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Authors	Khomami, Mahnaz Bahri;Moran, Lisa J.;Kenny, Louise C.;Grieger, Jessica A.;Myers, Jenny;Poston, Lucilla;McCowan, Lesley M. E.;Walker, James;Dekker, Gustaaf A.;Norman, Robert;Roberts, Claire T.
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Authors: Bahri Khomami, Mahnaz, PhD[1]; Moran, Lisa J, PhD[1, 2]*; Kenny, Louise, PhD[3]; Grieger, Jessica A, PhD [2, 4]; Myers, Jenny, PhD [5]; Poston, Lucilla, PhD [6]; McCowan, Lesley, PhD [7]; Walker, James, MD[8]; Dekker, Gustaaf, PhD [2, 4, 9]; Norman, Robert, MD[2,10]; Roberts, Claire T, PhD [2,4]

[1] Monash Center for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, 3168, Australia

[2] Robinson Research Institute, University of Adelaide, Adelaide, South Australia, 5005, Australia

[3] Department of Obstetrics and Gynecology, University College Cork, Cork, Ireland

[4] Adelaide Medical School, North Terrace, University of Adelaide, Adelaide, SA, 5000, Australia

[5] The Maternal and Fetal Health Research Center, University of Manchester, Manchester, United Kingdom

[6] Department of Women and Children's Health, King's College, London, United Kingdom

[7] Department of Obstetrics and Gynecology, University of Auckland, Auckland, New Zealand

[8] Department of Obstetrics and Gynecology, University of Leeds, Leeds, United Kingdom

[9] Women and Children's Division, Lyell McEwin Hospital, University of Adelaide, Adelaide 5112, Australia

[10] Fertility SA, Adelaide, South Australia, 5000, Australia.

* Bahri Khomami and Moran should be considered joint first author.

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Corresponding author: Lisa J. Moran

Address: Monash Center for Health Research and Implementation (MCHRI), Level 1, 43-51 Kanooka Grove, Clayton, Melbourne, Victoria, 3168, Australia

Email address: lisa.moran@monash.edu

Phone number: +613 8572 2664

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Summary

Objectives: To investigate the risk of pregnancy complications in women with and without polycystic ovary syndrome after consideration of lifestyle factors.

Design: Prospective cohort

Patients and measurements: Participants (n=5628) were apparently healthy nulliparous women with singleton pregnancies from the Screening for Pregnancy Endpoints study in New Zealand, Australia, United Kingdom and Ireland. Multivariable regression models were performed assessing the association of self-reported polycystic ovary syndrome status with pregnancy complications with consideration of lifestyle factors at the 15th week of gestation.

Results: Women with polycystic ovary syndrome (n=354) were older, had a higher socioeconomic index and body mass index and were less likely to consume alcohol and smoke but more likely to do vigorous exercise and take multivitamins. In univariable analysis polycystic ovary syndrome was associated with increased risk of gestational diabetes [OR: 2.2, 95% CI: 1.2,

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4.0]. In multivariable models, polycystic ovary syndrome was only significantly associated with decreased risk of large for gestational age [OR: 0.62, 95% CI: 0.40, 0.98] with a population attributable risk of 0.22%. None of the other outcomes were attributable to polycystic ovary syndrome status.

Conclusions: Polycystic ovary syndrome is associated with a lower risk of large for gestational age infants. In this low risk population, the risk of pregnancy complications was not increased in women with polycystic ovary syndrome who were following a healthy lifestyle. Further studies are warranted assessing the contribution of lifestyle factors to the risk of pregnancy complications in higher risk groups of women with and without polycystic ovary syndrome.

Key words: Birth weight, Large for gestational age, Preterm birth, Gestational diabetes, Gestational hypertension, Lifestyle, Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) affects 8-18% of reproductive-aged women.[1] According to the Rotterdam criteria, PCOS compromises at least two of the three features: menstrual irregularity, hyperandrogenism, and polycystic ovaries.[2] PCOS is associated with reproductive, metabolic and psychological dysfunction.[3] Insulin resistance (IR) is a key etiological feature in PCOS[4] which amplifies both ovarian dysfunction[5] and metabolic disturbances.[6] Obesity and a tendency to central obesity are also common among women with PCOS and can worsen the associated disorders.[7, 8] Pregnant women with PCOS are at an increased risk for pregnancy and birth complications such as gestational diabetes (GDM), gestational hypertension (GH), pre-eclampsia (PE), preterm birth, caesarean section and admission to neonatal intensive care unit.[9]

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In the general population, multiple risk factors including advanced maternal age,[10] certain ethnicities,[11] obesity and excessive gestational weight gain (GWG),[12] low socioeconomic status,[13] parity, multiple pregnancy,[14] pre-existing medical conditions[10] and high risk behaviors such as smoking and alcohol consumption,[11] vitamin or nutrient deficiencies[15] and low physical activity [16] increase the risk for pregnancy complications. Comparatively, a healthy lifestyle reduces the risk.[17-19] However, it is not known if the higher risk of pregnancy complications in PCOS is related to PCOS status *per se* or whether it is an indirect effect of a higher risk profile; and there may be both modifiable and non-modifiable risk factors associated with pregnancy complications in PCOS.

In the limited research examining the risk profile of women with PCOS relating to adverse pregnancy consequences, obesity, excessive GWG, pre-pregnancy IR and multiple pregnancies are reported in PCOS.[20] Alternatively, the pathophysiology of PCOS may contribute to pregnancy complications. Insulin sensitivity decreases over the course of a normal pregnancy. This, in conjunction with pre-existing IR, may further increase the risk of pregnancy complications in PCOS.[21, 22] The cause of infertility and higher rate of multiple pregnancies following fertility treatment may also contribute to pregnancy complications.[14, 21]

Given the short and long term health and economic burden of pregnancy complications for both mothers and infants,[23] the assessment of modifiable factors for primary prevention of pregnancy complications is crucial. There are research gaps regarding the relative contribution of lifestyle and non-lifestyle related factors to pregnancy complications in PCOS as a specific high risk group for pregnancy complications. Therefore, the aim of this study is to identify the risk of pregnancy complications among women with and without PCOS after consideration of lifestyle and non-lifestyle related factors.

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Materials and methods

Study design

This was a prospective cohort study of pregnant participants of the Screening for Pregnancy Endpoints (SCOPE) study.[24, 25] SCOPE is a multi-center prospective cohort study of low-risk, nulliparous women with singleton gestations from Auckland (New Zealand), Adelaide (Australia), Manchester, Kings, Leeds (United Kingdom) and Cork (Ireland), with the primary aim of developing screening tests for prediction of PE, spontaneous preterm birth (SPTB) and small for gestational age (SGA) babies. Women were invited for participation prior to 15±1 weeks' gestation and recruited between November 2004 and February 2011. Pregnancies at high risk for development of PE, SPTB and SGA were excluded. Each local ethics committee approved the study protocol [New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London and Manchester 06/MRE01/98 and Cork ECM5 (10)05/02/08], and all patients provided signed informed consent prior to participation.

Participants

All SCOPE women who met the inclusion criteria of the study (n=5628) were considered. Interview, physical examination and blood and urine sampling were performed for all participants at 15±1 weeks' gestation. Comprehensive clinical data were collected which included demographic and socio-economic information, past medical, obstetric and gynecological history and family history of any obstetric and medical disorders. Ongoing pregnancy data including dietary information, low-dose multivitamin supplementation, smoking, alcohol consumption and exercise activity were collected for all participants. Women were followed up until delivery for pregnancy outcomes and newborn measurements. The complete list of measured variables has been previously described.[24]

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Exposures

PCOS was defined as a self-report diagnosis including confirmatory self-report information about PCOS diagnosis through ultrasound and/or blood test. Self-reported diagnosis of PCOS has been validated in genetic studies to be similar to medically diagnosed PCOS.[26] Women were also asked whether they had received infertility treatment to conceive their current pregnancy and whether women with PCOS continued metformin throughout the first trimester. A socio-economic index (SEI) was defined based on the New Zealand SEI.[27] BMI was calculated using measured weight (kg) divided by measured height squared (m^2). Alcohol consumption and smoking were each considered as a binary variables based on drinking any amount of alcohol or smoking any number of cigarettes at the 15±1 weeks' visit. Multivitamin intake was assessed as frequency of intake (daily, less than daily and no intake). The number of times a woman engaged in physical activity per week in the last month was categorized as: vigorous exercise (resulting in heavy breathing or being out of breath) and moderate exercise (intensity level was not enough to result in heavy breathing or being out of breath).[28] Fruit and leafy vegetable intake were defined as frequencies consumed per day in the last month prior to the visit.

Outcomes

Gestational diabetes mellitus was defined using the new World Health Organization classification (fasting glucose of ≥5.1 mmol/L or following an Oral Glucose Tolerance Test, a 2 h level of ≥8.5 mmol/L) [29]. Universal screening was not employed for GDM in Ireland and the UK; women were only screened if they were identified as being at risk based on factors such as family history and BMI. Therefore, GDM analysis was confined only to women from Australia and New Zealand (n=3126).

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The type of prescribed treatment in women with GDM was documented. GH was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after the 20th week of pregnancy on at least two assessments 4-hours apart.[30] Preeclampsia was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or both, on at least two occasions four hours apart after 20 weeks' gestation but before the onset of labour, or postpartum, with either proteinuria (24 hour urinary protein ≥300 mg or spot urine protein: creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥++) or any multisystem complication of PE. [31-33] Spontaneous preterm birth was defined as spontaneous delivery before 37+0 weeks' gestation. Small- and large- for gestational age were defined as a birth weight <10th or >90th customized centile, respectively. Early GWG was calculated by maternal measured weight at the 15±1-week visit subtracted from weight at 20th week.

Statistical analyses

All statistical procedures were performed using Stata version 14 (StataCorp, 14 College Station, Texas, USA). All reported P values were 2-tailed, and a P value <0.05 was considered to be statistically significant for all analyses. Continuous outcomes were presented as mean ± standard deviation (SD) or median (first and third quartiles) and categorical outcomes were presented as frequency (proportions). Baseline comparisons between women with and without PCOS were analyzed by unpaired t-test or Mann-Whitney as appropriate for continuous data and chi-squared test for categorical data. Logistic regression models were used to estimate the odds ratio (OR) of development of each categorical pregnancy outcome as the dependent variable and PCOS status as an independent variable on unadjusted models and then on adjusted models with the additional independent variables of SCOPE recruitment center, infertility treatment, age, ethnicity (Caucasian vs. non-Caucasian), SEI, BMI, alcohol consumption, smoking and multivitamin intake at 15th week of gestation, exercise frequency

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and fruit and leafy vegetable intake. The same strategies were applied to linear regression models for continuous pregnancy outcomes (infant birth weight and early GWG). Additional independent variables included in individual adjusted analysis were family history of relevant complication (family history of GDM for GDM; family history of GH, PE or hypertension for GH and PE, and family history of SPTB for SPTB), infant sex (birth weight, SGA and LGA) and gestational age at week of measurement (birth weight, SGA and LGA). Models were constructed to avoid collinearity and assessed for standard assumptions. Regression models were constructed based on univariate associations between dependent and independent variables or on hypothesis testing. The proportion of each outcome in the population attributable to PCOS was calculated as [Population attributable risk (PAR)= b(RR - 1) / b(RR - 1) + 1 × 100] where RR is relative risk and b shows the proportion of women with PCOS.

Results

Of the 5628 pregnant SCOPE women, 354 (6.3%) women had PCOS. The baseline and lifestyle characteristics of participants by PCOS status are presented in Tables 1 and 2. Compared to women without PCOS, women with PCOS were older and had a higher weight, BMI and SEI. They were less likely to be smoking or drinking alcohol but more likely to be taking multivitamins, exercising vigorously and frequently, earning a higher income, be more educated, to have a professional occupation and to have received infertility treatment for their current pregnancy. Twenty-six women with PCOS were taking metformin during the first trimester.

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Of the 2078 screened women for GDM, the crude prevalence was higher among women with PCOS compared to non PCOS women [9.7 vs. 4.7%; OR: 2.2 95% CI 1.2, 4.0]. Of these, only 4 women without PCOS received metformin either alone or in combination with insulin after GDM diagnosis. The proportion of GH [7.3 vs. 8.4%; OR: 0.86 95% CI 0.57, 1.3] and PE (5.9 vs. 6.7%; OR: 0.88 95% CI 0.56, 1.4] and mean difference of early GWG [2.3±2.2 kg vs. 2.5±2.0 kg; OR: -0.22 95% CI -0.44, 0.004] were similar among women with PCOS compared to those without PCOS. On crude models, there were no differences in infant birth weight [3388.3±603.3 g vs. 3401.7±590.8 g; OR: -13.4 95% CI: -77.1, 50.2], prevalence of SGA [10.2 vs. 11.4%; OR: 0.88 95% CI: 0.62, 1.3], LGA [6.5 vs. 9.7%; OR: 0.65 95% CI: 0.42, 1.00] or SPTB [5.7 vs. 4.1%; OR: 1.4 95% CI: 0.87, 2.2] in infants born to mothers with PCOS compared to without PCOS.

In the multivariable models, early GWG [OR: -0.12 kg 95% CI: -0.35, 0.10] and infant birth weight [OR: 21.20 g 95% CI: -24.7, 67.10] were similar in women with and without PCOS. Figure 1 shows the association between PCOS and maternal and infant outcomes, after adjusting for a range of lifestyle exposures. There was no longer any association between PCOS status and any maternal or infant outcomes except for LGA [OR: 0.62 95% CI: 0.40, 0.98]. There was a lower proportion of LGA babies attributable to PCOS (0.22%, P=0.015) after adjustment for lifestyle and non-lifestyle factors.

Discussion

In this large prospective cohort study of pregnant women, PCOS was only significantly associated with a decreased risk of LGA babies after adjustment for lifestyle and non-lifestyle risk factors. While PCOS was crudely associated with increased risk for GDM,

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this was no longer maintained in the adjusted analyses. There were no significant associations between PCOS and other maternal or infant outcomes.

In the current study, pregnant women with PCOS were demonstrated to be following a healthier lifestyle with a lower rate of smoking and lower alcohol consumption but a higher proportion taking multivitamins and engaging in more frequent vigorous exercise. This is consistent with prior reports of women with PCOS having a greater risk perception for future lifestyle-related diseases such as obesity and diabetes[34] and a greater tendency to be following healthy lifestyle behaviors for weight management[35] compared to women without PCOS. This is possibly related to lifestyle advice being recommended as first-line treatment for PCOS in evidence-based guidelines.[36] Given their greater likelihood of being overweight or obese and having received infertility treatment for their current pregnancy, the women with PCOS in this study may also have received additional lifestyle management advice for these respective conditions.[37] We also found that women with PCOS were older in comparison to women without PCOS. Older women typically prepare themselves better for pregnancy through seeking information, following healthy lifestyle behaviors and managing their weight.[10] Similarly, women with PCOS had a higher SEI, income, educational and occupation level. These are considered surrogates for health status and healthy lifestyle behaviors; low SEI is associated with an increased risk of pregnancy complications.[13]

We demonstrate a 38% lower risk of LGA among women with PCOS after adjustment for lifestyle and non-lifestyle factors. Prior studies report an increased risk of adverse obstetric outcomes and also increased risk of metabolic complications in LGA babies later in life.[38, 39] While some prior studies have reported that PCOS is associated with a higher rate of LGA babies,[40-42] this was not supported by recent meta-analyses.[23, 43, 44] In the general population several factors including obesity, excessive GWG, diabetes mellitus, GDM, multiparity, age and certain ethnicities are associated with increased risk of LGA babies.[38, 39,

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[45] As overweight and obesity and diabetes mellitus are elevated in PCOS [7, 46] and the older age of women with PCOS, it may be expected that PCOS would be associated with a greater prevalence of LGA babies.[47] The reason for these disparate findings is unclear but may be related to the overall healthier profile in women with PCOS. The design of the SCOPE study accounted for the confounding effects of factors such as parity, pre-existing diabetes mellitus and ethnicity on LGA babies.[25] Additional factors such as GWG are also strongly predictive for LGA babies.[48, 49] Women with PCOS have generally higher longitudinal weight gain compared to women without PCOS [50] which could be expected to contribute to greater GWG. However, while BMI was higher at 15 weeks of gestation for women with PCOS, we observed similar early GWG for women with and without PCOS. As early GWG is a surrogate for total GWG,[51] this indicates that total GWG was likely similar between the two groups. This again highlights the lack of additional risk factors for pregnancy complications in women with PCOS in this low risk cohort.

We also found that women with and without PCOS had a similar risk for GDM, GH, PE, SGA and SPTB after consideration of lifestyle and non-lifestyle factors. This finding is in contrast to prior meta-analyses where PCOS was associated with increased risk of GDM, GH, PE and PTB although the relationship of PCOS with an increased risk of SGA is less consistently reported.[9, 23, 44] The reason for our discrepant findings is unclear but may be related to the SCOPE design with the inclusion of low risk women. Aging has been previously reported to be associated with worsened pregnancy outcomes.[10] However, only a small proportion of women with and without PCOS (15.8 vs. 12.5% respectively) were over 35 years as a previously characterized age threshold for increased pregnancy complications.[10] Given the role of IR and obesity in the pathophysiology of PCOS, women with PCOS are considered to be potentially at higher risk of GDM.[23] Excessive GWG, particularly early GWG, [51] can also further increase the risk of GDM in the general population by enhancing

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normal pregnancy induced IR in the second half of gestation.[52] Excessive GWG and diabetes in pregnancy, either pre-existing or new onset, are also independently associated with increased risk of miscarriage, GH, PE, SPTB, perinatal mortality, congenital malformation, macrosomia and caesarean section.[52, 53] The lack of an increased risk of pregnancy complications in the present study may therefore again be related to the similar early GWG and GDM and greater healthy lifestyle behaviors in women with PCOS. This is consistent with a study on 7985 nulliparous women which reported early GWG was a predictor for excessive total GWG, GDM, LGA birth and macrosomia.[51] This highlights that optimizing lifestyle prior to or early in pregnancy may be effective in reducing the risk of pregnancy complications.[51] This is in keeping with prior meta-analyses that reported antenatal diet and/or exercise interventions resulted in lower GWG[54-56] and GDM.[55]

This study has several strengths and limitations. A key strength was the prospective cohort design of the SCOPE study with repeated follow-ups over pregnancy. This minimizes recall bias with regards to pregnancy complications. The multi-center data collection and large sample size increase the generalizability of the results across a number of countries with regards to different demographic characteristics such as age, ethnicity, SEI and BMI and different lifestyles in terms of smoking and alcohol consumption.[57] Self-reported PCOS diagnosis was strengthened through collection of supporting self-report information on the use of blood tests or ultrasound to confirm diagnosis. While the use of more comprehensive assessments of dietary intake would have strengthened the study further, the use of single item questions for key food items such as fruit and vegetable intake are considered a reasonable proxy.[58]

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In conclusion, in this population of low-risk, nulliparous women with PCOS did not have a higher risk of adverse maternal and infant pregnancy complications in comparison to women without PCOS and instead had a lower risk of LGA births. They also had a more favorable lifestyle profile compared to women without PCOS. These findings highlight that following a healthy lifestyle may compensate for the risk of having PCOS for pregnancy complications. Thus risk estimation for pregnancy outcomes could be similarly performed in women with and without PCOS providing they have a similar health or lifestyle profile. These findings suggest that the beneficial effects of lifestyle modification on PCOS, as recommended by evidence-based PCOS guidelines,[36] may extend to improved pregnancy outcomes. However, this needs to be confirmed by assessing both healthy and at risk groups for pregnancy complications in women with well-defined PCOS and controls and with consideration of lifestyle factors.

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Data sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends:

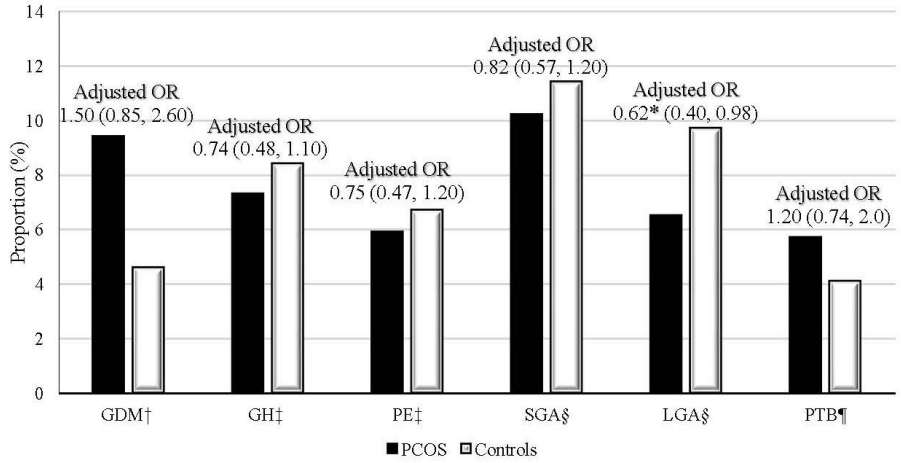
Figure 1- Maternal and infant pregnancy and birth complications in women with and without PCOS

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Figure 1- Maternal and infant pregnancy and birth complications in women with and without PCOS



PCOS: polycystic ovary syndrome; GDM: gestational diabetes mellitus; GH: gestational hypertension; PE: pre-eclampsia; SGA: small for gestational weight; LGA: large for gestational weight; SPTB: spontaneous preterm birth; OR: odds ratio.
Values are proportions and ORs (95% CI) for logistic regression adjusted for infertility treatment, age, ethnicity, SEI, BMI, alcohol consumption, smoking and multivitamin intake at 15th week of gestation, exercise frequency and fruit and leafy vegetable intake.
* P<0.05
†Multivariable model further adjusted for: SCOPE recruitment center and family history of GDM.
‡Multivariable model further adjusted for: SCOPE recruitment center and family history of GH, PE or hypertension.
§Multivariable model further adjusted for: SCOPE recruitment center, infant gender and gestational age at week of measurement.
¶Multivariable model further adjusted for: SCOPE recruitment center and family history of SPTB.

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