO), cases with normal ovaries (NO) and controls

<table>
<thead>
<tr>
<th></th>
<th>Symptoms and polycystic ovaries (cases + PCO)</th>
<th>Symptoms and normal ovaries (cases + NO)</th>
<th>Controls</th>
<th>Cases + PCO versus controls</th>
<th>Cases + NO versus controls</th>
<th>Cases + NO versus cases + PCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>67 (25.9, 26.1)</td>
<td>117 (24.1, 24.9)</td>
<td>66 (24.1, 25.0)</td>
<td>0.026 NS</td>
<td>0.011 NS</td>
<td>0.011 NS</td>
</tr>
<tr>
<td>WHR</td>
<td>59 (0.79, 0.83)</td>
<td>95 (0.79, 0.81)</td>
<td>55 (0.76, 0.79)</td>
<td>0.011 NS</td>
<td>0.005 NS</td>
<td>0.009 NS</td>
</tr>
<tr>
<td>Infertility (%)</td>
<td>64 (29.7)</td>
<td>110 (26.4)</td>
<td>60 (10.0)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Acne (%)</td>
<td>67 (16.4)</td>
<td>117 (10.3)</td>
<td>66 (18.2)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Miscarriages (%)</td>
<td>67 (19.4)</td>
<td>117 (23.9)</td>
<td>66 (28.8)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ovarian volume (cm³)</td>
<td>Right (7.8)</td>
<td>78 (5.40)</td>
<td>58 (5.53)</td>
<td>0.001 NS</td>
<td>NS</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Left (6.62)</td>
<td>78 (5.49)</td>
<td>58 (5.92)</td>
<td>NS</td>
<td>NS</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Mean follicle number in one plane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right (67)</td>
<td>9.39 (8.83, 9.94)</td>
<td>109 (5.06)</td>
<td>(4.70, 5.41)</td>
<td>5.05 (4.42, 5.67)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td></td>
<td>Left (67)</td>
<td>9.16 (8.68, 9.65)</td>
<td>109 (5.42)</td>
<td>(5.05, 5.80)</td>
<td>5.23 (4.60, 5.86)</td>
<td>&lt; 0.001 NS</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>68 (2.21)</td>
<td>114 (1.87)</td>
<td>66 (1.88)</td>
<td>0.063 NS</td>
<td>NS</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>Right (1.96, 2.47)</td>
<td>46.5 (1.74, 1.99)</td>
<td>114 (51.0)</td>
<td>(36.0, 66.7)</td>
<td>51.1 (37.5, 72.0)</td>
<td>0.039 NS</td>
</tr>
<tr>
<td></td>
<td>Left (32.0, 60.5)</td>
<td>5.88 (4.74, 7.01)</td>
<td>114 (4.44)</td>
<td>(3.76, 5.11)</td>
<td>4.02 (3.38, 4.67)</td>
<td>0.007 NS</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>68 (5.11)</td>
<td>113 (4.80)</td>
<td>64 (5.40)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Right (3.68, 9.70)</td>
<td>113 (3.25, 8.55)</td>
<td>64 (3.73, 7.55)</td>
<td>0.012 NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Left (3.03, 4.51)</td>
<td>4.77 (3.92, 5.47)</td>
<td>53 (4.18, 5.94)</td>
<td>0.033 NS</td>
<td>NS</td>
<td>0.040</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>63 (9.61)</td>
<td>114 (7.84)</td>
<td>65 (7.65)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Right (7.98, 11.2)</td>
<td>4.98 (7.22, 8.46)</td>
<td>65 (6.99, 8.31)</td>
<td>4.83 (4.72, 4.94)</td>
<td>0.045 NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Left (4.87, 5.09)</td>
<td>4.91 (4.78, 5.04)</td>
<td>65 (4.72, 4.94)</td>
<td>0.060 NS</td>
<td>NS</td>
<td>0.054</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>63 (0.63)</td>
<td>114 (0.70)</td>
<td>65 (0.70)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Right (0.57, 0.69)</td>
<td>114 (0.66, 0.73)</td>
<td>65 (0.64, 0.75)</td>
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</tbody>
</table>

Values are expressed as means (95% CI), medians (25th and 75th quartiles) for SHBG and LH, or percentages. Significance was tested with Student’s two-tailed t-test (using log-transformations to normalize distributions) or non-parametric Mann–Whitney–U test (for variables still skewed after log-transformation) and Pearson’s χ²-test for categorical variables.

BMI = body mass index; WHR = waist:hip ratio; SHBG = sex hormone-binding globulin; IGFBP-1 = insulin-like growth factor binding protein-1; NS = not significant.
However, this difference is not surprising given that our subjects were defined on the basis of self-reported symptoms unlike in other studies with symptomatic clinic-based patients. In one study of a volunteer population of young women aged 18–25 years, the prevalence of PCO was as high as 33% (Michelmore et al., 1999). Previous studies have reported that 92% of women with idiopathic hirsutism and 87% of women with oligomenorrhea have PCO (Adams et al., 1986) and that, of women attending a joint skin/endocrine clinic with hirsutism and/or androgenic alopecia, 81% of those with erratic cycles and 52% of those with normal cycles had PCO (O’Driscoll et al., 1994).

Our present general population-based study confirmed that, of women who report both hirsutism and oligomenorrhea, 70% have PCO. We have shown in our previous study that women with both symptoms have the most severe changes in hormonal profile (Taponen et al., 2003). We found that, of those who reported only oligomenorrhea, 48% had PCO and of those who reported only hirsutism, 18% had PCO. Supporting these results, the group with oligomenorrhea alone seemed to represent all cases (hirsutism and/or oligomenorrhea) with respect to hormonal profile and those with hirsutism alone were closer to the control group by hormonal findings (Taponen et al., 2003). The positive predictive value of oligomenorrhea and hirsutism was 70.4% and the negative predictive value 81.8%, further supporting the finding that these symptoms of PCOS are indicative of the morphology of the ovaries. The percentage of PCO in the group with hirsutism only was indistinguishable from that of the controls, which is partly explained by the symptom of hirsutism being truly subjective. This study showed that the prevalence of PCO in asymptomatic women is 18%, which confirms the results of previous clinic-based patient studies (Polson et al., 1988; Koivunen et al., 1999). Our results provide even more support to previous studies when one considers the fact that we excluded probably the most severe cases because of their use of oral contraceptives.

In our study population, cases with PCO had significantly higher BMI, WHR rate of infertility, ovarian volume, mean follicle number, FAI, insulin and glucose, lower SHBG and IGFBP-1 and a tendency to higher testosterone and lower glucose/insulin than controls. Compared with cases with normal ovaries, cases with PCO had higher BMI, ovarian volume, mean follicle number, testosterone, FAI and insulin and a tendency to lower SHBG and glucose/insulin. These results agree with our hypothesis that those with both symptoms and PCO have more marked biochemical changes than controls or cases with normal ovaries. Cases with normal ovaries but with symptoms of oligomenorrhea and/or hirsutism did not differ from the controls except in infertility rate, which was significantly higher in cases with normal ovaries. Cases with normal ovaries probably include those whose symptoms are mild, especially concerning hirsutism, and whose symptoms would not be classified as hirsutism if a clinical scale were applied. BMI was higher in cases with PCO than in cases with normal ovaries. Thus, cases with PCO form a high risk group for the development of type 2 diabetes, and these women should also receive lifestyle counselling from their physicians aimed at optimizing body weight. In our study, features of metabolic syndrome were studied in young adults, while clinical manifestations would usually appear later. Thus ongoing surveillance of this group of women will be important as they reach middle age.

In conclusion, women with symptoms of oligomenorrhea and/or hirsutism have more PCO than asymptomatic women and, of those with both symptoms, 70% have PCO. Women with symptoms and PCO have clinical and biochemical characteristics that are distinguishable from controls and women with symptoms and normal ovaries. Hence, ultrasound examination of the ovaries in women with oligomenorrhea and hirsutism seems to be a valuable tool in detecting those with the most severe biochemical findings and hence the greatest risk of adverse future health outcomes.

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