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Title: Increased maternal pregnancy complications in polycystic ovary syndrome appears to be independent of obesity- A systematic review, meta-analysis and meta-regression

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Abbreviations: PCOS: polycystic ovary syndrome; HA: hyperandrogenism; AnOvu: oligo/anovulation; PCOM: polycystic ovary morphology; IR: insulin resistance; GDM: gestational diabetes mellitus; GHTN: gestational hypertension; PE: pre-eclampsia; CS: caesarean section; IVF: in vitro fertilization; RCT: randomized controlled trial; NIH: national institute of health; AES: androgen excess society; ESHRE/ASRM: European society of human reproduction and embryology/American society for reproductive medicine; IOL: induction of labor; BMI: body mass index; SES: socioeconomic status; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cell count; CRP: C-reactive protein; FBS: fasting blood sugar; OGTT: oral glucose tolerance test; HOMA: homeostatic model assessment; SHBG: sex hormone binding glubolin; TT: total testosterone; FAI: free androgen index; NOS: Newcastle-Ottawa Scale; OR: odds ratios; CI: confidence interval; ART: assisted reproduction technology; REML: restricted maximum likelihood; GWG: gestational weight gain; NP: not provided; SMD: standardised mean difference; IOM: institute of medicine.

Abstract

Polycystic ovary syndrome (PCOS) is associated with an increased risk of maternal

pregnancy and delivery complications. However the impact of clinical features of PCOS and

other potential risk factors in PCOS is still unknown. We aimed to investigate the association

of PCOS with maternal pregnancy and delivery complications with consideration of risk

factors and potential confounders. The meta-analysis included 63 studies. PCOS was

associated with higher miscarriage, gestational diabetes mellitus, gestational hypertension,

pre-eclampsia, induction of labor and caesarean section. The association of PCOS with these

outcomes varied by geographic continent, PCOS phenotypes and study quality. Pre-eclampsia

and induction of labor were not associated with PCOS on body mass index-matched studies.

No outcome was associated with PCOS on assisted pregnancies. Age was significantly

associated with higher miscarriage on meta-regression. There were no studies assessing

perinatal depression. We confirm that PCOS is associated with an increased risk of maternal

pregnancy and delivery complications. The association of PCOS with the outcomes is

worsened in hyperandrogenic PCOS phenotypes, in specific geographic continents and in the

highest quality studies but disappears in assisted pregnancies. Future studies in PCOS are

warranted to investigate proper timing for screening and prevention of maternal pregnancy

and delivery complications with consideration of clinical features of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women with a prevalence of 6.8-13%.[1,2] It is characterized by hyperandrogenism (HA), oligo/anovulation (AnOvu) and/or polycystic ovary morphology (PCOM).[3] PCOS is associated with metabolic, reproductive and psychological features.[4] Women with PCOS have intrinsic insulin resistance (IR) which is mechanistically distinct from the IR associated with obesity and obesity will further worsen both IR and the clinical presentation of PCOS.[4-6] Women with PCOS are more likely to have increased oxidative stress[7] and to experience infertility requiring assisted conception and when they conceive, there is also an increased risk for pregnancy and delivery complications.[8-11]

Previous meta-analyses on pregnancy and delivery complications report an increased risk for miscarriage, gestational diabetes mellitus (GDM), gestational hypertension (GHTN), pre-eclampsia (PE) and caesarean section (CS) in women with PCOS.[8-11] Given the heterogeneity of PCOS and confounding variables associated with pregnancy complications, diverse risk factors may contribute to the increased rate of pregnancy complications in PCOS.[4] Obesity, IR, hyperandrogenism and increased oxidative stress may aggravate PCOS severity and modulate the rate of pregnancy and delivery complications.[5,7] Given that these features present differently across ethnicities,[12] pregnancy complications may also differ by ethnic background. Moreover, the higher rate of assisted reproduction in PCOS is likely an important risk factor for pregnancy outcomes.[13] Ovulation induction and in vitro fertilization (IVF) have been strongly associated with maternal pregnancy and delivery complications including increasing the rate of multiple pregnancy, an independent risk factor for pregnancy complications.[8,10]

Despite empirical evidence for an increased prevalence of maternal pregnancy and delivery complications in women with PCOS[8-11] there are still significant gaps in

understanding the potential pathophysiological pathways for these associations. This is likely due to both the complexity and heterogeneity of PCOS, the range of potential confounders for pregnancy complications and the variable methodology of conducted studies[4] with these factors often not considered in prior meta-analyses. The aims of this systematic review, meta-analysis and meta-regression were to assess the prevalence of pregnancy and delivery complications in women with and without PCOS and in consideration of clinical and biochemical symptoms of PCOS and potential confounders of these outcomes.

Methods

The protocol for this systematic review, meta-analysis and meta-regression was prospectively registered in the international register of systematic reviews PROSPERO (CRD 42017067147). The review was performed according to the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[14]

Search strategy

A comprehensive gold-standard systematic database search was conducted on the 4th of April 2017. The following electronic databases were used to identify relevant published literature: Medline, Medline in-process and other non-indexed citations, EMBASE and all EBM reviews including Cochrane Database of Systematic Reviews, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, American College of Physicians Journal Club, Cochrane Methodology Register, Health Technology Assessments, The Database of Abstracts of Reviews of Effectiveness and national health service Economic Evaluation Database. The specific terms used for the search are shown in the Supplementary Table 1. As a complementary search, bibliographies included in previous systematic review and meta-analyses on this topic and The International Clinical Trials Registry Platform Search Portal

(http://apps.who.int/trialsearch/) were also searched. The full search strategy related to a broader number of outcomes encompassing 2 separate systematic reviews.

Inclusion and exclusion criteria

We included observational studies with either a cohort or a case-control design. Case reports, case series and reviews were excluded. Eligible studies included women with and without PCOS which reported the relevant outcomes with studies that reported outcomes only in women with PCOS classified as ineligible. Only articles published in English and conducted on human participants were included. PCOS was defined according to any criteria used by each article including the National Institute of Health (NIH), Androgen Excess Society (AES), European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), clinician confirmation or self-report. Pregnancy and birth outcomes for this specific review included miscarriage, GDM, GHTN, PE, Induction of labor (IOL), CS and perinatal depression. The outcomes were defined according to how each article reported them with the methodology each article used being documented accordingly.

Study selection

Two independent reviewers (M.B.K and either of C.A or M.S) who were not blinded to the names of investigators or sources of publication identified and selected the studies that met the inclusion criteria at 2 stages (screening of titles and abstracts and reviewing potentially eligible full-texts). Inter-reviewer agreement for the inclusion of studies was almost perfect (kappa=0.88). Disagreements between reviewers were discussed and resolved with a third reviewer (L.J.M) through consensus or arbitration.

Data extraction and quality appraisal

Eligible studies were extracted and appraised by 2 independent reviewers (M.B.K and either C.A or M.S) per study. Any discrepancies were resolved by discussion and resolved by

making a consensus with the third reviewer (L.J.M). The data extracted included information on the author, year of publication, study design, study location, participants' characteristics and frequency of the outcomes. All information was entered into a researcher-developed data extraction form.

Extracted participants' characteristics data included demographic (age, body mass index (BMI), ethnicity, socioeconomic status (SES), smoking status and parity), clinical (PCOS phenotypes, acne and hirsutism scores, pre-pregnancy medical conditions, early pregnancy systolic (SBP) and diastolic blood pressure (DBP)) and biochemical (white blood cell count (WBC) and c-reactive protein (CRP), fasting blood sugar (FBS) and/or oral glucose tolerance test (OGTT), fasting insulin, homeostatic model assessment (HOMA), post OGTT insulin or glucose infusion rate on clamp study, sex hormone binding glubolin (SHBG), total testosterone (TT) and free androgen index (FAI)) information.

All included studies were assessed for risk of bias using the Newcastle-Ottawa Scale (NOS) for non-randomized studies[15] (Supplementary Table 2). Individual items assessed by NOS included: representativeness of the PCOS and non-PCOS groups, ascertainment and validity of PCOS status, pregnancy and delivery outcomes, comparability of groups by potential confounders on the basis of the design or analysis, early discontinuation of study, and rate of loss to follow ups. The NOS assesses the quality of studies in 3 domains of selection, comparability and outcome with maximum stars of 4, 2 and 3, respectively. Studies were ranked as poor, fair and good quality as per the number of stars awarded to each domain. To be considered as good quality, studies needed at least 3 stars in selection, 1 star in comparability and 2 stars in outcome domains. Fair quality studies were those with 2 stars in selection, at least 1 star in comparability and 2 stars in outcome domains. Studies which met none of these 2 thresholds were considered as poor quality. (Supplementary Table 3).

Data analysis

All the pregnancy and delivery complications for each study were expressed as odds ratios (OR) with 95% confidence intervals (CI) and combined using random effects model for meta-analysis. Studies reporting outcomes in multiple number of pregnancies per woman were excluded from the meta-analysis. Where there was an overlap between samples of different studies reporting on the same outcome, the study with the largest sample size for the corresponding outcome was included. To quantify statistical heterogeneity between studies, the I^2 statistic was estimated where $I^2>50\%$ implied significant heterogeneity. Sensitivity analyses were performed with the exclusion of studies where women were taking metformin during pregnancy.

Exploratory sub-group meta-analyses were conducted according to PCOS ovulatory (i.e. HA+PCOM), anovulatory (i.e. AnOvu+HA or AnOvu+PCOM or AnOvu+HA+PCOM), hyperandrogenic (i.e. HA+PCOM or AnOvu+HA or AnOvu+HA+PCOM) and non-hyperandrogenic (i.e. AnOvu+PCOM) phenotypes, the geographic continent where the study was conducted, BMI-matched design, specific BMI categories, mode of conception (spontaneous vs. assisted reproductive technology (ART)), singleton vs. multiple pregnancy and study quality (poor/fair/good). A further sub-group meta-analysis was performed to assess the association of PCOS status with GHTN, PE, IOL and CS in GDM affected women. Restricted maximum likelihood (REML)-based random effects meta-regression was perfomed to explore the influence of maternal age, SES, CRP, WBC, BMI, gestational weight gain (GWG), smoking, parity, multiple pregnancy, mean SBP and DBP, FBS, OGTT, SHBG, TT, FAI, acne and hirsutsim score on each outcome of interest if sufficient data was available (≥ 10 studies per co-efficient). For univariate meta-regression, relative ratio of mean values and frequencies were used, as appropriate. Knapp-Hartung method was used to estimate the between study variance (tau^2). Normal distrubution for mean values was checked using skewness-kurtosis test. There was no significant variable ($p<0.1$) to be included in the

multivariate meta-regression. We performed all analysis under supervision of an experienced statistician using Stata version 14 (StataCorp, 14 College Station, Texas, USA).

Results

Search results

Of a total of 4292 studies identified through the search, 77 studies met the inclusion criteria for the systematic review. For the meta-analysis, 14 studies were excluded (Supplementary Table 4) on the basis of reporting outcomes in multiple number of pregnancies per woman [16-21] and overlapping data,[22-29] resulting in 63 included studies (Figure 1).

Characteristics of included studies

The characteristics of 63 included studies are listed in Table 1 and Supplementary Table 5. Outcomes of interest were reported in a total of n=224136 pregnant women comprising 39 retrospective [23,30-67] (n=157899) and 24 prospective [68-91] (n=66237) studies. Eighteen studies were conducted in Europe,[34,35,39,40,45-47,49,60,61,67,73,77,79,84,86,87,91] 16 in Americas,[23,30,32,36,37,42,44,48,51,53,64,69,71,74,76,83] 23 in Asia,[31,33,41,43,50,52,54-58,62,63,65,66,68,72,75,80,85,88-90] 4 in Australia and New Zealand[38,59,70,82] and 2 in Africa.[78,81] Outcomes of interest by PCOS phenotypes were extractable from 3 studies in women with ovulatory,[60,78,87] 26 with anovulatory,[16,19,23,30-38,42,46,51,59-61,63,68,69,71,74,76,87] 19 with hyperandrogenic,[30,68,6919,23,33,36-38,42,46,51,70,76,7859-61,87] and 2 with non-hyperandrogenic[60,87] phenotypes of PCOS. Nine studies matched women with and without PCOS on the basis of BMI.[30,53,62,71,73,78,79,81,84] There was only 1 study reporting outcomes in multiple pregnancies with and without PCOS.[61] In 4 studies women with PCOS continued taking metformin during pregnancy.[43,47,48,77]

Table 1- Characteristics of included studies for pregnancy outcomes

Study	Country	Design	Risk of bias	PCOS	Controls	Matched characteristics	Outcomes
Levran 1990 [68]	Israel	Prospective cohort	High	N=76; Age= NP; BMI= NP	N= 95; Age= NP; BMI= NP;	Age, Weight	GDM
Wortsman 1991 [30]	USA	Retrospective cohort	High	N= 53; Age= 29 years; BMI= 26.67 kg/m^2	N= 2306; Age= NP; BMI= NP		GDM
Urman 1992 [69]	Canada	Prospective cohort	High	N= 4; Age= NP; BMI= NP	N= 10; Age= NP; BMI= NP	Age	Miscarriage
Homburg 1993 [31]	Israel	Retrospective case-control	Moderate	N= 47; Age= NP; BMI= NP	N= 38; Age= NP; BMI= NP	Age	Miscarriage
Lesser 1997 [32]	USA	Retrospective cohort	High	N= 24; Age= 29.8 years; BMI= 28.4 kg/m^2	N= 45; Age= 32 years; BMI= 23.4 kg/m^2		GDM, PE
Urman 1997 [33]	Turkey	Retrospective cohort	Moderate	N= 47; Age= 27.8 years; BMI= 25.1 kg/m^2	N= 100; Age = 28 years; BMI= 23.4 kg/m^2		GDM, GHTN
de Vries 1998 [34]	Netherlands	Retrospective cohort	Moderate	N= 81; Age= 29.5 years; BMI= 24.8 kg/m^2	N= 81; Age= 30.1 years; BMI= 23.5 kg/m^2		GDM, GHTN, PE
Fridstrom 1999 [35]	Sweden	Retrospective case-control	High	N= 33; age= 32 years; BMI= 24.5 kg/m^2	N= 66; age= 33 years; BMI= 23.2 kg/m^2	Age	GDM, GHTN, PE, CS
Radon 1999 [36]	USA	Retrospective cohort	Low	N= 22; Age = 32.4 years; BMI= 28.9 kg/m^2	N= 66; Age = 31.1 years; BMI= 28 kg/m^2	Age, Weight	GDM, PE
Kashyap 2000 [37]	Canada	Retrospective cohort	High	N= 22; Age = NP; BMI= 25.8 kg/m^2	N= 27; Age = NP; BMI= 23.4 kg/m^2		GHTN

Vollenhoven 2000 [38]	Australia	Retrospective cohort	Moderate	N= 60; Age = NP; BMI= 27.1 kg/m^2	N= 60; Age = NP; BMI= 26.5 kg/m^2	Age	GDM
Wang 2001 [70]	Australia	Prospective cohort	Low	N= 373; Age = 31.4 years; BMI= 26.3 kg/m^2	N= 365; Age = 32.7 years; BMI= 24.3 kg/m^2		Miscarriage
Bjercke 2002 [39]	Norway	Retrospective cohort	Moderate	N= 52; Age = 31.3 years; BMI= 26.3 kg/m^2	N= 355; Age = 32.7 years; BMI= 21.9 kg/m^2		GDM, GHTN, PE, CS
Haakova 2003 [40]	Czech Republic	Retrospective cohort	Low	N= 66; Age = 29 years; BMI= 23.7 kg/m^2	N= 66; Age = 29.8 years; BMI= 23.2 kg/m^2	Age	GDM, GHTN, CS
Turhan 2003 [41]	Turkey	Retrospective cohort	High	N= 38; Age = 27.6 years; BMI= 31.5 kg/m^2	N= 136; Age = 26.6 years; BMI= 23.6 kg/m^2		GDM, GHTN, PE, IOL, CS
Sir-Petermann 2005 [71]	Chile	Prospective cohort	High	N= 47; Age = 24.6 years; BMI= NP	N= 180; Age = 26.2 years; BMI= NP	Age, BMI, SES	GDM
Al-Ojaimi 2006 [72]	Bahrain	Prospective cohort	High	N= 134; Age = 29.4 years; BMI= 30.9 kg/m^2	N= 479; Age = 28.3 years; BMI= 29.4 kg/m^2		GDM, GHTN, PE
Dokras 2006 [42]	USA	Retrospective cohort	Low	N= 46; Age = NP; BMI= NP	N= 108; Age = NP; BMI= NP	Weight	Miscarriage, GDM, PE, CS
Kovo 2006 [43]	Israel	Retrospective cohort	Moderate	N= 33; Age = 30.1 years; BMI= 27.7 kg/m^2	N= 66; Age = 30.7 years; BMI= 25.2 kg/m^2	Age	GDM, GHTN, CS
Lo 2006 [44]	USA	Retrospective cohort	Moderate	N= 1542; Age = 31.4 years; BMI= NP	N= 91391; Age = 30.0 years; BMI= NP		GDM
Hu 2007 [73]	UK	Prospective cohort	Low	N= 22; Age = 31.5 years; BMI= 24.4 kg/m^2	N= 22; Age = 31.47 years; BMI= 24.2 kg/m^2	Age, BMI, Parity	GHTN, PE
Palep-Singh 2007 [45]	UK	Retrospective cohort	High	N= 120; Age = NP; BMI= NP	N= 95; Age = NP; BMI= NP		Miscarriage

Study	Country	Design	Quality	PCOS group	Control group	Adjusted	Outcomes
Sir-Petermann 2007 [74]	Chile	Prospective cohort	Moderate	N= 48; Age= 29 years; BMI= 28.6 kg/m²	N= 51; Age= 26 years; BMI= 33.4 kg/m²		GHTN
Koivunen 2008 [46]	Finland	Retrospective cohort	High	N= 92; Age= NP; BMI= NP	N= 2371; Age= NP; BMI= NP		Miscarriage
Beydoun 2009 [23]	USA	Retrospective cohort	Low	N= 28; Age= 32.3 years; BMI= 30.6 kg/m²	N= 23; Age= 32.5 years; BMI= 23.9 kg/m²	Age	Miscarriage
Bolton 2009 [47]	Ireland	Retrospective cohort	High	N= 66; Age = 32.3 years; BMI= NP	N= 66; Age = 32.3 years; BMI= NP	Age, Parity	GDM
Gupta 2009 [75]	India	Prospective cohort	Moderate	N= 56; Age= NP; BMI= NP	N= 56; Age= NP; BMI= NP	Age, Weight	GDM, GHTN
Alshammari 2010 [48]	Canada	Retrospective cohort	Moderate	N= 44; Age = 32.6 years; BMI= 30.8 kg/m²	N= 127; Age = 34 years; BMI= 24.8 kg/m²		GHTN, CS
Altieri 2010 [49]	Italy	Retrospective cohort	Low	N= 15; Age = 34.7 years; BMI= 24.3 kg/m²	N= 214; Age = 32.7 years; BMI= 23.1 kg/m²		GDM, GHTN, PE, CS
Anderson 2010 [76]	USA	Prospective cohort	High	N= 39; Age = 30.1 years; BMI= 30.8 kg/m²	N= 31; Age = 32.4 years; BMI= 25.1 kg/m²		CS
Li 2010 [50]	China	Retrospective case-control	High	N= 34; Age = 31.6 years; BMI= 26.2 kg/m²	N= 70; Age = 31.5 years; BMI= 22.4 kg/m²		PE
De Leo 2011 [77]	Italy	Prospective cohort	High	N= 98; Age = 32 years; BMI= 28.3 kg/m²	N= 110; Age = 33 years; BMI= 26.6 kg/m²		Miscarriage, GDM, GHTN, PE
Dmitrovic 2011 [51]	USA	Retrospective cohort	Moderate	N= 17; Age = 29 years; BMI= 32 kg/m²	N= 17; Age = 31 years; BMI= 26 kg/m²		GDM
Nejad 2011 [52]	Iran	Retrospective cohort	Low	N= 52; Age= NP; BMI= NP	N= 47; Age= NP; BMI= NP		Miscarriage

Nouh 2011 [78]	Egypt	Prospective cohort	Low	N= 40; Age = 25.5 years; BMI= 24.2 kg/m^2	N= 40; Age = 26 years; BMI= 23.9 kg/m^2	Age, BMI	Miscarriage, GDM, GHTN, PE, CS
Palomba 2012 [79]	Italy	Prospective cohort	Low	N= 42; Age = 28.3 years; BMI= 27.9 kg/m^2	N= 84; Age = 28.4 years; BMI= 27.3 kg/m^2	Age, BMI	GHTN, PE, IOL, CS
Reyes-Munoz 2012 [53]	Mexico	Retrospective cohort	Moderate	N= 52; Age = 29.1 years; BMI= 27.5 kg/m^2	N= 52; Age = 29 years; BMI=27.5 kg/m^2	Age, BMI, Parity	Miscarriage, GDM, PE
Wang 2013 [80]	China	Prospective cohort	Low	N= 144; Age = 30.8 years; BMI= 23.0 kg/m^2	N= 594; Age = 29.1 years; BMI= 20.0 kg/m^2		Miscarriage, GDM, GHTN
Ashrafi 2014 [54]	Iran	Retrospective cohort	Low	N= 234; Age= 29.6 years; BMI= 26.1 kg/m^2	N= 468; Age= 28.5 years; BMI= 25.6 kg/m^2		GDM
Elkholi 2014 [81]	Egypt	Prospective cohort	Moderate	N= 200; Age = 23.4 years; BMI= 31.7 kg/m^2	N= 200; Age = 23.2 years; BMI= 31.8 kg/m^2	Age, BMI, SES	Miscarriage, GDM, GHTN, PE, CS
Foroozanfard 2014 [55]	Iran	Retrospective cohort	Low	N= 130; Age = 28.8 years; BMI= 28.0 kg/m^2	N= 131; Age = 29.3 years; BMI= 27.7 kg/m^2		GHTN, PE, CS
Huang 2014 [56]	China	Retrospective cohort	Low	N= 50; Age= 29.8 years; BMI= NP	N= 39; Age= 30.0 years; BMI= NP	Age	Miscarriage
Joham 2014 [82]	Australia	Prospective cohort	High	N= 222; Age= NP; BMI= NP	N= 4011; Age= NP; BMI= NP		GDM, GHTN
Lathi 2014 [83]	USA	Prospective cohort	Low	N= 59; Age= 32.5 years; BMI= 26.0 kg/m^2	N= 287; Age= 36.3 years; BMI= 22.7 kg/m^2		Miscarriage
Li 2014 [57]	China	Retrospective cohort	Low	N= 38; Age= NP; BMI= NP	N= 289; Age= NP; BMI= NP	Age	Miscarriage
Liu 2014 [58]	China	Retrospective cohort	High	N= 20; Age= 30.5 years; BMI= NP	N= 166; Age= 31.6 years; BMI= NP		Miscarriage

Naver 2014 [91]	Denmark	Prospective cohort	Moderate	N= 459; Age = 31.6 years; BMI= 22.9 kg/m^2	N= 5409; Age = 30.7 years; BMI= 23.4 kg/m^2		GDM, GHTN, PE, IOL, CS
Palomba 2014 [84]	Italy	Prospective cohort	Low	N= 150; Age = 27.8 years; BMI= 27.3 kg/m^2	N= 150; Age = 27.4 years; BMI= 27.0 kg/m^2	Age, BMI	Miscarriage, GDM, GHTN, PE, CS
Zhang 2014 [85]	China	Prospective cohort	High	N= 27; Age = 29.6 years; BMI= 24.4 kg/m^2	N= 27; Age = 29.9 years; BMI= 22.8 kg/m^2		Miscarriage
Doherty 2015 [59]	Australia	Retrospective cohort	Moderate	N= 2566; Age = NP; BMI= NP	N= 25660; Age = NP; BMI= NP	Age	GDM, PE, CS
Kollmann 2015 [60]	Austria	Retrospective cohort	Low	N= 177; Age = 29.6 years; BMI= 24.3 kg/m^2	N= 708; Age = 30 years; BMI= 22.5 kg/m^2		GDM, GHTN, PE, CS
Koster 2015 [86]	Netherlands	Prospective cohort	Low	N= 73; Age = 31.1 years; BMI= 26 kg/m^2	N= 209; Age = 31.7 years; BMI= NP		GDM, IOL, CS
Lovvik 2015 [61]	Sweden	Retrospective cohort	Low	N= 223; Age = NP; BMI= NP	N= 20742; Age = NP; BMI= NP		PE, CS
Mumm 2015 [87]	Denmark	Prospective cohort	Low	N= 157; Age = 29 years; BMI= 26.1 kg/m^2	N= 1037; Age = 29 years; BMI= 23.3 kg/m^2		GDM, GHTN, PE, IOL, CS
Pan 2015 [88]	Taiwan	Prospective cohort	Low	N= 3109; Age = NP; BMI= NP	N= 31090; Age = NP; BMI= NP	Age	GDM
Sawada 2015 [62]	Japan	Retrospective cohort	Low	N= 49; Age = 31.7 years; BMI= 24.4 kg/m^2	N= 49; Age = 31.9 years; BMI= 24.2 kg/m^2	Age, BMI, Parity	GDM, GHTN, CS
Wan 2015 [63]	China	Retrospective cohort	Low	N= 24; Age = 31.4 years; BMI= 22.8 kg/m^2	N= 224; Age = 31.1 years; BMI= 21.4 kg/m^2	Age	GDM, GHTN, PE
Aktun 2016 [89]	Turkey	Prospective cohort	Low	N= 150; Age = 29.3 years; BMI= 22.9 kg/m^2	N= 160; Age = 30.8 years; BMI= 21.4 kg/m^2		GHTN, PE, CS

Sterling 2016 [64]	Canada	Retrospective cohort	Low	N= 71; Age = 33 years; BMI= 24.6	N= 323; Age = 35 years; BMI= 23.6	GDM, CS
Wang 2016 [90]	China	Prospective cohort	Low	N= 119; Age = 32.9 years; BMI= 22	N= 664; Age = 32.9 years; BMI= 21	Miscarriage
Wang 2016 [65]	China	Retrospective case-control	High	N= 1361; Age = NP; BMI= NP	N= 15921; Age = NP; BMI= NP	Miscarriage
Xiao 2016 [66]	China	Retrospective cohort	Low	N= 352; Age = 29.7 years; BMI= NP	N= 2037; Age = 28.6 years; BMI= NP	GDM, CS
Klevedal 2017 [67]	Sweden	Retrospective cohort	Low	N= 37; Age = 27 years; BMI= 28.7 kg/m^2	N= 126; Age = 29.5 years; BMI= 23.4 kg/m^2	GDM, GHTN, PE, CS

BMI: body mass index; CS: Caesarean section; GDM: gestational diabetes mellitus; GHTN: gestational hypertension; IOL: induction of labour; NP: not provided for pregnancy in PCOS vs. controls; PE: pre-eclampsia; SES: socioeconomic status.

Out of all included studies, BMI was measured pre-conception for 24 studies.[23,32-35,39-41,43,49,53-55,62,63,70-72,76,77,80,81,83,85] Compared to women without PCOS, women with PCOS had significantly higher pre-conception BMI (standardised mean difference (SMD): 0.63 kg/m^2, 95% CI: 0.42, 0.84; I^2= 92.1%).

Twelve studies measured GWG.[32,33,35,40,41,49,53,71,72,76,79,89] Of these, only 1 study mentioned the initial and last time points for weight measurements [72] while the last time point for measurement is not stated in other studies. None of the included studies reported GWG by the Institute of Medicine (IOM) GWG recommendations according to pre-conception BMI. Compared with women without PCOS (n=2048), women with PCOS (n=870) showed significantly higher GWG (SMD: 0.26 kg, 95% CI: 0.03, 0.50; I^2= 82.6%). There was no study on GWG in which women were taking metformin during pregnancy.

Outcomes

Figure 2 shows pooled and individual ORs for the outcomes of interest. Table 2_a-2_f show results from sub-group meta-analyses.

Miscarriage- Twenty-one studies reported miscarriage in 3196 women with and 21934 women without PCOS. Miscarriage was defined as pregnancy loss prior to 20th week of gestation by 3 studies[42,53,70] and as early pregnancy loss (6-8 weeks) confirmed by ultrasound.[65] Women with PCOS had a higher prevalence of miscarriage (OR: 1.59, 95% CI: 1.11, 2.28) (Figure 2_A). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher prevalence of miscarriage in PCOS (OR: 1.71, 95% CI: 1.19, 2.45). On sub-group analysis (Table 2_a), the rate of miscarriage remained significantly higher in ovulatory and hyperandrogenic phenotypes, for those from Australia and New Zealand and Africa, BMI-matched studies, women with BMI<30 kg/m^2 and BMI>30 kg/m^2, spontaneous conception modes, and good quality studies. The odds for miscarriage was greater for ovulatory phenotype, those from Africa, BMI-matched studies, BMI<30 kg/m^2, spontaneous conception and good quality studies.

Table 2_a- Sub-group analysis of miscarriage

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	1	9.75 (1.16, 82.11)	0.0%
	Anovulatory	5	1.02 (0.70, 1.48)	0.0%
	Hyperandrogenic	6	1.40 (1.06, 1.86)	8.0%
	Non-hyperandrogenic	0		
Geographic continent	Europe	4	1.19 (0.60, 2.36)	73.4%
	Americas	6	1.31 (0.79, 2.16)	22.5%
	Asia	8	1.60 (0.76, 3.36)	91.1%
	Australia & New Zealand	1	1.52 (1.11, 2.06)	.%
	Africa	2	4.26 (2.56, 7.08)	0.0%
BMI	Matched	4	3.92 (2.56, 6.01)	0.0%
	<30 (kg/m^2)	2	3.89 (1.79, 8.47)	0.0%
	>30 (kg/m^2)	2	2.73 (1.11, 6.73)	68.7%
Conception mode	Spontaneous	1	9.75 (1.16, 82.11)	.%
	ART	12	1.22 (0.94, 1.57)	31.0%

	Poor quality	7	0.96 (0.79, 1.62)	1.2%
Study quality	Fair quality	4	1.29 (0.36, 4.57)	84.3%
	Good quality	10	2.16 (1.34, 3.47)	79.9%

Gestational diabetes mellitus- Thirty-nine studies assessed GDM in 11565 women with and 177296 women without PCOS. The GDM definition was not consistent across these studies. Compared to women without PCOS, women with PCOS showed higher prevalence of GDM (OR: 2.89, 95% CI: 2.37, 3.54) (Figure 2_B). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher prevalence of GDM in PCOS (OR: 2.83, 95% CI: 2.33, 3.44). On sub-group analysis (Table 2_b), the higher prevalence was retained for ovulatory, anovulatory and hyperandrogenic phenotypes, women from Europe, Americas, Asia and Australia and New Zealand, BMI-matched and non-matched studies, women with BMI<30 kg/m^2, spontaneous conception modes, fair and good quality studies. The odds for GDM was greater for ovulatory, anovulatory, hyperandrogenic phenotypes, those from Europe and Americas, for BMI<30 kg/m^2 and good quality studies.

Table 2_b-Sub-group analysis of gestational diabetes mellitus

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	6.66 (1.92, 23.19)	28.4%
	Anovulatory	15	3.05 (1.90, 4.90)	71.2%
	Hyperandrogenic	11	3.44 (2.11, 5.61)	68.2%
	Non-hyperandrogenic	2	4.20 (0.20, 88.58)	78.2%
Geographic continent	Europe	13	3.31 (1.57, 6.97)	77.5%
	Americas	9	3.26 (2.009, 5.27)	47.3%
	Asia	12	2.73 (1.88, 3.96)	84.1%
	Australia & New Zealand	3	2.40 (1.79, 3.23)	39.9%
	Africa	2	4.68 (0.10, 223.95)	85.3%
BMI	Matched	7	2.85 (1.41, 5.78)	60.5%
	<30 (kg/m^2)	3	3.25 (1.35, 7.82)	46.6%
	>30 (kg/m^2)	3	1.43 (0.89, 2.29)	0.0%
Conception mode	Spontaneous	1	35.53 (2.02, 624.72)	.%
	ART	3	2.03 (0.86, 4.79)	55.8%
Study quality	Poor quality	10	1.96 (1.05, 3.64)	63.9%
	Fair quality	11	2.94 (1.87, 4.62)	56.4%
	Good quality	18	3.33 (2.48, 4.46)	85.4%

Gestational hypertension- Twenty-nine studies reported GHTN in 2698 women with and 14856 women without PCOS. GHTN was defined as SBP ≥ 140mmHg or DBP ≥ 90 mmHg in 2 studies,[80] [62] as SBP ≥ 140mmHg or DBP ≥ 90 mmHg after 20th week of gestation in 10 studies,[33,37,40,49,60,72,74,75,81,84] as SBP ≥ 140mmHg or DBP ≥ 90 mmHg after first trimester or 15 mmHg increment in DBP compared to measured DBP in the first trimester in 1 study,[34] as DBP ≥ 90 mmHg at 2 occasions during pregnancy in 1 study,[39] as SBP ≥ 140mmHg or DBP ≥ 90 mmHg after 20th week of gestation or SBP ≥ 150mmHg or DBP ≥ 100 mmHg during labor in 2 studies[35,63] and as SBP ≥ 140mmHg or DBP ≥ 90 mmHg after 20th week of gestation which got normal 4-6 weeks after delivery in 1 study.[73] Definition was not provided in the remaining twelve studies. On meta-analysis, women with PCOS were more likely to have GHTN compared to women without PCOS (OR: 2.58, 95% CI: 1.95, 3.41) (Figure 2_C). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher rate of GHTN in PCOS (OR: 2.62, 95% CI: 1.99, 3.45). On sub-group analysis (Table 2_c), the significant increase in the rate of GHTN in women with PCOS was retained for ovulatory, anovulatory and hyperandrogenic phenotypes, women from Europe, Americas, Asia, Australia and New Zealand, BMI- matched and non-matched studies, women with BMI<30 kg/m^2, spontaneous conception modes, and across study qualities. The odds for GHTN was greater for ovulatory, anovulatory and hyperandrogenic phenotypes, those from Americas, BMI<30 kg/m^2, spontaneous conception and good quality studies. Where all participants had GDM,[48,55,79,89] the higher rate of GHTN in PCOS was retained (OR: 2.74, 95% CI: 1.86, 4.03).

Table 2_c-Sub-group analysis of gestational hypertension

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	7.78 (2.54, 23.78)	4.0%
	Anovulatory	8	3.71 (1.85, 7.42)	61.5%
	Hyperandrogenic	5	5.29 (3.05, 9.18)	9.2%
	Non-hyperandrogenic	2	4.13 (0.36, 47.28)	65.3%
Geographic	Europe	13	2.41 (1.26, 4.63)	71.6%

continent	Americas	2	11.49 (1.98, 66.67)	0.0%
	Asia	11	2.65 (2.03, 3.45)	0.0%
	Australia & New Zealand	1	2.52 (1.78, 3.58)	.%
	Africa	2	3.27 (0.25, 42.39)	74.5%
BMI	Matched	6	2.42 (1.20, 4.88)	23.9%
	<30 (kg/m^2)	4	3.25 (1.87, 5.65)	0.0%
	>30 (kg/m^2)	2	1.66 (0.85, 3.23)	
Conception mode	Spontaneous	2	11.12 (1.97, 62.78)	0.0%
	ART	1	3.30 (0.63, 17.36)	.%
Study quality	Poor quality	6	2.38 (1.29, 4.39)	55.3%
	Fair quality	8	2.22 (1.08, 4.54)	67.1%
	Good quality	15	3.06 (2.25, 4.16)	16.3%

Pre-eclampsia- Twenty-six studies assessed PE in 5896 women with and 65669 women without PCOS. PE was defined as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg and proteinuria after 20th week of gestation in 2 studies,[36,81] as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg and proteinuria>300 mg/day after 20th week of gestation in 13 studies,[33,35,49,50,53,60,61,63,72,73,84,89,91] as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg and proteinuria or 2 of the followings: hemoglobin $\geq$8.0 mmol/L, thrombocytopenia, liver enzyme elevation, rise of plasma uric acid concentration in 1 study [34] and as SBP $\geq$140 mmHg or DBP $\geq$90 mmHg and proteinuria $\geq$++ using urine stick in 1 study.[39] The other 9 studies did not provide the definition used for PE. The prevalence of PE was significantly higher in women with PCOS (OR: 1.87, 95% CI: 1.55, 2.25) (Figure 2$_D$). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher prevalence of PE in PCOS (OR: 1.87, 95% CI: 1.56, 2.25). On sub-group analysis (Table 2$_d$), PE remained significantly associated with PCOS in ovulatory, anovulatory, hyperandrogenic phenotypes, those from Europe, Asia, Australia and New Zealand, women with BMI<30 kg/m^2, spontaneous conception and across study qualities. The odds for PE was greater for ovulatory and hyperandrogenic phenotypes, women from Asia, BMI-matched studies, women with BMI<30 kg/m^2, spontaneous conception poor and good quality studies. Where all participants had GDM,[50,55,79,89] the higher rate of PE in PCOS was retained (OR: 2.72, 95% CI: 1.77, 4.19).

Table 2_d-Sub-group analysis of pre-eclampsia

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	5.25 (2.00, 13.76)	0.0%
	Anovulatory	10	1.67 (1.23, 2.26)	31.9%
	Hyperandrogenic	8	1.75 (1.26, 2.43)	41.5%
	Non-hyperandrogenic	2	0.70 (0.13, 3.71)	0.0%
Geographic continent	Europe	13	1.81 (1.39, 2.36)	5.8%
	Americas	3	1.85 (0.44, 7.85)	69.3%
	Asia	7	2.63 (1.80, 3.83)	0.0%
	Australia & New Zealand	1	1.66 (1.46, 1.88)	.%
	Africa	2	2.59 (0.30, 22.74)	73.4%
BMI	Matched	6	2.18 (1.00, 4.74)	42.3%
	<30 (kg/m^2)	4	2.96 (1.25, 7.02)	17.7%
	>30 (kg/m^2)	3	1.15 (0.66, 2.02)	0.0%
Conception mode	Spontaneous	2	9.16 (1.61, 52.29)	0.0%
	ART	2	1.30 (0.57, 2.97)	0.0%
Study quality	Poor quality	5	2.91 (1.27, 6.63)	17.4%
	Fair quality	7	1.66 (1.48, 1.87)	0.0%
	Good quality	14	2.12 (1.53, 2.95)	24.2%

Induction of labor- Five studies reported IOL in 769 women with and 6875 women without PCOS. The rate of IOL was significantly higher in women with PCOS (OR: 2.55, 95% CI: 1.23, 5.30) (Figure 2$_E$). There was no study in which women were taking metformin during pregnancy. On sub-group analysis (Table 2$_e$), the higher rate of IOL was retained for anovulatory and hyperandrogenic phenotypes, women from Asia, poor and fair quality studies. The odds of IOL was the greatest for a retrospective study from Asia with poor quality. There was only 1 study reporting IOL in women with GDM in which the rate of IOL was similar in women with and without PCOS (OR: 1.25, 95% CI: 0.56, 2.77).

Table 2_e- Sub-group analysis of induction of labor

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	1	2.13 (0.79, 5.75)	.%
	Anovulatory	1	1.81 (1.08, 3.01)	.%
	Hyperandrogenic	1	2.34 (1.44, 3.80)	.%
	Non-hyperandrogenic	1	0.30 (0.04, 2.24)	.%
Geographic continent	Europe	4	1.81 (0.94, 3.47)	77.7%
	Americas	0		
	Asia	1	11.82 (2.96, 47.22)	.%
	Australia & New Zealand	0		
	Africa	4	3.47 (1.36, 8.85)	86.4%

BMI	Matched	1	1.25 (0.56, 2.77)	.%
	<30 (kg/m^2)	0		
	>30 (kg/m^2)	0		
Conception mode	Spontaneous	0		
	ART	0		
Study quality	Poor quality	1	11.82 (2.96, 47.22)	.%
	Fair quality	1	1.29 (1.01, 1.65)	.%
	Good quality	3	3.20 (0.79, 12.89)	84.2%

Caesarean section – Twenty-five studies reported CS in 6227 women with and 67856 women without PCOS. The rate of CS was significantly higher in women with PCOS compared to those without PCOS (OR: 1.39, 95% CI: 1.23, 1.57) (Figure 2$_F$). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher rate of CS in PCOS (OR: 1.37, 95% CI: 1.21, 1.56). On sub-group analysis (Table 2$_f$), higher rate of CS was remained for women with anovulatory, hyperandrogenic and non-hyperandrogenic phenotypes of PCOS, women from Europe, Asia and Australia and New Zealand, BMI-matched and non-matched studies, BMI<30 kg/m^2, spontaneous conception mode, fair and good quality studies. The odds was greater in non-hyperandrogenic women with PCOS and spontaneous conception. Where all participants had GDM,[48,55,79,89] the higher rate of CS in PCOS was retained (OR: 1.72, 95% CI: 1.26, 2.37).

Table 2_f-Sub-group analysis of Caesarean section

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	2.07 (0.70, 6.15)	66.7%
	Anovulatory	7	1.63 (1.52, 1.74)	0.0%
	Hyperandrogenic	7	1.62 (1.52, 1.73)	0.0%
	Non-hyperandrogenic	2	2.25 (1.02, 4.98)	63.3%
Geographic continent	Europe	12	1.33 (1.13, 1.56)	22.4%
	Americas	3	1.14 (0.77, 1.68)	0.0%
	Asia	7	1.26 (1.05, 1.51)	0.0%
	Australia & New Zealand	1	1.65 (1.54, 1.77)	.%
	Africa	2	1.93 (0.68, 5.47)	72.4%
BMI	Matched	5	1.55 (1.14, 2.10)	2.3%
	<30 (kg/m^2)	3	1.93 (1.27, 2.94)	0.0%
	>30 (kg/m^2)	2	1.19 (0.80, 1.79)	0.0%
Conception mode	Spontaneous	1	3.62 (1.34, 9.77)	.%
	ART	2	1.09 (0.71, 1.67)	0.0%
Study quality	Poor quality	3	1.22 (0.73, 2.04)	0.0%

Fair quality	6	1.44 (1.11, 1.85)	67.2%
Good quality	16	1.36 (1.18, 1.56)	17.1%

Depression- We found no studies assessing perinatal depression in women with and without PCOS.

Meta-regression

While studies on GHTN, PE, and CS were not significantly heterogeneous ($I^2 \leqslant 50\%$), we observed significant heterogeneity ($I^2 > 50\%$) for miscarriage, GDM and IOL. For miscarriage and GDM, meta-regression analyses were performed to investigate the source of heterogeneity (Table 3) but due to insufficient number of studies on IOL we were unable to investigate potential confounders. On meta-regression, age was significantly associated with increased rate of miscarriage (P=0.001) and reduced the tau^2 value from 0.46 to 0.12, indicating that 74.9% of between study variance on pooled analysis on miscarriage is likely explained by age. However age was not associated with GDM (P=0.759). BMI was not associated with miscarriage (P=0.513) and GDM (P=0.783). Multiple pregnancy could not also explain the observed heterogeneity in GDM (P=0.301). There were insufficient data or no observations to perform meta-regression on socioeconomic status, acne, hirsutism, pre-pregnancy diabetes mellitus and hypertension, blood pressure, WBC, CRP, glucose and insulin homeostasis, reproductive hormones, smoking status and parity.

Table 3- Univariate meta-regression analysis of possible confounders on maternal pregnancy outcomes in women with and without PCOS

	No. Studies	Coefficient (95% CI)	p-value	tau^2
Miscarriage				
Age (years)	13	13.87 (6.83, 20.92)	0.001	0.12
BMI (kg/m^2)	9	0.05 (-0.04, 0.15)	0.513	0.63
GDM				
Age (years)	26	-1.99 (-17.56, 13.59)	0.795	1.14
BMI (kg/m2)	24	0.94 (-6.04, 7.92)	0.783	0.86
Multiple pregnancy	22	0.05 (-0.05, 0.16)	0.301	0.43

Discussion

In this systematic review, meta-analysis and meta-regression in 224136 women, we report that women with PCOS have a higher prevalence of miscarriage, GDM, GHTN, PE, IOL and CS. On sub-group analyses the odds were greater in ovulatory phenotype for miscarriage, GDM, GHTN and PE; in women born in Africa for miscarriage, in Europe for GDM, in Americas for GHTN and in Asia for PE and IOL; in spontaneous conception for miscarriage, GDM, GHTN, PE and CS; in good quality studies for miscarriage, GDM and GHTN. The significantly increased odds were retained for miscarriage, GDM, GHTN and CS on BMI-matched studies.

We confirm a prior meta-analysis reporting a higher risk for miscarriage in PCOS.[11] Prior research reports the risk factors for miscarriage, both in PCOS and in the general population, include obesity and ART use.[4,92] Of these, we report the increased rate of miscarriage was retained in BMI-matched studies, studies for women with either BMI below or above 30kg/m^2 and that miscarriage in PCOS was not associated with BMI in meta-regression. However, the higher rate of miscarriage was not maintained for post ART pregnancies. Given that there were no post ART pregnancies among BMI-matched studies, the higher rate of hormonal medications in PCOS[93] may have masked the impact of obesity on miscarriage. We also note that the higher prevalence of miscarriage in PCOS was maintained in hyperandrogenic phenotypes[46,84] and for women from Australia and New Zealand and Africa. This is consistent with previous literature reporting a higher rate of miscarriage in Asian women with PCOS compared to Caucasians[45] and a role of hyperandogenism[25,94] in miscarriage. Our finding of age being associated with increased rate of miscarriage on meta-regression is consistent with advanced maternal age, particularly above 35 years, being a risk factor for miscarriage.[92,94] The independent influence of PCOS is

still difficult to determine and overall it appears likely that other factors significantly contribute to miscarriage in PCOS.

When assessing metabolic disorders in pregnancies, women with PCOS had higher rates of GDM, GHTN and PE compared to women without PCOS consistent with prior literature.[8-11] In the general population, obesity, excessive GWG, IR, hyperandrogenism, inflammation and ethnicity are known risk factors for these disorders with GDM also being an independent risk factor for GHTN and PE.[66,80,89,95-98] We report the higher prevalence of GDM and GHTN in PCOS were not maintained for non-hyperandrogenic phenotypes, women from Africa, BMI>30 kg/m^2 and those conceiving after ART although we note the small number of studies for these sub-groups (n=2-3). Given the results of GDM, GHTN and PE on sub-group analyses are similar, these probably share important risk factors as highlighted by prior research.[99] Higher hypertensive disorders in GDM affected pregnancies were maintained with a greater odds for women with PCOS suggesting that hypertensive disorders in PCOS likely occur independently from GDM but are worsened by GDM which is supported by a prior report of oxidative stress profile in PCOS being higher than non-PCOS but similar to GDM.[7] Despite this, higher PE in PCOS was not retained for those from Americas, BMI-matched studies and assisted conception mode. This may potentially be due to either small sample size (n=1-4) or all the 3 studies from Americas being conducted in overweight/obese women.[36,42,53] Both our and prior findings[80] suggest that PCOS is an independent risk factor for pregnancy-related metabolic disorders, which is exacerbated by obesity. These are of critical importance for consideration in screening and management given that GDM, GHTN and PE may proceed to life-threatening complications for mother and offspring,[100,101] increasing intervention for delivery,[101-104] and increasing diabetes mellitus and cardiometabolic risk in both mothers and infants.[98,105,106]

We report here higher IOL and CS in PCOS. Pregnancies with associated complications are more likely to involve delivery interventions improving maternal and infant outcomes.[101,103,104] The higher rate of CS may be related to the higher IOL in PCOS given that failure in IOL results in increased rate of CS.[103] The increased IOL and CS in PCOS may also relate to the higher rate of GDM in PCOS given GDM results in increased rate of macrosomia[103] or IOL and/or CS for prevention of macrosomia at term.[103,104] Previous reports of similar rates of macrosomia in women with and without PCOS,[8,9,11] despite higher rates of GDM in PCOS, may be therefore explained by higher rate of preventive deliveries. This was confirmed on our results on CS in GDM affected pregnancies with and without PCOS. Alternatively, severe PE necessitates interruption of pregnancy either through IOL or CS.[103,104] Here, the prevalence of IOL and CS differed across phenotypes, geographic continent and BMI-matched and non-matched studies with the small numbers for some sub-groups, particularly for IOL. These might be due to different odds of GDM, PE and fetal disorders across these sub-groups. Although the main indication for CS was not reported by included studies, we report the CS rate was similar in women with and without PCOS post ART. This may be related to the fact that mothers who have received infertility treatment generally are more likely to request an elective CS for fear of adverse infant outcomes.[104]

We report here that rates of miscarriage, GDM, GHTN, PE, IOL and CS differed by geographic continent, PCOS phenotypes and adiposity. Observed differences in the outcomes across geographic continent are possibly due to ethnic differences in hyperandrogenism, IR and obesity in PCOS.[12,45] While the ovulatory phenotype being a subset of hyperandrogenic phenotypes, the greater rate in ovulatory phenotype is unclear and possibly due to either higher rate of ART in other hyperandrogenic phenotypes which generally increases the rate of adverse outcomes or small sample size. The fact that some outcomes were worsened in hyperandrogenic PCOS phenotypes may relate to the reciprocal relationship between

hyperandrogenism and IR (either intrinsic or extrinsic related to obesity)[4,107] in PCOS. This likely aggravates sex hormone imbalances which contribute to adverse pregnancy and birth outcomes through endometrial abnormalities like thickening the endometrium,[108] dysregulating angiogenesis[92] and inducing a state of inflammation in endometrium[94,109-111] and consequently impacting on implantation and placentation[25,92,108] The prevalence of outcomes did not significantly change on exclusion of studies using metformin during pregnancy which is consistent with prior literature on miscarriage,[112] GDM[113] and PE.[114] With regards to study quality, higher miscarriage, GDM, GHTN, PE and CS were confirmed on good quality studies with the lowest risk of bias, validating the observed results on these outcomes. However, IOL was not confirmed on good quality studies which limits the generalizability of this finding.

Strengths of this review are the use of sub-group analyses for a range of potential confounders, meta-regression for exploring the source of heterogeneity and exclusion of studies reporting outcomes in multiple number of pregnancies per woman for further methodological consistency. Limitations include lacking non-English studies, more than half of included studies (n=34) having moderate to high risk of bias, 1 study having less than 30 participants in total, some studies having less than 30 participants with PCOS (n=10), some studies with less than 30 participants at each group (n=6), insufficient number of studies for sub-group analysis by PCOS phenotypes due to differing PCOS definitions, lack of definition or inconsistent reporting of obstetric outcomes, lack or inconsistent reporting of ethnicity across included studies, limited outcomes being reported according to BMI categories, spontaneous conception, pregnancies from ovulation induction and multiple pregnancies, lack of sufficient number of observations on the majority of confounding variables for meta-regression and lack of data on perinatal depression and the impact of depression on pregnancy outcomes in women with and without PCOS.

We report in this systematic review, meta-analysis and meta-regression that women with PCOS were more likely to have miscarriage, GDM, GHTN, PE, IOL and CS. While, miscarriage, GDM, GHTN, PE and CS were increased independent of obesity, the prevalence of all outcomes were similar in women with and without PCOS with BMI>30 kg/m^2, highlighting obesity as a key risk factor. The significant increased rates for miscarriage, GDM, GHTN, PE and IL were not maintained for non-hyperandrogenic PCOS phenotype. The prevalence of all outcomes differed by geographic continent. The higher prevalence of miscarriage, GDM, GHTN, PE, IOL and CS in PCOS were also related to assisted reproduction use. These outcomes remained significantly associated with PCOS in singleton pregnancies except for CS and in good quality studies except for IOL. These findings highlight that PCOS is an important risk factor for maternal pregnancy and delivery complications independent of obesity but the impact is significantly worsened by hyperandrogenic phenotypes for GDM, GHTN, PE, IOL and CS; in women from Africa for miscarriage, from Europe for GDM, from America for GHTN, from Asia for PE and IOL and in spontaneous pregnancies for miscarriage, GDM, GHTN, PE and CS. Further research is warranted investigating the impact of PCOS on pregnancy and delivery complications in women with well-defined PCOS status with consistently defined obstetric outcomes. Pregnancy-related psychological disorders in PCOS also need further study. This is critical for timely identification of high risk groups to improve prevention and management.

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Figure legends list:

Figure 1- PRISMA flowchart of study selection

Figure 2: Meta-analyses for miscarriage, gestational diabetes mellitus, gestational hypertension, pre-eclampsia, induction of labour and caesarean section in women with and without PCOS

A: Miscarriage

B: Gestational diabetes mellitus

C: Gestational hypertension

D: Pre-eclampsia

E: Induction of labour

F: Caesarean section

4292 Retrievals from databases and expert reviewers

342 Duplicate removal

3950 Studies screened by title and abstract

3847 Studies excluded

103 Studies assessed in detail for eligibility

26 Studies excluded

8 No outcome of interest

7 Non-original paper

2 No control group

9 Ineligible population

77 Studies included in the systematic review

14 Studies excluded

6 Reported reporting outcomes in multiple number of pregnancies per woman

8 Overlapping data between studies

63 Studies included in the meta-analysis

Figure 1- PRISMA flowchart of study selection

16x20mm (600 x 600 DPI)

Study	OR (95% CI)	PCOS n/N	Controls n/N	Weight%
Urman 1992	3.00 (0.14, 64.26)	1/4	1/10	1.16
Homburg 1993	0.52 (0.20, 1.35)	11/47	14/38	4.87
Wang 2001	1.51 (1.11, 2.06)	93/373	116/645	6.96
Dokras 2006	1.60 (0.66, 3.85)	10/46	16/108	5.10
Palep-Singh 2007	1.26 (0.62, 2.58)	23/120	15/95	5.69
Koivunen 2008	1.05 (0.64, 1.73)	21/92	521/2371	6.43
Beydoun 2009	0.94 (0.27, 3.34)	7/28	6/23	3.85
De Leo 2011	0.46 (0.20, 1.05)	9/98	20/110	5.24
Nejad 2011	0.67 (0.24, 1.88)	8/52	10/47	4.59
Nouh 2011	9.75 (1.16, 82.11)	8/40	1/40	2.05
Reyes-Munoz 2012	2.04 (0.18, 23.22)	2/52	1/52	1.68
Wang 2013	5.41 (3.67, 7.96)	76/220	58/652	6.76
Elkholi 2014	4.05 (2.40, 6.84)	69/200	23/200	6.35
Huang 2014	1.64 (0.38, 7.01)	6/50	3/39	3.34
Lathi 2014	0.66 (0.32, 1.37)	10/59	68/287	5.62
Li 2014	2.26 (1.09, 4.71)	13/38	54/289	5.62
Liu 2014	1.43 (0.30, 6.89)	2/20	12/166	3.05
Palomba 2014	3.38 (1.47, 7.80)	24/150	8/150	5.25
Zhang 2014	2.84 (0.50, 16.14)	5/27	2/27	2.71
Wang 2016	3.27 (2.06, 5.19)	35/119	75/664	6.54
Wang 2016	0.93 (0.75, 1.16)	93/1361	1160/15921	7.14
Overall (I-squared = 82.8%, p = 0.000)	1.59 (1.11, 2.28)	526/3196	2184/21934	100.00

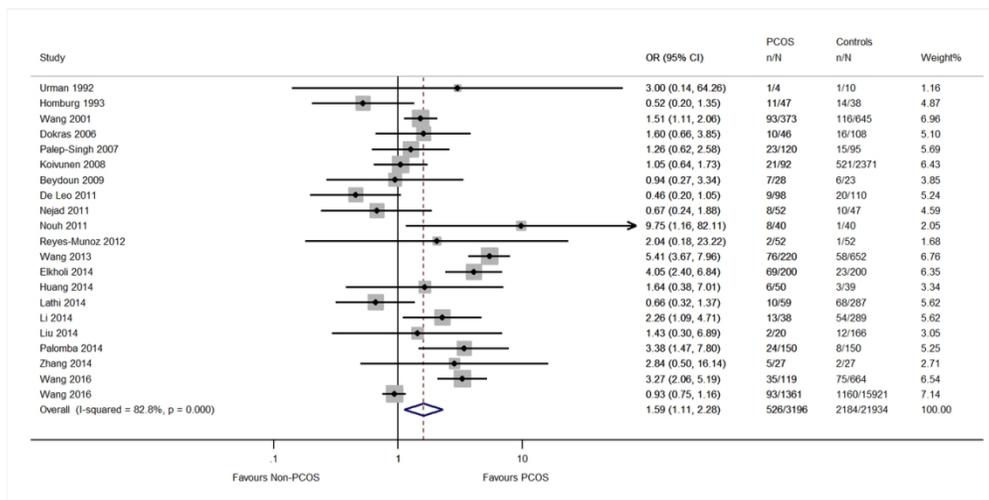Favours Non-PCOS   Favours PCOS

Figure 2_A: Miscarriage

59x29mm (600 x 600 DPI)
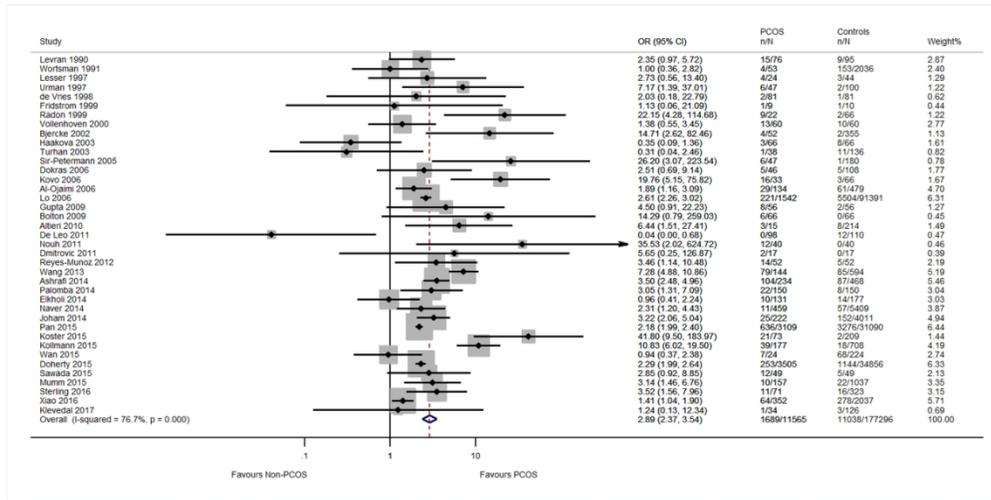
Figure 2_B: Gestational diabetes mellitus

59x29mm (600 x 600 DPI)

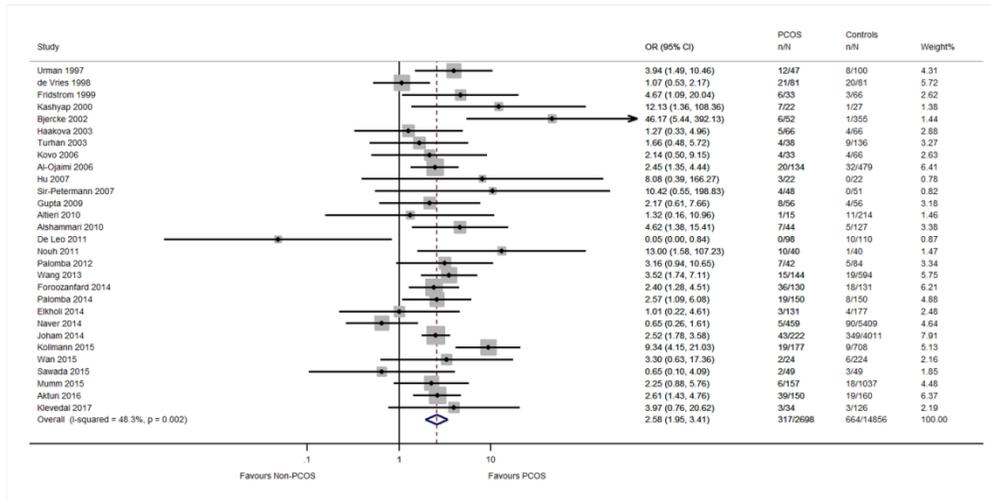| Study	OR (95% CI)	PCOS n/N	Controls n/N	Weight%
Urman 1997	3.94 (1.49, 10.46)	12/47	8/100	4.31
de Vries 1998	1.07 (0.53, 2.17)	21/81	20/81	5.72
Fridstrom 1999	4.67 (1.09, 20.04)	6/33	3/66	2.62
Kashyap 2000	12.13 (1.36, 108.36)	7/22	1/27	1.38
Bjercke 2002	46.17 (5.44, 392.13)	6/52	1/355	1.44
Haakova 2003	1.27 (0.33, 4.96)	5/66	4/66	2.88
Turhan 2003	1.66 (0.48, 5.72)	4/38	9/136	3.27
Kovo 2006	2.14 (0.50, 9.15)	4/33	4/66	2.63
Al-Ojaimi 2006	2.45 (1.35, 4.44)	20/134	32/479	6.41
Hu 2007	8.08 (0.39, 166.27)	3/22	0/22	0.78
Sir-Petermann 2007	10.42 (0.55, 198.83)	4/48	0/51	0.82
Gupta 2009	2.17 (0.61, 7.66)	8/56	4/56	3.18
Altieri 2010	1.32 (0.16, 10.96)	1/15	11/214	1.46
Alshammari 2010	4.62 (1.38, 15.41)	7/44	5/127	3.38
De Leo 2011	0.05 (0.00, 0.84)	0/98	10/110	0.87
Nouh 2011	13.00 (1.58, 107.23)	10/40	1/40	1.47
Palomba 2012	3.16 (0.94, 10.65)	7/42	5/84	3.34
Wang 2013	3.52 (1.74, 7.11)	15/144	19/594	5.75
Foroozanfard 2014	2.40 (1.28, 4.51)	36/130	18/131	6.21
Palomba 2014	2.57 (1.09, 6.08)	19/150	8/150	4.88
Elkholi 2014	1.01 (0.22, 4.61)	3/131	4/177	2.48
Naver 2014	0.65 (0.26, 1.61)	5/459	90/5409	4.64
Joham 2014	2.52 (1.78, 3.58)	43/222	349/4011	7.91
Kollmann 2015	9.34 (4.15, 21.03)	19/177	9/708	5.13
Wan 2015	3.30 (0.63, 17.36)	2/24	6/224	2.16
Sawada 2015	0.65 (0.10, 4.09)	2/49	3/49	1.85
Mumm 2015	2.25 (0.88, 5.76)	6/157	18/1037	4.48
Aktun 2016	2.61 (1.43, 4.76)	39/150	19/160	6.37
Klevedal 2017	3.97 (0.76, 20.62)	3/34	3/126	2.19
Overall (I-squared = 48.3%, p = 0.002)	2.58 (1.95, 3.41)	317/2698	664/14856	100.00

Favours Non-PCOS   Favours PCOS

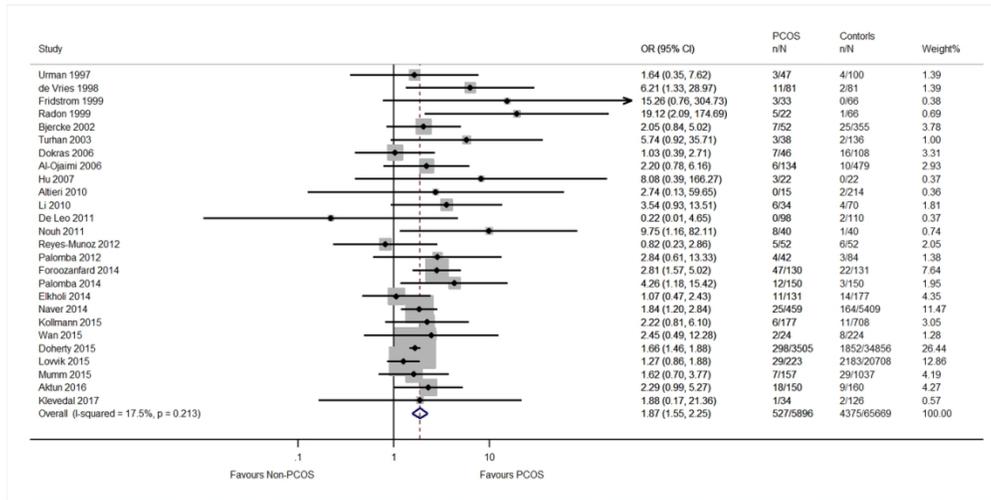Figure 2_C: Gestational hypertension

59x29mm (600 x 600 DPI)

Figure 2_D: Pre-eclampsia
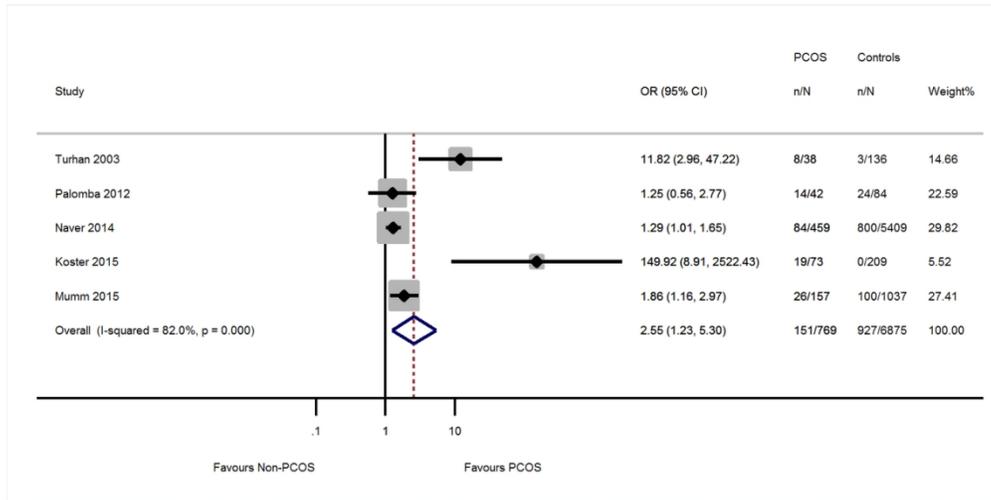
59x29mm (600 x 600 DPI)
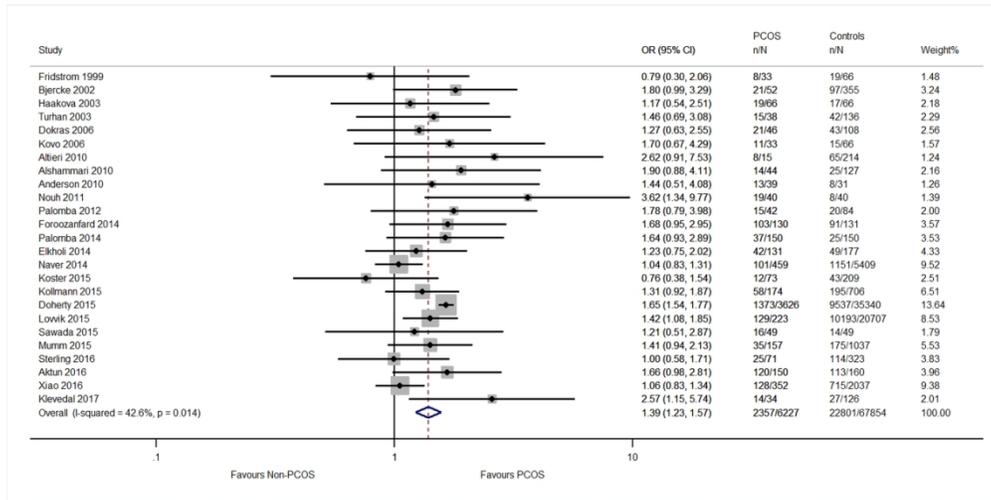
Figure 2_E: Induction of labour

59x29mm (600 x 600 DPI)

Figure 2_F: Caesarean section

59x29mm (600 x 600 DPI)