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Do the Adult Daughters of PCOS Patients Develop PCOS and Is This Due to an Androgenized Uterine Environment-An Online Epidemiological Survey

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Abstract

Objectives: Several inconsistent studies have investigated whether the uterine environment of androgenized pregnant women is a risk factor for an in-utero developmental imprinted predisposition towards subsequent polycystic ovarian syndrome (PCOS) among their female offspring. These are difficult to compare due to variable parameters and subject selection criteria. Few epidemiological studies have analyzed the incidence of PCOS amongst adult daughters of PCOS affected women previously. Our study aimed to investigate risk factors relating to the development of PCOS in the female offspring of PCOS patients.

Methods: We used a questionnaire to collect a mother-to-daughter medical history and relevant information, in order to understand risk factors, which might relate to the presence of PCOS daughters of PCOS patients.

Results: Of four hundred and one responses, 131 participants were included in the final analysis. There was no statistical association with the subsequent development of PCOS amongst female offspring of women with PCOS. However, there was a significantly higher prevalence of post-term birth among PCOS mothers. Nevertheless, the major determinant of risk of subsequent incidence of PCOS amongst daughters was a higher BMI, regardless of the mothers BMI.

Conclusion: Socio-economic family influences, affecting BMI, may be the reason for any mother to daughter association with PCOS.

Keywords: Androgenism; Body mass index; Online questionnaire; Polycystic ovarian syndrome; Term of labour

Introduction

Polycystic ovary syndrome is a frequent female endocrinopathy, estimated to affect at least five percent of women during their reproductive age [1]. However, some women do not display all of the diagnostic symptoms and/or do not seek medical help, so the prevalence of PCOS may even be as high as 20% [2]. The syndrome was initially described in the 1930s by Stein and Leventhal as cystic ovaries, menstrual irregularities, hirsutism, and obesity [3]. Due to its heterogeneous nature, the exact diagnostic criteria has always been difficult and in 2003, PCOS diagnostic criteria were defined as the presence of two out of three features (after the exclusion of other pathologies); oligomenorrhoea and/or anovulation; clinical and/or biochemical hyperandrogenism; and polycystic ovaries [4].

The development of PCOS is believed to be highly influenced by environmental factors including obesity, unhealthy diet, sedentary lifestyle, inflammatory processes and infectious agents and toxins [5,6]. Furthermore, the intrauterine environment may play an important role

in the aetiology of PCOS: Both animal-based models and human clinical studies, indicate a connection between the exposure of the fetus to elevated androgen levels in utero and the occurrence of PCOS or PCOS-associated features in childhood, adolescence and adult life [7-10]: Prenatally androgenized female rodents have shown altered regulation of Gonadotropin Releasing Hormone (GnRH) neurons [7,8] and the exposure of sheep to androgens in their mid-pregnancy resulted in the reduction of the GnRH network efficiency [7].

Rhesus monkeys, subjected to androgens during pregnancy, demonstrated multi-follicular ovaries and reduced menstrual periodicity in adult life [9]. In utero, androgen, exposed animals expressed variable features of the PCOS phenotypes in adult life, depending on the time and level of exposure to androgens. Although not proven statistically, this subjectively association of an epigenetic familial trend could bring us closer to the understanding of the diversity of PCOS phenotypes and its molecular pathology. In humans, the fetus is protected against excesses of maternal testosterone by placental aromatase – that converts androgens into estrogens [7]. However, as with all biological controls, placental aromatase maybe functionally compromised and fetal androgen exposure ensues. Factors contributing to a placental failure to mount an effective barrier are:

aromatase deficiency [11], stress [9], and high insulin concentrations [12].

It has been demonstrated that women born after term, or born to malnourished mothers, showed high luteinizing hormone (LH) serum levels in adulthood [10]. Although at the very bottom end of the PCOS phenotypic spectrum, this may indicate circumstances that enable androgens to surpass natural protective mechanisms and presumably set hypothalamic responses in the developing fetus to be more androgenic. Applying this reasoning further, high testosterone levels in pregnant women with PCOS, together with insulin resistance (which is frequently a co-feature of the syndrome), may provide suitable conditions allowing for fetal androgen exposure and hence predispose female offspring to developing PCOS in adult life.

Given the capacity of body fat tissue aromatase to convert estrogens to testosterone several studies have tried to find an association between obesity, high birth weight, and the subsequent development of PCOS by female offspring. Two previous studies reported that birth weight from infants born to PCOS-affected mothers were significantly lower in comparison of the control group [13,14]. However, the opposite findings have also been reported [15].

The question of whether or not there is any relationship between birth weight and PCOS in adult life has also been addressed: There are two distinct patterns reported in the literature: (1) a higher incidence of polycystic ovaries among overweight women who were born large for gestational age to obese mothers; and (2) high incidence of PCOS among lean women who were born after term [10].

In this study, the self-reported mother/daughter medical history of four hundred and one cases were collected and after applying rigorous exclusion criteria 131 were analyzed in order to examine any relationship between maternal PCOS and PCOS among their adult daughters. Furthermore, the prevalence of the syndrome with regards to the birth weight and pre-term or post term delivery was also investigated.

Methods

An online questionnaire was developed and placed on PCOS related websites and online forums including Polycystic Ovary Syndrome (PCOS) (available at: <https://www.facebook.com/PCOSstrong>), PCOS Research (available at: <https://www.facebook.com/PCOSResearch>), PCOS Awareness Association (available at: <https://www.facebook.com/PCOSAwarenessAssociation>), PCOS Diva (available at: <https://www.facebook.com/pcosdiva>), and PCOS (available at: <https://www.facebook.com/HealthySmartsMD>). Links to the survey were published on these websites from which an administrators' agreement was received.

The questionnaire consisted of three parts: (1) questions about the participant (mother); (2) questions about the pregnancy; (3) questions about the daughter. (see supplemental data). Responses received within 48 hours (between the 15th and 17th February 2014) were collected.

Questionnaires were vetted for final data analysis and excluded on the basis of:

- 1) Sections Incomplete.
- 2) Other prevailing medical conditions self-reported.
- 3) Medication taken during pregnancy.
- 4) Alcohol consumption taken during the pregnancy.
- 5) Maternal age did not exceed 30 years.

6) Daughters at time of completion of questionnaire were 18 or over years of age.

7) Those self-reporting symptoms of PCOS but not reporting having been clinically diagnosed with PCOS.

In the analysis PCOS was defined in daughter as those reporting having been diagnosed with PCOS.

Ethics and data protection

Ethical approval was obtained from the Middlesex University, School of Health & Social Sciences, Natural Sciences Ethics sub-Committee. An anonymous online questionnaire, and participant consents was implicit in its completion.

Data analysis

The data were analyzed using Minitab software version 16. Chi-Square analysis was performed on categorical data, Two-sample T-tests on continuous numerical data (following positive variance and normality test results) and Mann-Whitney test on non-parametric data with the level of significance set at 0.05 and correlation interval (CI) of 95%.

Results

Within the two-day period in which the survey was run, 401 responses were received. 155 were excluded as the response questionnaire was missing crucial data (daughter's age, PCOS status, risk behaviors during the pregnancy); 115 were excluded for failing one or more of the other exclusion criteria (Figure 1).

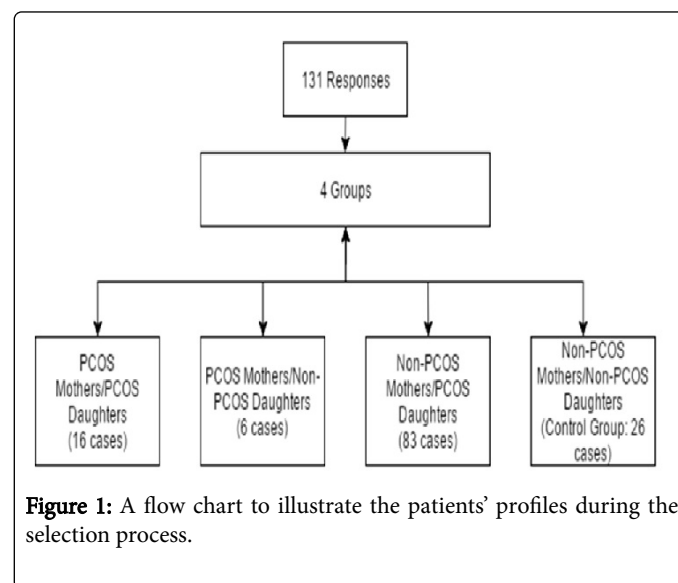


Figure 1: A flow chart to illustrate the patients' profiles during the selection process.

Statistical analysis of responses was based on 131 respondent pairs (32.7% of the initial number). Within this cohort, 22 mothers (16.8%) and 99 (75.6%) of daughters were diagnosed with PCOS; 109 (83.2%) mothers and 32 (24.4%) daughters did not have PCOS.

Of the 22 mothers with PCOS, 16 women (72.7% of the group) reported daughters with a diagnosis of PCOS and 6 (27.3%) PCOS affected mothers reported daughters without a diagnosis of PCOS. Conversely, of the 109 mothers without PCOS, 26 (23.9%) of their daughters were also unaffected by PCOS, but 83 (76.1%) had developed PCOS (Figure 1).

Maternal weight status before the pregnancy		
Maternal weight status	PCOS Daughters	Non-PCOS Daughters
Underweight**	8 (8.1)	4 (12.5)
Normal**	71 (71.7)	25 (78.1)
Overweight**	20 (20.2)	3 (9.38)
Women's birth weight in relation to their PCOS status (born in term only)		
	PCOS Women	Non-PCOS Women
N	80	62
Birth Weight (g)*	3420 (± 516)	3305 (± 550)
PCOS among mothers in relation to their daughters' PCOS status		
	PCOS Daughters	Non-PCOS Daughters
PCOS Mothers**	16 (16.2)	6 (18.8)
Non-PCOS Mothers**	83 (83.8)	26 (81.2)
Daughters' BMI in relation to maternal PCOS status		
	PCOS Mothers	Non-PCOS Mothers
N	21	100
Daughter's BMI*	28.46 (± 8.18)	32.93 (± 9.82)
Daughters' BMI in relation to their PCOS status		
	PCOS Daughters	Non-PCOS Daughters
N	90	31
Daughters' BMI*	34.59 (±9.35)	25.08 (±6.74)
Daughters' birth weight in relation to maternal PCOS status		
	PCOS Mothers	Non-PCOS Mothers
N	20	107
Daughters' Birth Weight (g)*	3303 (±489)	3333 (±634)
Women's birth term in relation to their PCOS status		
Birth term	PCOS Women	Non-PCOS Women
Before term**	13 (11.3)	17 (14.4)
In term**	84 (73.0)	92 (78.0)
After term**	18 (15.7)	9 (7.6)
The prevalence of post-term birth among women in regard to their PCOS status		
Birth term	PCOS Women	Non-PCOS Women
Before/In term**	96 (83.5)	109 (92.4)
After Term**	19 (16.5)	9 (7.6)
*mean (±SD); ** n (%)		

Table 1: Analysis of the potential risk factors in relation to PCOS status.

Maternal age at the time of giving birth was compared between both groups and no significant difference was found, ensuring at the same

time that samples are representative. Groups were also similar in terms of risk behaviors during the pregnancy (smoking, stress). The mean age of all reported daughters was 29.4 (±6.4) years [25.9 (±5.7) years for healthy daughters and 30.5 (±6.2) for PCOS diagnosed daughters].

No significant differences were found in terms of their birth weights between PCOS and non-PCOS women. Also, no correlation was observed between whether they were diagnosed as PCOS and their birth term (before term, in term or after term); however there was a significant difference in the prevalence of the history of post-term birth among PCOS women in comparison to the control group (Table 1 and Figure 2).

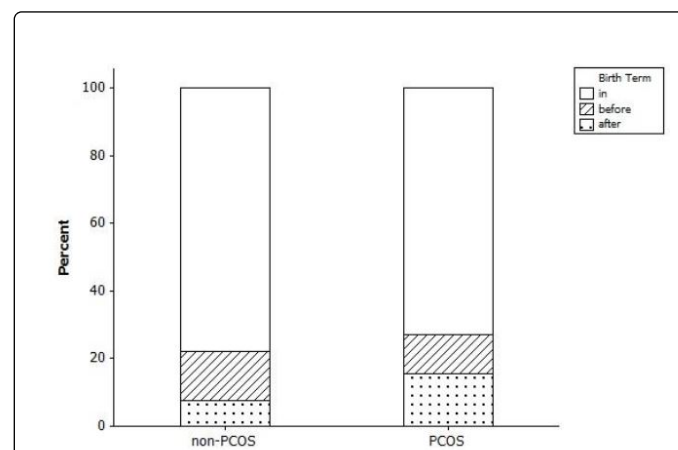


Figure 2: Comparison of the birth terms of the PCOS and non-PCOS women. The percentage prevalence of pre-term birth (dotted areas) was significantly higher in PCOS group (16.5%) than in group of women not diagnosed with PCOS (7.6%).

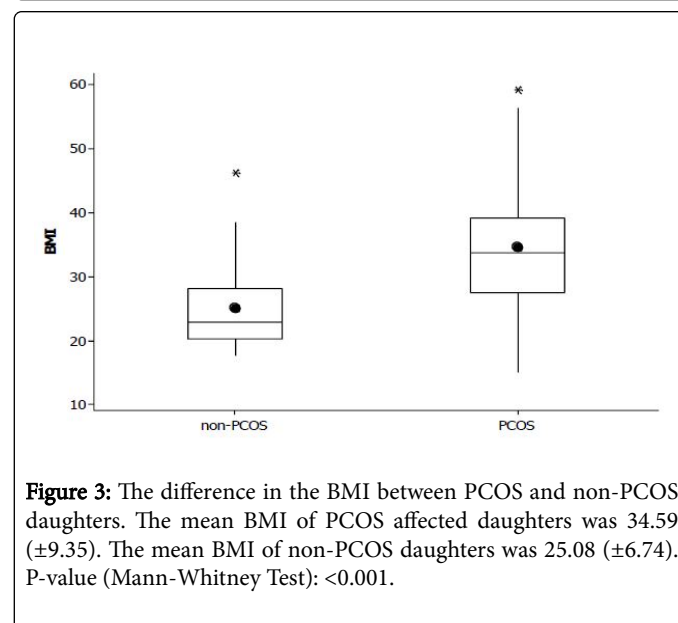


Figure 3: The difference in the BMI between PCOS and non-PCOS daughters. The mean BMI of PCOS affected daughters was 34.59 (±9.35). The mean BMI of non-PCOS daughters was 25.08 (±6.74). P-value (Mann-Whitney Test): <0.001.

Among the diagnosed mothers, only two (12.5%) were born after term. No significant differences were found between maternal birth weights in relation to their PCOS status. Based on the Chi-Square analysis, none of these factors, which are maternal body weight; the term of delivery for the baby and maternal PCOS status, has been found to correlate with their likelihood of giving birth to a daughter

who will develop into PCOS at later stage. PCOS daughters were found to have significantly higher body mass index (BMI), however their BMIs were not associated with their mothers' PCOS status nor with their own birth weight (Table 1 and Figure 3).

Discussion

There are no substantive epidemiological or prospective studies, which report a statistical prevalence of PCOS among adult daughters of PCOS women; although many have suggested a link. These studies reported the incidence of only one of the syndrome's indications [16,17] or were based on the analysis of relatively young daughters [18,19] where the unequivocal diagnosis of PCOS was not established. This study directly addressed the question of a link between diagnosed maternal PCOS and subsequent development of diagnosed PCOS in female offspring.

Although it possesses certain advantages (relatively large sample size, demanding inclusion criteria, and the analysis of adult daughters), it also has its limitations, in that the accuracy of the data collected could not be verified. Indeed, although applying a strict inclusion criteria we almost certainly only selected firmly clinically diagnosed PCOS patients; (32.7% of the responders). This may constitute an extreme subset of this heterogeneous condition and not the wider picture. Furthermore, the ethnicity of respondents was not evaluated and the pregnancy complications were not assessed. Never-the-less, no association was found between maternal PCOS and PCOS development among their adult daughters. The frequency of having a PCOS affected mother among PCOS women was found to be relatively low and similar to the frequency of having a PCOS mother among unaffected daughters.

Several studies have suggested that high maternal testosterone levels or maternal PCOS, were associated with low birth weight among babies born [14,20,21]. However, other studies did not support those findings [22,23]. Similarly, we found no significant differences between the birth weights of female infants born to PCOS mothers and controls.

As stated above, our stringent inclusion criteria may have excluded the two thirds of respondent women as their symptoms were largely un-confirmed and at the lower end of the spectrum of PCOS or "PCOS-like" disease. However, the biochemical circumstantial evidence is not strongly supportive of such a hypothesis of a large subset of PCOS-Like symptoms due to in-utero androgen exposure: during pregnancy, placental aromatase protects the fetus against maternal androgens [24]. Impaired activity of this and other placental enzymes has been postulated to potentially lead to fetal androgen exposure [25] and placental post-maturity, arising as a result of prolonged gestation, was hypothesized to be the most likely factor leading to such enzymatic insufficiency [10]. A significantly higher percentage of PCOS population were post-term (Chi-Square analysis: $p < 0.05$; (Figure 2 and Table 1). However, the biological significance, of this is unknown: Aromatase is a non-rate limiting enzyme, conversion of androgens into estrogens is substrate rather than enzyme dependent, and because of its placental abundance, even less than one percent of normal placental levels is sufficient to protect against fetal virilisation [26,27]. Therefore the hypotheses that aromatase capacity maybe overwhelmed post-term by high androgen levels of maternal origin, as a mechanism leading to preferentially susceptibility to PCOS-like symptoms, is likely to be a rare rather than common event.

Significantly the mean BMI of PCOS daughters was statistically higher (34.59 ± 9.35) in comparison to the control group (25.08 ± 6.74) (Figure 3) which is in agreement with known obesity prevalence

among PCOS women [28]. However their BMI was not dependent on having a PCOS neither affected mother nor related to their birth weight, contrary to other studies [10].

Re-examination of the data from all respondents may show a different correlation but this will have no validity power in confirmed PCOS diagnosis and may be more a social "mother to daughter" attitudinal identification of symptoms and behaviors. To firmly settle the question of is there a familial associated in confirmed diagnosis of PCOS in mothers and daughters is to recruit only PCOS patient who are not overweight. This would require a repeat of this study but aiming for 20,000 plus responses and an examination of a very small minority of clinically confirmed PCOS in mothers who are non-obese and neither are their adult daughters.

Although maternal hyperandrogenism during pregnancy has been proposed to be a potential risk factor of PCOS among female offspring [29,30]; our epidemiological study shows no familial association of mother to daughter PCOS. Indeed, the only clearly pre-determining factor to PCOS development is BMI. Thus, any such Maternal to Daughter relationship in PCOS development must be considered in light of socio-economic influence of being over-weight, rather than any in-utero epigenetic molecular endocrine factors.

Declaration of Interest

Authors declare that we have no conflicts of interest.

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