Title: Postnatal depression in a community-based study of women with polycystic ovary syndrome

Running heading: Postnatal depression in PCOS

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Abstract

Introduction: Women with polycystic ovary syndrome (PCOS) are susceptible to depression and anxiety, so may also be at risk for postnatal depression (PND). This study investigates whether women with PCOS have an elevated risk of PND.

Material and methods: Cross-sectional data for parous women (n=566) were available from a birth cohort. PCOS was diagnosed using the Rotterdam criteria. Details of reproductive history, pregnancy, birth, and PND were obtained through structured interview. Comparisons were made between women with and without PCOS using logistic regression analysis, including the investigation of interactions.

Results: A positive but statistically non-significant association was found between PCOS and PND (OR=1.6, 95% CI 0.9-2.9). Compared to their counterparts, women with PCOS were substantially more likely to have difficulty conceiving (OR=5.2, 95% CI 2.9-9.4), to have conceived with medical assistance (OR=11.6, 95% CI 5.5-24.4), and to have pregnancy complications (gestational diabetes, pregnancy-induced hypertension, or pre-eclampsia, OR=2.0, 95% CI 1.1-3.5). Where women with PCOS had a history of miscarriage or conceived with medical assistance, the combination interacted ($p = 0.06$ and $p < 0.05$, respectively), with over half of such women having PND.

Conclusions: Whilst women with PCOS may not have an excess risk of PND overall, those who had suffered a miscarriage or required medical assistance to conceive were at substantially elevated risk. Findings point to vulnerability inherent in PCOS being amplified, either by stressful experiences on the pathway to pregnancy/childbirth or by specific fertility treatment regimens.

Key words: polycystic ovary syndrome, postnatal depression, postpartum depression, infertility, pregnancy complications, stress, infertility, miscarriage

Abbreviations:

BMI

Body mass index

CES-D

Centre for Epidemiological Studies Depression Scale

PND

Postnatal depression

PCOS

Polycystic ovary syndrome

Key message

As the first study to investigate postnatal depression (PND) risk for women with polycystic ovary syndrome, we revealed a substantially greater risk of PND if miscarriages were experienced or medical assistance to conceive sought.

Introduction

Maternal depression associated with pregnancy and childbirth, known as postnatal depression (PND), is a debilitating condition that can have a significant impact on the health and wellbeing of the woman, her child and her wider family (1, 2). PND is likely to be under-diagnosed but is estimated to affect 10-20% of mothers in western countries (2-4).

Polycystic ovary syndrome (PCOS) is an endocrine disorder, manifesting in symptoms that include hirsutism and menstrual irregularity. Women with PCOS have increased susceptibility to depression and anxiety (5), which is an identified risk factor for PND (2, 4). This susceptibility could be due to their perturbed hormonal and metabolic profiles, or to distress created by PCOS symptoms and their management (6-8).

In addition, women with PCOS often have difficulty conceiving as well as complications during pregnancy, which may contribute to stress and dissatisfaction and, thereby, to PND (2, 4). To elaborate, women with PCOS have elevated risk of miscarriage, gestational diabetes, pregnancy-induced hypertension and pre-eclampsia (9). Impaired fertility means that women with PCOS are frequently clients of fertility clinics (5, 10, 11), a source of stress during treatment (12, 13). Pregnancies achieved with medical assistance are, in turn, associated with increased risk of complications (14-16). Finally, women with PCOS have relatively more neonates that are preterm or small for gestational age, partly due to an excess of twin pregnancies following use of ovulation induction drugs (9).

Thus women with PCOS are likely to have a variety of risk factors for PND, including a history of depressive symptoms, experience of miscarriage, obstetric and perinatal complications, but there has been no investigation of PND in this group to date. As PCOS is the most common endocrine disorder in women of reproductive age (8), affecting between 9 and 18% (18), it may contribute to a substantial burden of PND.

We aim to address this gap in knowledge by comparing the occurrence of PND in women with and without PCOS in a well characterized community-based sample. We

also explore whether prior experiences of difficulty conceiving, medically assisted conception, pregnancy complications or suboptimal birth outcomes contribute to any increased risk of PND.

Materials and methods

This work is based on the first wave of follow up undertaken for a retrospective cohort study of women, thus it has a cross-sectional design. Cohort participants were born in 1973-1975 in a large maternity hospital in Adelaide, South Australia. Around 30 years later, the 2199 eligible female births were traced. The 1984 (90.2%) women who were confirmed to be living, without any severe impairment, were invited to participate by letter and telephone. (For further details of the cohort establishment, see (17).)

After acceptance, first wave data were obtained from 947 (49.1%) women at a median age of 30.2 years. Participants were broadly representative of all eligible female births, although with a slightly greater proportion of mothers from the highest socio-economic category (8.8 vs. 5.5%, as derived from postcode of residence (18)). Among participants, 568 (60.0%) had given birth to one or more children by the time of follow up, and all but two completed questions on PND; these 566 women form the current analysis set.

In an appointment with a trained research nurse, women completed a structured interview and a series of questionnaires. Administration was in person for over three quarters of women and by telephone for the remainder, principally because they no longer resided in Adelaide. The structured interview covered many aspects of women's lives, symptoms of PCOS, and medical history, including pregnancies. For women seen in person, height and weight were measured following standard protocols, otherwise self-reports were obtained.

The Rotterdam criteria were used to identify women with PCOS (19), i.e. a positive diagnosis of PCOS required the presence of at least two of the following three symptoms: oligo or amenorrhea; clinical and/or biochemical hyperandrogenism;

polycystic ovaries. The process of identifying these symptoms has been described in detail elsewhere (17). Briefly, women provided details of their menstrual cycle and menstrual irregularity was defined as chronic amenorrhea, a cycle length of < 21 or > 35 days, or variation of > 4 days between cycles. Women were shown pictures representing the modified Ferriman-Gallwey scale which were compared with body hair, or reports of the extent prior to removal, to classify hirsutism, with a score of more than 7 corresponding to clinical hyperandrogenism. Women were asked to provide a morning blood sample as soon as convenient after the appointment, where possible in the follicular phase; free testosterone was used to determine biochemical hyperandrogenism. Women with at least one symptom were offered a transvaginal ultrasound to ascertain the presence of polycystic ovaries.

Women who reported a pregnancy of more than 20 weeks were asked whether they had experienced depression when pregnant or postnatally. This was cross-checked against another section of the structured interview concerning depression in which women provided details of episodes, whether clinically diagnosed, and any treatment. The Centre for Epidemiological Studies Depression Scale (CES-D) was also completed, with a score of 16 or more indicating current symptoms consistent with clinical depression (20, 21).

Women provided a pregnancy history that included miscarriages, premature birth (< 37 weeks gestation) and multiples. Women were asked whether they had difficulty conceiving and, if so, for details. These included whether a practitioner of any kind was consulted (including alternative medicine) and whether conception occurred with medical assistance (including ovulation induction drugs, in vitro fertilization or other procedures). Women reported whether or not they had gestational diabetes, pregnancy-induced hypertension, or pre-eclampsia.

At follow up, women reported the highest level of education they had reached and whether they were living with a partner at the time of follow up (married or defacto). Age at first birth was determined from the dates of birth of the woman and her first born child. Body mass index (BMI), using measured or self-reported height and weight, was calculated as weight (kg) divided by the square of height; women were

classified as overweight or obese using cut-offs of 25 kg/m^2 and 30 kg/m^2, respectively.

Statistical analysis

Almost all variables required for this analysis were categorical so, for simplicity, age was classified in five year bands. There were some missing data items (n=25 for BMI, n=41 for CES-D), as women did not have to provide information if they were uncomfortable about any question(s). There were two missing values for PND (both in women who did not have PCOS), resulting in analyses being based on n=566 complete cases.

Variables denoting aspects of reproductive history and pregnancy complications were considered in the analysis. It is debatable as to whether these should be treated as confounders or as mediators of possible associations between PCOS and PND. From a theoretical perspective, we decided to treat them as mediators with the potential to amplify any susceptibility to PND inherent in the women with PCOS. Socio-economic status, indicated by educational attainment, is an established independent risk factor for PND (4), so it was considered as a potential confounder although we did not anticipate it would be influential as the distributions for women with and without PCOS had previously been shown to be similar (17).

Descriptive statistics with proportions represented as percentages were generated. Logistic regression was undertaken to produce odds ratios and 95% confidence intervals for the association between PCOS and PND, as well as between possible confounders/mediators and PND. Logistic regression was also used to assess interactions of PCOS status and variables characterizing the course through conception-pregnancy-birth in relation to the outcome of PND.
All data were analyzed in Stata version 14.1 (StataCorp LP, College Station, TX, USA).

Ethical approval

Study procedures conformed to the principles of the Declaration of Helsinki and approval was gained from the institutional review board of the hospital ethics committee and the University of Adelaide (H/36/99, March 2000). All participants gave informed written consent.

Results

In the analysis set of parous women, 52 (9.2%) met the Rotterdam criteria for PCOS. Three women had menstrual irregularities, hyperandrogenism and PCO; 7 had only menstrual irregularities and PCO; 8 had only hyperandrogenism and PCO; 27 had menstrual irregularities and hyperandrogenism, and some of these woman may also have had PCO as only half of those offered an ultrasound accepted.

Table 1 reports the characteristics of parous women with and without PCOS. Compared to other women, those with PCOS were substantially heavier (three in five with a BMI meeting the obese classification) and more likely to have depressive symptoms (half exceeding the clinical cut off on the CES-D scale) at the time of follow up. Women with PCOS were less likely to have completed high school and, although the majority were currently living with a partner, the proportion was not as high as for their counterparts.

All women in this analysis set had given birth. The association between PND and PCOS was not statistically significant, although the prevalence of PND among women with PCOS was observed to be greater than among other women (37% compared with 27%), as shown in Table 2.

Also as shown in Table 2, half of women with PCOS reported difficulty conceiving and a third had conceived with medical assistance; this was markedly different from the reproductive profile of other women as the elevated odds ratios indicate. During pregnancy, women with PCOS were twice as likely as their counterparts to have had complications of high blood pressure, pre-eclampsia and/or gestational diabetes.

Figure 1 presents subgroups of women with specific risk factors for PND to depict the joint influence of PCOS and each risk factor. Among women who had experienced miscarriage, those with PCOS were more likely to have PND than those without (56% vs. 26%, $p < 0.05$). Among women who conceived with medical assistance, those with PCOS were more likely to have PND than those without (56% vs. 11%, $p < 0.01$). Of note, overlap in the subgroup who had experienced miscarriage and the subgroup who had conceived with medical assistance was limited (around 25%). Logistic regression analysis formally confirmed a PCOS x miscarriage interaction (OR = 3.5, 95% CI 1.0-13.1) and a PCOS x assisted conception interaction (OR = 10.7, 95% CI 1.6-72.8).

Discussion

In a simple analysis, the association between PCOS and PND was not statistically significant, although the data may suggest a positive trend: over one in three parous women with PCOS had PND, whereas in women without PCOS the prevalence was around one in four. Reproductive profiles of women with PCOS contrasted with those of other women, in terms of difficulty conceiving, mode of conception, pregnancy complications and neonatal outcomes, although not all increases in risk were statistically significant, particularly where events were less common. Two factors were formally shown to interact with PCOS and elevate PND, a history of miscarriage, and requiring medical assistance to conceive. In both instances, the combination of an adverse reproductive exposure and PCOS was associated with occurrence of PND in over one in two women.

In agreement with our findings on depressive symptoms at interview, other studies of women with PCOS have reported that they have an elevated risk of depression and anxiety (5, 6, 22). While distressing symptoms associated with PCOS may contribute to relatively poor mental health profiles (6, 7), a large meta-analysis showed that physical symptoms including hirsutism, infertility and obesity did not fully account for associations between PCOS and depression, anxiety or emotional distress (22). Biochemical characteristics of PCOS were not considered in the meta-analysis and may also contribute (23).

Our findings concerning the reproductive profiles of women with PCOS are in agreement with those reported previously, including difficulties conceiving (10, 11), and requiring medical assistance to conceive (5, 11). Existing studies have demonstrated that women with PCOS have an elevated prevalence of miscarriage (9), suggesting that the lack of a statistical significance for some differences observed in our study reflects the relatively modest sample size.

The interactions between PCOS and both history of miscarriage and medically assisted conception in relation to PND demonstrate the role of the path to pregnancy/birth in increased susceptibility to PND. Patterns in our data suggest that a wider range of fertility-related exposures could potentially exacerbate susceptibility, but a larger sample would be needed to explore this.

There are several possible explanations for these findings. One is that the underlying endocrine profile of PCOS predisposes some women to PND in addition to subfertility. In women with PCOS, elevated androgens have been shown to be associated with negative affect and depressive symptoms (24). In other women, elevated androgens pre- and post-partum have been associated with PND (25), but results are inconsistent (26, 27), and the relationship between androgens and mood disorders in women remains controversial (20, 29).

It is also possible that a heightened stress response in women with PCOS culminates in PND when difficulties with conception/pregnancy are encountered. Hyper-responsivity of the hypothalamic-pituitary-adrenal axis has been proposed to contribute to poor mental health, including depression, in women with PCOS (30, 31). Studies have also shown that, compared to controls matched for age and BMI, women with PCOS (without diagnoses of mental disorders) have greater plasma adrenocorticotropic hormone and serum cortisol levels following an experimental stressor, despite similar levels of emotional distress (reported state anxiety) (30). Such hyper-responsivity may mean women with PCOS are less resilient to stress caused by infertility, treatment and pregnancy complications. The possibility that interactions between stressful exposures and the endocrine system in PCOS could

contribute to a range of symptoms and disorders has been raised by several authors (6, 22, 32).

Thirdly, it is possible that specific aspects of assisted reproductive treatment contribute to PND. Exposure to ovulation induction during fertility treatment has been related to both miscarriage and mood disorders (33, 34). Women with PCOS are sensitive to ovulation induction with regard to the adverse outcome of ovarian hyperstimulation syndrome, during which mood disorders are common (34).

This is the first study to specifically investigate the relationship between PCOS and PND. A strength of this study is the use of a community-based sample, thus considering a more representative group of women with PCOS than possible with clinic-based samples.

This study has several limitations. A proportion of women with either anovulation or hyperandrogenism declined the invitation to have an ultrasound to assess ovaries for the presence of cysts. Consequently there is likely to be a degree of under-ascertainment of PCOS, with some women in the group without PCOS probably misclassified. This would have a conservative influence on results (i.e. reducing observed differences between the groups with and without PCOS). The analysis sample had to comprise parous women, which meant the sample size was relatively modest, resulting in some established differences between women with and without PCOS (e.g. history of miscarriage) trending in the expected direction but not achieving statistical significance. Alternatively, these may truly be null associations.

Our findings suggest that women with PCOS may be susceptible to PND especially when they have reproductive health problems. We endorse the need for research on ovulation stimulation protocols for this patient population to reduce the risk of adverse outcomes, as highlighted by others (35). Given that many women with PCOS have contact with health services before conception, there is an opportunity for greater awareness, monitoring and support to prevent PND.

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Legends:

Figure 1. Prevalence of PND in parous women with and without PCOS, overall, and within subgroups based on risk factors for PND; * denotes $p < 0.05$.

Table 1. Characteristics of parous women at first wave of cohort follow up (n=566)

Table 2. The occurrence of reproductive health problems and pregnancy or birth complications among parous women with and without PCOS (n=566)

Table 1. Characteristics of parous women at first wave of cohort follow up (n=566)

Characteristic	PCOS n = 52		Without PCOS n = 514		*p* -value
	n	(%)	n	(%)	
Age (years)					0.81
< 30	12	(23.1)	111	(21 .6)	
≥ 30	40	(76.9)	403	(78.4)	
BMI (kg/m^2), n=541					< 0.01
Lean or normal (BMI < 25)	12	(24.5)	227	(46.1)	
Overweight (25 ≤ BMI <30)	8	(16.3)	128	(26.0)	
Obese (BMI ≥ 30)	29	(59.2)	137	(27.9)	
Current depression symptoms (CES-D > 16), n=525	22	(47.8)	157	(32.8)	0.04
Living with a partner	33	(63.5)	389	(75.7)	0.05
Age at first birth (years)					0.21
< 25	28	(53.9)	251	(48.8)	
25 - 29	23	(44.2)	217	(42.2)	
≥ 30	1	(1.9)	46	(9.0)	
Children					0.09
1	25	(48.1)	186	(36.2)	
2+	27	(51.9)	328	(63.8)	
Educational attainment					0.05
Some high school	26	(50.0)	192	(37.4)	
Completed high school	15	(28.9)	238	(46.3)	
Tertiary	11	(21.2)	84	(16.3)	

Table 2 The occurrence of reproductive health problems and pregnancy or birth complications among parous women with and without PCOS (n=566)

Characteristic	PCOS n = 52		Without PCOS n = 514		Odds ratio	95% CI
	n	(%)	n	(%)		
Postnatal depression	19	(36.5)	137	(26.7)	1.6	[0.9-2.9]
Had difficulty conceiving	27	(51.9)	88	(17.1)	5.2	[2.9-9.4]
Consulted a practitioner re fertility	21	(40.4)	47	(9.1)	6.7	[3.6-12.6]
Medical assistance to conceive	16	(30.8)	19	(3.7)	11.6	[5.5-24.4]
History of miscarriage	16	(30.8)	108	(21.0)	1.7	[0.9-3.1]
Pregnancy complications	20	(38.5)	125	(24.3)	2.0	[1.1-3.5]
Preterm birth (<37 weeks)	11	(21.2)	74	(14.4)	1.6	[0.8-3.2]
Multiple birth	3	(5.8)	19	(3.7)	1.6	[0.5-5.6]