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Prevalence of polycystic ovary syndrome in women from opposite-sex twin pairs

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Abstract

Intrauterine androgens of a male fetus may influence the female fetus in opposite sex-twin pairs. Because female intrauterine overexposure to androgens could lead to polycystic ovary syndrome (PCOS), the prevalence of PCOS should be higher in women from opposite-sex twin pairs. Therefore, the aim of the current study was to evaluate the prevalence of PCOS in women from opposite-sex twin pairs compared to women from same-sex twin pairs, sisters, and female spouses of twins. Data from 1325 monozygotic twins, 1191 dizygotic twins (711 women from same-sex twin pairs and 480 women from opposite-sex twin pairs), 745 sisters of twins and 218 spouses of male twins were evaluated. PCOS was defined as less than nine natural menstrual cycles a year combined with either hirsutism or acne. The prevalence of PCOS was compared using a chi-squared test. Binary logistic regression analyses were conducted to test for confounding effects of smoking, age and body mass index. No significant differences in PCOS prevalence were found between women from same-sex twin pairs (either monozygotic or dizygotic), opposite-sex twin pairs, sisters and spouses. The prevalence of PCOS is not different in women from opposite-sex and same-sex twin pairs, singleton sisters, or spouses. This indicates that possible androgen exposure of the female fetus, caused by a shared intrauterine environment with a male fetus, does not result in PCOS-like traits.

Introduction

There are some indicators that intrauterine androgens of a male fetus may influence females of opposite-sex twin pairs. Animal studies show that sex hormones can diffuse through the fetal membranes and the amniotic fluid and therefore are able to influence the developing fetus. Studies in mammals show even permanently altered hormone levels, reproductive organs, aggressive behaviour and susceptibility to endocrine disruption within females who were positioned between males in utero. This intrauterine effect is attributable to the transfer of testosterone from male fetuses to adjacent female fetuses [1-3]. It has been shown that intrauterine over-exposure to androgens in the non-human primate leads to female offspring with polycystic ovary syndrome (PCOS)-like traits [2,4]. In humans, females of an opposite-sex twin pair had fewer offspring and therefore a reduced lifetime fecundity in a historical data set collected from twins born in Finland between 1734 and 1888. This study suggested that females (N=31) born as part of an opposite-sex twin pair were 25% less likely to reproduce than female twins (N=35) born as part of a same-sex twin pair [5]. Acquisition of testosterone from the male co-twin was suggested as a possible cause. However, Medland et al. [6] showed that in modern populations from Australia, The Netherlands and the United States there were no reproduction differences among female twins from same-sex (N=1979) and opposite-sex (N=913) dizygotic (DZ) pairs. In all three samples, there were no differences in the number of children, age of first pregnancies, or psychological femininity between women from same-sex or opposite-sex twin pairs [6]. If women of opposite-sex twin pairs have reduced fecundity through androgen excess produced by the male co-twin and such overexposure causes PCOS like symptoms, then a higher prevalence of PCOS among the females of opposite-sex twin pairs is expected. PCOS is defined, according to the Rotterdam criteria, by at least two of the following criteria: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism (defined as acne/hirsutism or elevated serum androgen levels), or polycystic ovaries on ultrasound (defined as a volume > 10 cc or > 12 follicles smaller then 10 mm in both ovaries) [7]. For this study data on oligo- or anovulation, acne, and hirsutism are obtained by self-report. The aim of the current study was to evaluate the prevalence of PCOS in women of an opposite-sex twin cohort compared with females from same-sex twin pairs, singleton sisters, and biologically unrelated women (spouses of male twins).

Subjects and Methods

Subjects

This study is part of an ongoing twin family study on health-related behaviour in participants of The Netherlands Twin Register [8,9]. For this study, data of the 2000 survey were used (N=4228). Subjects were excluded when sufficient data on menstrual cycle, acne or hirsutism were missing (N= 749). A total of 1325 female monozygotic (MZ) twins, 1191 DZ twins (711 women from same-sex twin pairs and 480 women from opposite-sex twin pairs), 745 sisters of twins, and 218 spouses of male twins were included in the study. Twin zygosity was based on (longitudinal) questionnaire data or, when available, on DNA typing. Agreement between zygosity based on questionnaire data and zygosity based on DNA results is 96%. PCOS was defined as oligomenorrhea combined with hyperandrogenism [10]. Information about cycle irregularity, excessive hair growth, and acne was obtained from the following questions: 1) What was the number of menstrual cycles per year when not using contraception ? (Answer categories: nine or more, less then nine, less then six, two or less); 2) Do you suffer from increased hair growth? (Answer categories: yes, no); and 3) Do you suffer from acne/pimples? (Answer categories: yes, no). Furthermore, the survey provided information on date of birth, height, weight and smoking habits. Group characteristics are listed in table 1.

Statistical Analyses

We used chi-squared tests to compare the prevalence of PCOS between female MZ twins, female DZ twins, females from opposite-sex twin pairs, sisters of twins and spouses of male twins. In addition, binary logistic regression analyses were used to test for confounding effects of body mass index (BMI), age, and smoking initiation. BMI data were divided into three categories: less then 20, 20-25, and more then 25 kg/m^2. Age was put into the model as a categorical variable, with two groups: less then 30 and 30-45 yr. Women over 45 yr of age were excluded from the analyses (N = 324). From the total sample of 3479 this resulted in a sample used in these analyses of 3155 (MZ = 1176, DZ = 647, females of a dizygotic opposite-sex twin pair (DOS) = 454, sisters of a twin = 664, and spouses = 214). Smoking initiation was a dichotomous variable with two categories: yes, 1 or no, 0. Because data from twins and singleton sisters are not independent, all analyses have also been done using a random selection of just 1 person per family. This resulted in a total sample of 2343 subjects (MZ females = 783, DZ females = 449, DOS females = 427, sisters of a twin = 466, spouses = 218), after age selection a sample of 2151 remained for these analyses (MZ = 686, DZ = 406, DOS = 425, sisters of a twin = 420, spouses = 214).

Results

Characteristics of the study population are described in table 1. Mean age in the PCOS group was 2 years lower than in the non-PCOS group. BMI and smoking status did not differ between groups.

Table 1 The characteristics of the total and random study population

	PCOS	Non-PCOS	P[a]
Total population (n)	98	3381	
Age (yr)	27.1 (9.1)	30.0 (9.8)	0.005
BMI (kg/m^2)	23.0 (4.8)	22.8 (3.7)	0.645
Smoking status			
Yes	38	1435	
No	60	1944	0.466
Random selection (n)	65	2278	
Age (yr)	25.7 (8.5)	29.7 (9.6)	0.001
BMI (kg/m^2)	22.1 (4.2)	22.8 (3.7)	0.119
Smoking status			
Yes	21	972	
No	44	1305	0.095

[a] Student's t test for age and BMI or chi-squared test for smoking status.

The prevalence of PCOS in twins (MZ, DZ and DOS), their sisters, and spouses of twins is reported in table 2. A chi-squared test (p = 0.970; df = 4) showed that the PCOS prevalence between the groups did not differ significantly. When comparing only women from MZ, DZ and DOS twin pairs, these results are virtually the same (chi-squared: p = 0.948; df = 2), indicating that there are no significant differences in PCOS prevalence between these groups. Analyses done with one random person per family showed almost the same results (chi-squared: p = 0.943; df = 4). A chi-squared test for six or less or two or less menstruations per year in DOS, MZ, DZ female twins, spouses of twins and sisters of twins showed no significant differences between these groups (p = 0.278; df = 4), indicating no differences in the prevalence of severe oligo- or amenorrhea between DOS twins and the other groups.

The association between PCOS and being a female from an opposite-sex twin pair was tested in a binary logistic regression model with and without BMI, age and smoking initiation as possible confounders (table 3). Results, both in the total and in the random sample, indicate that being a female of an opposite-sex twin pair is not associated with PCOS. These results are not altered by correcting for BMI, age, or smoking status.

Table 2 The prevalence of PCOS within the different twins, their sisters and spouses

	PCOS	Non-PCOS	% PCOS
MZ twins	36	1289	2.7
Female DZ twins	21	690	3.0
Females of an opposite-sex twin	13	467	2.7
Sisters of a twin	23	722	3.1
Spouses of a twin	5	213	2.3
Total	98	3381	2.9

PCOS is defined as less then nine menstruations per year and acne or hirsutism.

Table 3 Results of the binary logistic regression analyses

	Total population (N = 3479)			Random selection (N = 2343)		
	β	OR	CI	B	OR	CI
Model 1						
Females from an opposite-sex twin pair	-0.047	0.954	0.528-1.725	0.016	1.016	0.538-1.919
Model 2						
Females from an opposite-sex twin pair	-0.037	0.963	0.531-1.750	0.014	1.014	0.534-1.926
BMI group 1	-0.056	0.946	0.557-1.605	0.027	1.027	0.549-1.926
BMI group 2	0.120	1.128	0.595-2.140	-0.201	0.818	0.353-1.892
Age <30 yr	0.486	1.626	0.683-3.873	1.050	2.858	0.677-12.068
Age 30-45 yr	0.200	1.221	0.489-3.052	0.710	2.034	0.453-9.133
Smoking inititation	-0.046	0.955	0.621-1.467	-0.278	0.757	0.442-1.297

Table 3 shows the results of the binary logistic regression analyses with PCOS as the dependant variable and being a female from an opposite-sex twin pair as the primary determinant. Model 1 indicates the crude model, model 2 is after correction for possible confounders (BMI, age and smoking initiation). BMI is divided into 3 groups (<20, 20-25, and >25 kg/m^2). Group 1 is used as reference. Age groups are: 1) < 30 yr, and 2) between 30 and 45 yr. Smoking initiation: yes, 1; no, 0. Results are shown for both the total population and a random selection of one person per family. OR, Odds ratio; CI, confidence interval.

Discussion

According to our observations, the prevalence of PCOS does not differ significantly between women from opposite-sex or same-sex twin pairs, singleton sisters of twins, and biologically unrelated women (spouses of male twins). This indicates that intrauterine hormonal environmental conditions probably do not strongly contribute to the development of PCOS, provided that there are differences between women from opposite-sex and dizygotic same-sex twin pairs in their uterine environment. With regard to the latter, solid human data are not available except for some demographic findings that suggest differences in androgen exposure [11]. If intrauterine exposure to androgens contributes to the development of PCOS, these androgens are more likely to come from the female fetus itself rather than from the male co-twin. This is compatible with the finding that PCOS is highly heritable as shown in Dutch twin families [10]. Furthermore, there is accumulating evidence for a genetic basis of PCOS [12-19]. Because offspring of PCOS mothers share some of the maternal traits, another possible source of androgens is the mother, but maternal androgen excess is unlikely to affect the fetus because excessive placental aromatase activity presents as an effective barrier [20]. Recent studies show that hyperandrogenism in women who develop PCOS may be due to polymorphisms in the sex-hormone-binding globuline (SHBG) and androgen receptor genes [21]. This underlines again the genetic component which seems most important in developing PCOS. The prevalence of PCOS in the present study is rather low compared to other countries where 6-10 % is reported [22-27]. Nevertheless, it is in accordance with another study reporting a PCOS prevalence in The Netherlands of around 3-4 % for oligomenorrhea combined with hyperandrogenism [28]. This difference in prevalence between studies may be due to characterizing the PCOS phenotype. According to the Rotterdam criteria, there are three possible polycystic ovary phenotypes: 1) oligomenorrhea and hyperandrogenism; 2) oligomenorrhea and PCOS ovaries; 3) hyperandrogenism and PCOS ovaries [7]. For this study, we have chosen the first phenotype to represent a PCOS female because ultrasound data have been shown earlier to be nonspecific, with PCOS ovaries present in as many as 20-25% of the general population [29]. Furthermore, this phenotype is shown to be highly heritable [10] and in our sample reliable ultrasound data were not available since data were collected with a mailed questionnaire. One could argue that PCOS might be difficult to diagnose with self-report data on acne, hirsutism and oligo-or amenorrhea, but studies by Taponen et al. [30,31] showed that the prevalence of PCOS was as high as 70 % in women reporting both oligo- or amenorrhea and hirsutism. The combination of these symptoms could reliably identify women with typical PCOS endocrine profiles [30,31]. Age might be a possible confounder in this study because PCOS women were significantly younger than non-PCOS women. However, the absolute difference was less than 3 years. Regression analyses showed no difference in PCOS prevalence between the different types of twins, their sisters and spouses, before and after correction for age. Although the mean BMI was normal in both groups, there were obese subjects in the study population, and therefore analyses were done with and without correction for BMI. We have shown that the PCOS prevalence in our population is independent of BMI.

We conclude that there are no indications that the prevalence of PCOS is higher in females from opposite-sex twin pairs compared with women from same-sex twin pairs, a singleton sister of a twin, and biologically unrelated women (spouses of male twins). This may indicate that possible androgen overexposure of the female fetus, caused by a shared intrauterine environment with a male fetus, does not result in PCOS-like traits.

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