The impact of self-reported oligo-amenorrhea and hirsutism on fertility and lifetime reproductive success: results from the Northern Finland Birth Cohort 1966

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STUDY QUESTION: To what extent do self-reported oligo-amenorrhea and hirsutism affect reproductive performance (childlessness, age at first delivery, family size and miscarriage rates)?

SUMMARY ANSWER: At the age of 44, among women with both self-reported oligo-amenorrhea and hirsutism the prevalence of childlessness was not significantly different from non-symptomatic women but they had a smaller family size than non-symptomatic women.

WHAT IS KNOWN ALREADY: Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by oligo-amenorrhea or amenorrhea, hyperandrogenism and hirsutism and it is the most frequent cause of anovulatory infertility, but there are few studies on the reproductive capacity of women with PCOS. In our previous population-based cohort study the women with self-reported oligo-amenorrhea and hirsutism were found to have more infertility problems and smaller family size than non-symptomatic women at the age of 31.

STUDY DESIGN, SIZE, DURATION: A prospective population-based cohort study. The population of the study is derived from the prospective Northern Finland Birth Cohort 1966 (NFBC1966), comprising all expected births from the year 1966 in the two northern-most provinces of Finland (n = 12 058). Of them, 5889 were females. Enrollment in this database begun at the 24th gestational week and so far data have been collected from the subjects at the ages of 1, 14 and 31 years.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A postal questionnaire including questions about oligo-amenorrhea and hirsutism was sent to all women at the age of 31 (n = 5608, response rate 81%, n = 4535) and a clinical examination was performed (attendance rate 76.5%). Those who reported both hirsutism and oligo-amenorrhea were defined as women with both symptoms (n = 153). Data on pregnancies/deliveries were obtained from the Finnish Medical Birth Register (FMBR) in 2010 when the women were 44 years old.

MAIN RESULTS AND THE ROLE OF CHANCE: Women with both symptoms had delivered at least one child as often as non-symptomatic women [75.2 versus 79.0%, adjusted odds ratio (OR) 0.86, 95% confidence intervals (CI) 0.57–1.30], were of similar age [mean (SD)] at first delivery [27.7 (4.81) versus 27.3 (4.71)] and had similar incidence of miscarriages. However, non-symptomatic women had more often ≥2 deliveries (61.6 versus 52.9%, adjusted OR 0.70, 95% CI 0.49–1.00, P = 0.048) and had larger family size [mean (SD)] [2.4 (1.4) versus 1.9 (0.8), P < 0.001]. Women with both symptoms had been treated more often for infertility than non-symptomatic women (6.1 versus 2.4%, adjusted OR 2.74, 95% CI 1.14–6.60, P = 0.024).
Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder suffered by 5–10% of women in reproductive age (Dahlgren et al., 1992; Franks, 1995). The etiology of PCOS remains unknown, though there is strong evidence of genetic component of this syndrome (Legro et al., 1998; Franks, 2008). PCOS is characterized by oligo-menorrhea or amenorrhea, hyperandrogenism and hirsutism (Franks, 1995). Insulin resistance, obesity and anovulatory infertility are also common symptoms among PCOS-symptomatic women (Roos et al., 2011).

As PCOS is a heritable syndrome and is associated with infertility problems, it would be expected that over time the prevalence of this syndrome should have diminished. Yet, it is still a common disorder in developed countries. It has been suggested that the phenotypic characteristics of women with this disorder, particularly hyperandrogenism, insulin resistance and impairment of pancreatic β cell function, may confer a fertility advantage in contemporary or pre-industrial societies subject to chronic and seasonal food shortage (Azziz et al., 2011; Corbett and Morin-Papunen, 2013). Conversely, obesity is present in 30–75% of women with PCOS (Ehrmann, 2005; Liang et al., 2011; Moran et al., 2013), and obese women experience decreased ovulation and pregnancy rates compared with lean women with PCOS (Galtier-Dereure et al., 1997; Baghdadi et al., 2012).

This is one of the few studies in which the impact of PCOS symptoms on lifetime reproductive success can be measured. In the present study, we took advantage of a large cohort of women at the end of their reproductive life span, as they turned 44 years in 2010. The primary aim of this study was to investigate the effects of symptoms of PCOS on reproductive performance (age at first delivery, family size and miscarriage rates) and to investigate whether women with self-reported oligo-menorrhea and hirsutism have a decreased family size and/or are more often childless than non-symptomatic women.

Materials and Methods

The population is derived from the prospective Northern Finland Birth Cohort 1966 (NFBC 1966), comprising all expected births from the year 1966, in the two northernmost provinces of Finland (n = 12,058) (Rantakallio, 1988). Of them, 5889 were females. Enrollment in this database begun at the 24th gestational week and so far data on the subjects has been collected at the ages of 1, 14 and 31 years.

At the age of 31, 5608 of these women received, and 4535 (81%) of them answered a questionnaire. The questions considering hirsutism and oligo-menorrhea were as follows: (i) is your menstruation cycle >35 days more than twice a year? and (ii) do you have excessive body hair? Information on infertility problems was inquired as follows: have you been ever treated for infertility? Of the women who were included in the final study population 24.8% reported hirsutism or/and oligo-menorrhea, 10.9% hirsutism alone, 10.5% oligo-menorrhea alone and 3.4% reported both symptoms. Women with both oligo-menorrhea and hirsutism were classified as ‘women with both symptoms’. The women with only one symptom were excluded from the analyses. The reference group (non-symptomatic women) included all subjects without any symptom of PCOS (Rantakallio, 1988; Taponen et al., 2004; Koivunen et al., 2008).

Of the women who completed the questionnaire, 4074 women living in Northern Finland or in the metropolitan area were invited to a clinical examination, which 3115 (76.5%) women attended. Clinical examination included anthropometric measures, blood pressure, some blood tests, physical performance tests, skin prick allergy tests, spirometry and data from questionnaires completed in the research center or at home. Examination was performed by nurses in local health centers. Body mass index (BMI) at the age of 31, was calculated as the ratio of weight (kg) and height squared (m²) obtained from the clinical examination. BMI data were available for 2086 non-symptomatic women and 90 women with both symptoms. The study population was divided into four categories: underweight (BMI < 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²) and obese (> 30.0 kg/m²), according to the criteria of World Health Organization (WHO, 2006). Subjects who were pregnant at the time of clinical examination (n = 357) were excluded from BMI calculations.

Data on women’s pregnancies and deliveries up until the end of 2010 were obtained from the Finnish Medical Birth Register (FMBR). The FMBR, active since 1987, is currently run by the National Institute for Health and Welfare (THL). For each delivery in Finland, a structured form for FMBR is completed by the delivery hospital, including demographic and health data of the mother, the course and complications of the pregnancy and the delivery, and the perinatal health of the new-born at the age of 7 days. As some birth data are
missing in the FMBR, the register is supplemented with data compiled by the Population Register Center on live births (and with data compiled by Statistics Finland on stillbirths and deaths during the first week of life). After these additions, the registration of birth is 100%.

This study was approved by the ethical committee of the University of Oulu.

The flowchart of the study is presented in Figure 1.

Statistical methods
The χ² test was used to compare categorical variables (at least one delivery, at least two deliveries, over 35 years old at the time of first delivery and at least one miscarriage) between the study groups. The distributions of continuous variables were normal; therefore comparisons of continuous variables (number of deliveries and mother’s age at the time of first delivery) were made by using Student’s t-test. Univariate and multivariate logistic regression models were employed to estimate the association of oligo-amenorrhea and hirsutism with reproductive outcome. The results are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). The data were adjusted for the following variables: consumption of alcohol (g/day), smoking (no or occasionally/yes), BMI (as continuous variable) and socioeconomic status (white collar, blue collar, workers, others, farmers). Statistical analyses were performed by using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). The number of individuals in separate analyses varies due to non-response to some items. A P-value of <0.05 was considered significant.

Results
Number of deliveries
At the age of 44, women with both symptoms had given birth to at least one child as often as non-symptomatic women (adjusted OR 0.86, 95% CI 0.57 – 1.30, P = 0.472) (Table I). However, non-symptomatic women had two or more deliveries more often than women with both symptoms (adjusted OR 0.70, 95% CI 0.49 – 1.00, P = 0.048) (Table I). Moreover, women with both symptoms had smaller family size than non-symptomatic women [2.4 (1.4) versus 1.9 (0.8), P < 0.001] (Table I).

Age at delivery
Women with both symptoms delivered their first child at a similar age as non-symptomatic women and at late maternal age (first delivery at the age of 36 or later) as often as the non-symptomatic women (7.8 versus 7.0%, P = 0.738) (Table I).

Miscarriages and infertility
Women with both symptoms had a similar cumulative incidence of at least one miscarriage as non-symptomatic women (Table I), but had been treated more often for infertility than non-symptomatic women (6.1 versus 2.4%, crude OR 2.61, 95% CI 1.17 – 5.83, P = 0.019; adjusted OR 2.74, 95% CI 1.14 – 6.60, P = 0.024).

Reproductive performance in different BMI groups
At the age of 44, women with both symptoms had delivered at least one child as often as the non-symptomatic women, when compared with same BMI group (Table II). Normal weight [1.9 (0.8) versus 2.4 (1.4), P = 0.047] and obese women [1.7 (0.7) versus 2.6 (1.6), P = 0.017] with both symptoms of PCOS had significantly fewer deliveries compared with non-symptomatic normal weight and obese women, respectively (Table II).

Age at marriage (asked at the age of 31)
Women with both symptoms got married 0.7 years earlier than the non-symptomatic women, although the difference did not reach statistical significance [24.0 (3.4) versus 24.7 (3.5) years, P = 0.098].

Discussion
Our data from the NFBC 1966 gave us an excellent opportunity to investigate the relationship between PCOS symptoms and fertility in a large cohort of Caucasian women who turned 44 years in 2010. Our main findings were that women with both symptoms had delivered their first child at similar age as non-symptomatic women, and that they delivered at least one child as often as non-symptomatic women. At the age of 44, however, women with both symptoms had a smaller family size and had less often delivered two or more children than non-symptomatic women. Obesity at the age of 31 decreased family size in this group.

Figure 1 Flowchart of the study population. Data on women’s pregnancies and deliveries until the end of 2010 were obtained from the Finnish Medical Birth Register.
Strengths and limitations of study

Our study is by far the largest general population-based study in which a self-reported symptom-based approach with information on both oligo-amenorrhea and hirsutism has been used to investigate associations between self-reported symptoms of PCOS and reproductive performance in women until the end of their reproductive lifespan. Self-reporting may also be a limitation of the study while the diagnosis of oligo-amenorrhea and hirsutism was based on a questionnaire, making possible a bias in reporting symptoms. Hirsutism, in particular, is the most obviously subjective symptom and is influenced by differing perceptions of excess body hair, and is therefore easily over-reported. However, we have previously shown that self-reported oligo-amenorrhea and hirsutism can distinguish most women with the typical endocrine and metabolic profiles of PCOS (Taponen et al., 2003, 2004). Moreover, the presence of both oligo-amenorrhea and hirsutism is consistent with both the NIH and the Rotterdam criteria for diagnosis of PCOS (Taponen et al., 2003, 2004; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The PCOS-symptomatic women got married at a slightly younger age than the non-symptomatic women. However, the mean difference (0.4 years) between the study groups is small and in the direction of overestimating reproductive success in women with PCOS, and is therefore unlikely to detract from the significance of the observed difference in reproductive outcome. Our study based on a questionnaire is likely to have included also women with relatively mild symptoms of PCOS, possibly decreasing the differences between the study groups. Lastly, only the women who had delivered at least once were recorded in the FMBR, thus excluding from the study those who had...

Table I  Deliveries and mother’s age at first delivery in the symptomatic and non-symptomatic women

<table>
<thead>
<tr>
<th></th>
<th>Non-symptomatic women</th>
<th>Oligo-menorrhea and hirsutism</th>
<th>P-value (both symptoms versus non-symptomatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2625–3340</td>
<td>115–153</td>
<td></td>
</tr>
<tr>
<td>At least one delivery (n/%)</td>
<td>2639/79.0</td>
<td>115/75.2</td>
<td>0.254</td>
</tr>
<tr>
<td>Crude OR (95% CI)</td>
<td>1.00</td>
<td>0.80 (0.55–1.17)</td>
<td>0.255</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.00</td>
<td>0.86 (0.57–1.30)</td>
<td>0.472</td>
</tr>
<tr>
<td>2 Deliveries or more (n/%)</td>
<td>2059/61.6</td>
<td>81/52.9</td>
<td>0.031</td>
</tr>
<tr>
<td>Crude OR (95% CI)</td>
<td>1.00</td>
<td>0.70 (0.51–0.97)</td>
<td>0.031</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>1.00</td>
<td>0.70 (0.49–1.00)</td>
<td>0.048</td>
</tr>
<tr>
<td>Number of deliveries mean (SD)</td>
<td>2.4 (1.4)</td>
<td>1.9 (0.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Mother’s age at the time of first delivery mean (SD)</td>
<td>27.3 (4.71)</td>
<td>27.7 (4.81)</td>
<td>0.383</td>
</tr>
<tr>
<td>Over 35 years old at the time of first delivery (n/%)</td>
<td>185/7.0</td>
<td>9/7.8</td>
<td>0.738</td>
</tr>
<tr>
<td>At least one miscarriage (n/%)</td>
<td>611/23.3</td>
<td>29/25.2</td>
<td>0.630</td>
</tr>
</tbody>
</table>

Univariate and multivariate logistic regression analysis was employed with ‘at least one delivery’ and ‘two deliveries or more’ as the outcome variables and ‘oligo-amenorrhea and hirsutism’ as the predictive variable.

aThe number of non-symptomatic and symptomatic women in separate analyses varies due to non-response to some items.

bAdjusted for consumption of alcohol (g/day), smoking, BMI and socioeconomic status.

Table II  Deliveries in different BMI groups in the symptomatic and non-symptomatic women

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>No deliveries (n/%)</th>
<th>At least one delivery (n/%)</th>
<th>P-value (compared with same BMI group in non-symptomatic)</th>
<th>Number of deliveries, mean (SD)</th>
<th>P-value (compared with same BMI group in non-symptomatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>74</td>
<td>17/23.0</td>
<td>57/77.0</td>
<td>2.3 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>1429</td>
<td>241/16.9</td>
<td>1188/83.1</td>
<td>2.4 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>489</td>
<td>90/18.4</td>
<td>399/81.6</td>
<td>2.5 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>179</td>
<td>38/21.2</td>
<td>141/78.8</td>
<td>2.6 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligo-menorrhea and hirsutism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>38</td>
<td>10/26.3</td>
<td>28/73.7</td>
<td>0.129</td>
<td>1.9 (0.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Overweight</td>
<td>25</td>
<td>2/8.0</td>
<td>23/92.0</td>
<td>0.283</td>
<td>2.2 (0.8)</td>
<td>0.381</td>
</tr>
<tr>
<td>Obese</td>
<td>28</td>
<td>7/25.0</td>
<td>21/75.0</td>
<td>0.628</td>
<td>1.7 (0.7)</td>
<td>0.017</td>
</tr>
</tbody>
</table>
experienced miscarriages and/or infertility treatments but did not have a live birth. This feature could potentially decrease the differences in incidence of miscarriages and/or infertility treatment between symptomatic and non-symptomatic subjects. BMI was measured once at the age of 31 and may not reflect levels of obesity which pertained throughout the reproductive period.

Comparison with other studies
To our knowledge, this is the first study investigating the fertility of women with self-reported oligo-amenorrhea and hirsutism until the end of their reproductive life. We found that women with self-reported oligo-amenorrhea and hirsutism had delivered their first child at similar age as non-symptomatic women and they delivered at least one child as often as non-symptomatic women. There are only few studies considering the reproductive performance of women with PCOS. One study, in which the diagnosis of PCOS included transvaginal ultrasound imaging of the ovaries, reported 91 women with PCOS and 87 healthy control women aged 35 years or more at the time of the follow-up. In that study women with PCOS had delivered at least one child as often as control women which is in line with our results (Hudecova et al., 2009). In another study, 33 women with PCOS (with proven polycystic ovarian morphology) and 132 healthy control women, aged 40–59 years, were examined. Contrary to our findings, women with PCOS in this small cohort tended to remain childless more often than did the control women (24 versus 16%), although this difference did not reach statistical significance (Dahlgren et al., 1992). That study, however, included mainly women exhibiting more severe symptoms of PCOS who were seeking infertility treatment, and thus do not necessarily represent a general population. A recent population-based cohort study compared 3787 births among women with a diagnosis of PCOS and 1191336 births among women without such a diagnosis. Women with PCOS were more likely to be nulliparous than women without symptoms (53 versus 43.8%). Unlike the present study, that study was a register based cross-sectional study, and it included only women with an established diagnosis of PCOS (Roos et al., 2011). Family size of women with symptoms of PCOS was not investigated in any of the above-mentioned studies.

Our previous study from this same study population (Koivunen et al., 2008) showed that at the age of 31, women with symptoms of PCOS had given birth successfully to 1–2 children as often as non-symptomatic women, despite suffering from infertility problems more often than non-symptomatic women. In the present study, we found that women with both symptoms had also thereafter sought infertility treatment significantly more frequently than non-symptomatic women. Previous studies, however, have displayed much higher rates for assisted reproduction in women with PCOS (Roos et al., 2011), which may be explained by the fact that PCOS-symptomatic women in the present study exhibit a much milder phenotype of the syndrome and by the fact that women who had sought fertility treatments but did not have a live birth were not registered in the FMBR. All in all, these findings suggest that the fertility of women with symptoms of PCOS can usually be restored by infertility treatment.

Nevertheless, it must be noted that women suffering from both oligo-amenorrhea and hirsutism had a slightly smaller family size than non-symptomatic women, and obese women with both symptoms had the smallest family size, in line with our previous results at the age of 31. Although the difference between women with both symptoms and non-symptomatic women (0.5 of a child) is small, it does represent, if real and sustained across generations, a selection intensity of up to 50% per generation against the phenotype. Selection intensities of this magnitude are very large in comparison with, for example the magnitude of positive selection for sickle cell heterozygosity in highly malarious areas (Bodmer, 1965).

Our previous study has shown that self-reported oligo-amenorrhea and/or hirsutism and obesity, but not overweight, had independent and adverse effects on fecundability, and women suffering from both obesity and PCOS symptoms experienced the lowest fecundability (Koivunen et al., 2008). The present study confirms this earlier result. Numerous previous studies have already shown that obesity, especially central obesity, impairs reproduction, and that intra-abdominal fat accumulation is typically increased in PCOS-symptomatic women, even independently of obesity (Davies, 2006; Rachon and Teede, 2010). In a recent meta-analysis of 15 studies, lean women with PCOS had significantly higher ovulation and pregnancy rates than obese women with PCOS (Baghdadi et al., 2012).

Importantly, we found no increased risk of miscarriage among women with both symptoms, in contrast to most previous studies suggesting a 2–5-fold risk for miscarriage among women with PCOS compared with control population. Most of these studies, however, have focused on hospital-based and obese subjects, including only women seeking infertility treatment (Sagle et al., 1988; Watson et al., 1993; Glueck et al., 1999; Wang et al., 2002). The present results confirm our previous findings in this same cohort, in which symptomatic women had similar cumulative incidence of at least one spontaneous abortion as non-symptomatic women and the number of spontaneous abortions per woman did not differ between symptomatic and non-symptomatic women (Koivunen et al., 2008). Other reported series have also noted normal early pregnancy loss rates in women with the syndrome (Dahlgren et al., 1992; Winter et al., 2002). It is important to note that we did not have data on pregnancy losses of women who did not have at least one live birth. Therefore, this result should be interpreted with caution and has to be checked in later questionnaires in this same study population.

All in all, the present findings are in line with our previous results at the age of 31 in this same cohort (Koivunen et al., 2008) and suggest that, even at more advanced age, women with both symptoms did not quite match the parity of healthy non-symptomatic women, and that infertility treatment did not always restore normal reproductive capacity in these women.

Conclusions and policy implications
In conclusion, the present study indicates that women with self-reported oligo-amenorrhea and hirsutism had their first child at the same age and were not more often childless when compared with non-symptomatic women in the same cohort. Women with both symptoms, however, had a smaller family size compared with non-symptomatic women and obese women with both symptoms had the worst prognosis as regards reproduction. This finding emphasizes the importance of lifestyle interventions to reduce the prevalence of obesity in this group of women. However, the impact of self-reported oligo-amenorrhea and hirsutism on fertility and family size was limited, suggesting that women with PCOS from infertility clinics represent a more severe phenotype than
those from the general population. Lastly, the follow-up of this cohort until age of 44 years confirmed that the results obtained at the age of 31 remain valid throughout their reproductive life.

**Authors’ roles**

A.P., S.F., A.-L.H., M.-R.J., S.C., M.V., L.M.-P. conceived and designed the study. A.B., M.V. and S.W. analysed the data and M.V., S.W., L.M.-P. and A.B. contributed to its interpretation. S.W. and M.V. drafted equally the manuscript and all authors participated in the revision process and have approved this submission for publication. A.B., M.V., S.W. and L.M.-P. had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Conflict of interest**

None of the authors has any conflict of interest to declare.

**References**


