Title: The role of maternal obesity in infant outcomes in polycystic ovary syndrome- A systematic review, meta-analysis and meta-regression

Mahnaz Bahri Khomami[1] B & M Midwifery; Anju E. Joham[1, 2] Ph.D.; Jacqueline A Boyle[1, 3] Ph.D.; Terhi Piltonen[4] Ph.D.; Chavy Arora[3] MD.; Michael Silagy[3] MD.; Marie L. Misso[1] MBBS; Helena J. Teede[1, 2, 5] Ph.D.; Lisa J. Moran[1] Ph.D.

Affiliations:

1. Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia 3168

2. Diabetes and Vascular Medicine Unit, Monash Health, Melbourne, Victoria, Australia 3168

3. Department of Obstetrics and Gynaecology, Monash Health, Melbourne, Victoria, Australia 3168

4. Department of Obstetrics and Gynecology, PEDEGO Research Unit, Medical Research Center, Oulu University Hospital, University of Oulu, Oulu, Finland

5. Monash Partners Academic Health Sciences Centre, Melbourne, Victoria, Australia 3181

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Corresponding author: Lisa J Moran

Address: Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia 3168

Email address: lisa.moran@monash.edu

Phone number: +613 8572 2664

Abbreviations: PCOS: polycystic ovary syndrome; AnOvu:oligo/anovulation; HA: hyperandrogenism; PCOM: polycystic ovary morphology; IR: insulin resistance; SGA: small for gestational age; LBW: low birth weight; NICU: neonatal intensive care unit; LGA: large for gestational age; GWG: gestational weight gain; BMI: body mass index; BW: birth weight; PTB: preterm birth; CCAs: Cochrane Clinical Answers; ACP: American College of Physicians; CMR: Cochrane Methodology Register; HTA: Health Technology Assessments; DARE: The Database of Abstracts of Reviews of Effectiveness; NHS: national health service; EED: Economic Evaluation Database; NIH: National Institute of Health; AES: Androgen Excess Society; ESHRE/ASRM: European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine; IUGR: intrauterine growth restriction; SES: socioeconomic status; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cell; CRP: C-reactive protein; FBS: fasting blood sugar; OGTT: oral glucose tolerance test; HOMA: homeostatic model assessment; GDM: gestational diabetes mellitus; SHBG: sex hormone binding globulin; TT: total testosterone; FAI: free androgen index; NOS: Newcastle-Ottawa Scale; OR: odds ratio; CI: 95% confidence interval; SMD: standardised mean difference; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; REML: Restricted maximum likelihood; IOM: Institute of Medicine; RCT: randomised controlled trial.

Abstract

Polycystic ovary syndrome (PCOS) is associated with worsened pregnancy and infant outcomes, higher body mass index (BMI) and longitudinal weight gain. Despite most of clinical features of PCOS being risk factors for worsened infant outcomes in the general population, their impact on infant outcomes in PCOS is unknown. We aimed to investigate the association of PCOS with infant outcomes considering maternal adiposity, other known risk factors and potential confounders. The meta-analyses included 42 studies in 7041 women with and 63722 women without PCOS. PCOS was associated with higher gestational weight gain (GWG) and with higher preterm birth and large for gestational age and with lower birth weight with this association varying by geographic continent, PCOS phenotypes and study quality. However PCOS was associated with none of these outcomes on BMI-matched studies. Gestational diabetes was significantly associated with an increased preterm birth on meta-regression. We report for the first time that GWG is higher in PCOS. Infant outcomes vary by geographic continent and study quality but are similar in BMI-matched women with and without PCOS. This suggest that infant outcomes in PCOS may be related to maternal obesity. These novel findings warrant future studies in PCOS investigating screening and management of infant outcomes with consideration of maternal obesity.

Introduction

Polycystic ovary syndrome (PCOS) affects 5-20% of reproductive-aged women.[1] It is diagnosed by a combination of oligo/anovulation (AnOvu), clinical and/ biochemical hyperandrogenism (HA), and/or polycystic ovary morphology (PCOM) after ruling out other aetiologies[2] which results in 4 different PCOS phenotypes.[3] PCOS is a complex endocrinopathy with a wide range of clinical and subclinical reproductive (oligo/anovulation, infertility and adverse maternal and infant pregnancy outcomes), metabolic (obesity, gestational diabetes, diabetes mellitus and cardiovascular risk factors) and psychological (depression and anxiety) features.[4] Insulin resistance (IR) is proposed as a key aetiological feature in PCOS which is both present intrinsically in PCOS [5] and can be further augmented by obesity which worsens the presentation and associated complications of PCOS.

There is growing evidence that infants born to mothers with PCOS are more likely to be premature,[6-9] small for gestational age (SGA),[7] low birth weight (LBW),[6,8] be admitted to neonatal intensive care units (NICU)[6,8] and having higher perinatal mortality,[6,9] compared to those born to mothers without PCOS. Worsened infant outcomes such as a higher risk for large for gestational age (LGA) and macrosomia have been previously associated with obesity[10] and excess gestational weight gain (GWG).[11] These are potential important confounding factors in regard to infant outcomes in PCOS as both obesity [12] and longitudinal weight gain [13] are more prevalent in women with PCOS. Women with a higher BMI have higher rates of exceeding recommended GWG.[11,14] However, the limited research examining GWG in PCOS shows conflicting results with either similar[15,16] or higher GWG[17,18] for women with PCOS. The association of excess GWG with adverse infant outcomes in PCOS is also unclear. In women with similar BMI and GWG, PCOS status did not influence birth weight (BW), preterm birth (PTB), SGA, macrosomia, and LGA birth,[15,16] whereas PCOS was associated with a greater prevalence of SGA birth in women with similar BMI but higher

GWG in PCOS.[17] Additional features in PCOS such as IR and diabetes mellitus,[19] inflammation,[20] infertility, higher rate of multiple pregnancies related to infertility treatments[21] are also known risk factors for adverse infant outcomes and may explain the elevated rate of adverse infant outcomes in women with PCOS.

While a growing body of literature addressing the harmful influence of individual clinical features of PCOS on infant outcomes in the general population,[10,11,22,23] these are currently poorly investigated in the context of PCOS.[6-9] A lack of consensus in this field may also be related to features such as the heterogeneity of PCOS, variable methodology and potential confounders of adverse infant outcomes.[4] We aimed to perform a systematic review, meta-analysis, and meta-regression assessing the association of PCOS with infant outcomes, exploring the impact of clinical and biochemical features of PCOS on infant outcomes and examining the impact of potential confounders on the observed heterogeneity.

Methods

The protocol of 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.[24]

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 (CCAs), Cochrane Central Register of Controlled Trials, American College of Physicians

(ACP) Journal Club, Cochrane Methodology Register (CMR), Health Technology Assessments (HTA), The Database of Abstracts of Reviews of Effectiveness (DARE) and national health service (NHS) Economic Evaluation Database (NHS EED). 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

Observational studies including both cohort and case-control studies were included. Case reports, case series, and reviews were excluded. Eligible studies needed to include women with and without PCOS which reported the relevant outcomes with studies reporting outcomes only among women with PCOS deemed as ineligible. Only articles published in English and conducted on humans 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. The outcomes of interest for this specific review were infant outcomes including intrauterine growth restriction (IUGR), PTB, BW, SGA, macrosomia and LGA. We also looked at the pregnancy-related BMI and GWG as important risk factors of infant outcomes. 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 and M.S) who were not blinded to the names of investigators or sources of publication screened 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 independently by 2 independent reviewers (M.B.K and either of C.A and M.S) per study. Any discrepancies were discussed and resolved through consensus with the third reviewer (L.J.M). The data extracted included information on the authors, year of publication, study design, study location, participants' characteristics and mean and standard deviation (SD) or frequency of the outcomes. Extracted participants' characteristics data included demographic (age, BMI, country of study, ethnicity, socioeconomic status (SES), smoking status, and parity), clinical (PCOS phenotypes, acne and hirsutism scores, pre-conception medical conditions, and early pregnancy systolic (SBP) and diastolic blood pressure (DBP)), hypertensive disorders in pregnancy (HDP) 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, gestational diabetes (GDM), sex hormone binding globulin (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-randomised studies[25] (Supplementary Table 2). Individual items assessed by NOS included: representativeness of the PCOS and non-PCOS groups, ascertainment and validity

of PCOS status and outcomes of interest, 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

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. The categorical pregnancy outcomes for each study were expressed as odds ratios (OR) with 95% confidence intervals (CI) and combined using the random effect model for meta-analysis. For BMI, GWG, and BW standardised mean difference (SMD) with 95% CI pooled for all studies were calculated using the random effect model for meta-analysis. 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 and the exclusion of studies with self-reported PCOS diagnosis. The certainty of evidence for each outcome was assessed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[26] using the Gradepro software[27] (Supplementary Table 4).

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, GDM and non-GDM, non-HDP and study quality (poor/fair/good).

Restricted maximum likelihood (REML)-based random effects meta-regression was perfomed to explore the influence of maternal age, SES, CRP, WBC, BMI, GWG, smoking, parity, multiple pregnancy, mean SBP and DBP, HDP, FBS, OGTT, GDM, SHBG, TT, FAI, acne, and hirsutism 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 distribution 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 using Stata version 14 (StataCorp, 14 College Station, Texas, USA).

Results

Search results

A total of 4292 studies were identified through the search. Of these, 103 studies were retrieved for full-text review. Fifty studies did not meet the inclusion criteria, resulting in 53 studies for the systematic review. For the meta-analysis, of these 53 studies, 11 studies were excluded (Supplementary Table 5) on the basis of reporting outcomes in multiple number of

pregnancies per woman [28-32] and overlapping data,[20,33-37] resulting in 42 included studies (Figure 1).

Characteristics of included studies

The characteristics of 42 included studies are listed in Table 1 and Supplementary Table 6. Outcomes of interest were reported in a total of n=70763 pregnancies comprising 28 retrospective (n=60162) and 15 prospective (n=10601) studies. Sixteen studies were conducted in Europe, 10 in Americas, 12 in Asia, 2 in Australia and New Zealand, and 2 in Africa. There was one study with self-reported PCOS diagnosis.[38] Outcomes of interest by PCOS phenotypes were extractable from 4 studies in women with ovulatory, 23 with anovulatory, 20 with hyperandrogenic, and 2 with non-hyperandrogenic phenotypes of PCOS. In 8 studies, women with and without PCOS were matched on the basis of BMI. There was only 1 study limited to multiple pregnancies in both women with and without PCOS.[39]

Figure 1- PRISMA flowchart of study selection

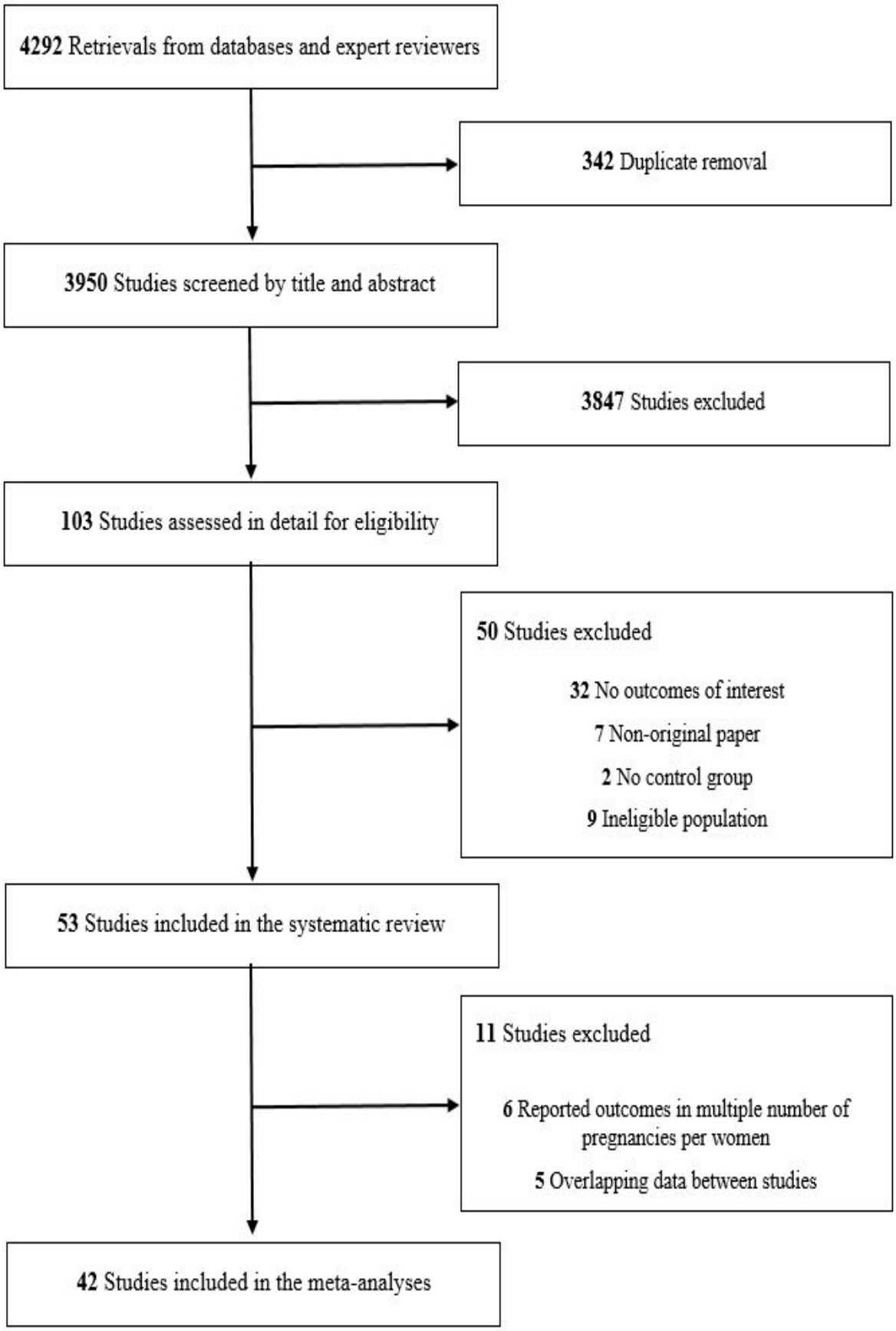


Table 1- Characteristics of included studies for pregnancy outcomes

Study	Country	Design	Risk of bias	PCOS	Controls	Matched characteristics	Outcomes
Wortsman 1991 [40]	USA	Retrospective cohort	High	N= 53; age= 29; BMI= 26.67 kg/m^2; GDM= 4; HDP= NP	N= 2306; age= NP; BMI= NP; GDM= 153; HDP= NP		BW, Macrosomia
Lanzone 1995 [41]	Italy	Prospective cohort	High	N= 12; age= NP; BMI= 24 kg/m^2; GDM= NP; HDP= 1	N= 22; age= NP; BMI= NP; GDM= NP; HDP= NP		GWG, BW
Urman 1997 [42]	Turkey	Retrospective cohort	Moderate	N= 47; age= 27.8; BMI= 25.1 kg/m^2; GDM= 6; HDP= 15	N= 100; age= 28; BMI= 23.4 kg/m^2; GDM= 2; HDP= 12		GWG, PTB, Macrosomia
Fridstrom 1999 [43]	Sweden	Retrospective case-control	High	N= 33; age= 32; BMI= 24.5 kg/m^2; GDM= 1; HDP= 9	N= 66; age= 33; BMI= 23.2 kg/m^2; GDM= 1; HDP= 3	Age	GWG, PTB, BW
Radon 1999 [44]	USA	Retrospective cohort	Low	N= 22; age= 32.4; BMI= 28.9 kg/m^2; GDM= 9; HDP= 5	N= 66; age= 31.1; BMI= 28 kg/m^2; GDM= 2; HDP= 1	Age, Weight	BW
Vollenhoven 2000 [45]	Australia	Retrospective cohort	Moderate	N= 60; age= NP; BMI= 27.1 kg/m^2; GDM= 13; HDP= NP	N= 60; age= NP; BMI= 26.5 kg/m^2; GDM= 10; HDP= NP	Age	BW
Bjercke 2002 [46]	Norway	Retrospective cohort	Moderate	N= 52; age= 31.3; BMI= 26.3 kg/m^2; GDM= 4; HDP= 13	N= 355; age= 32.7; BMI= 21.9 kg/m^2; GDM= 2; HDP= 26		PTB, BW
Haakova 2003 [47]	Czech Republic	Retrospective cohort	Low	N= 66; age= 29; BMI= 23.7 kg/m^2; GDM= 3; HDP= 5	N= 66; age= 29.8; BMI= 23.2 kg/m^2; GDM= 8; HDP= 4	Age	GWG, PTB, BW
Turhan 2003 [48]	Turkey	Retrospective cohort	High	N= 38; age= 27.6; BMI= 31.5 kg/m^2; GDM= 1; HDP= 7	N= 136; age= 26.6; BMI= 23.6 kg/m^2; GDM= 11; HDP= 11		GWG, IUGR, PTB, BW, Macrosomia
Sir-Petermann 2005 [17]	Chile	Prospective cohort	High	N= 47; age= 24.6; BMI= NP; GDM= 6; HDP= 2	N= 180; age= 26.2; BMI= NP; GDM= 1; HDP= NP	Age, BMI, SES	GWG, PTB, BW, SGA, LGA
Al-Ojaimi 2006 [49]	Bahrain	Prospective cohort	High	N= 134; age= 29.4; BMI= 30.9 kg/m^2; GDM= 29; HDP= 26	N= 479; age= 28.3; BMI= 29.4 kg/m^2; GDM= 61; HDP= 42		GWG, PTB, BW, Macrosomia
Dokras 2006 [50]	USA	Retrospective cohort	Low	N= 46; age= NP; BMI= NP; GDM= 5; HDP= 7	N= 108; age= NP; BMI= NP; GDM= 5; HDP= 16	Weight	PTB

Kovo 2006 [51]	Israel	Retrospective cohort	Moderate	N= 33; age= 30.1; BMI= 27.7 kg/m^2; GDM= 16; HDP= 7	N= 66; age= 30.7; BMI= 25.2 kg/m^2; GDM= 3; HDP= 4	Age	PTB, BW
Bolton 2009 [52]	Ireland	Retrospective cohort	High	N= 66; age= 32.3; BMI= NP; GDM= 6; HDP= NP	N= 66; age= 32.3; BMI= NP; GDM= 0; HDP= NP	Age, Parity	PTB, BW, SGA, LGA
Alshammari 2010 [38]	Canada	Retrospective cohort	Moderate	N= 44; age= 32.6; BMI= 30.8 kg/m^2; GDM= 44; HDP= 7	N= 127; age= 34; BMI= 24.8 kg/m^2; GDM= 127; HDP= 5		PTB, LGA
Altieri 2010 [53]	Italy	Retrospective cohort	Low	N= 15; age= 34.7; BMI= 24.3 kg/m^2; GDM= 3; HDP= 1	N= 214; age= 32.7; BMI= 23.1 kg/m^2; GDM= 8; HDP= 13		GWG, PTB, BW
Anderson 2010 [54]	USA	Prospective cohort	High	N= 39; age= 30.1; BMI= 30.8 kg/m^2; GDM= 0; HDP= 0	N= 31; age= 32.4; BMI= 25.1 kg/m^2; GDM= 0; HDP= 0		GWG, BW, SGA, LGA
Li 2010 [55]	China	Retrospective case-control	High	N= 34; age= 31.6; BMI= 26.2 kg/m^2; GDM= 34; HDP= 6	N= 70; age= 31.5; BMI= 22.4 kg/m^2; GDM= 70; HDP= 4		PTB, BW, SGA, Macrosomia, LGA
De Leo 2011 [56]	Italy	Prospective cohort	High	N= 98; age= 32; BMI= 28.3 kg/m^2; GDM= 0; HDP= 0	N= 110; age= 33; BMI= 26.6 kg/m^2; GDM= 12; HDP= 12		PTB, BW
Dmitrovic 2011 [57]	USA	Retrospective cohort	Moderate	N= 17; age= 29; BMI= 32 kg/m^2; GDM= 2; HDP= 0	N= 17; age= 31; BMI= 26 kg/m^2; GDM= 0; HDP= 0		PTB, BW, SGA, LGA
Nouh 2011 [58]	Egypt	Prospective cohort	Low	N= 40; age= 25.5; BMI= 24.2 kg/m^2; GDM= 12; HDP= 18	N= 40; age= 26; BMI= 23.9 kg/m^2; GDM= 0; HDP= 2	Age, BMI	PTB, SGA, LGA
Mehrabian 2012 [59]	Iran	Retrospective cohort	Low	N= 40; age= 27.0; BMI= 26.8 kg/m^2; GDM= 0; HDP= 0	N= 40; age= 28.2; BMI=26.4 kg/m^2; GDM= 0; HDP= 0	Age, BMI, SES	GWG, BW
Palomba 2012 [15]	Italy	Prospective cohort	Low	N= 42; age= 28.3; BMI= 27.9 kg/m^2; GDM= 42; HDP= 11	N= 84; age= 28.4; BMI= 27.3 kg/m^2; GDM= 84; HDP= 8	Age, BMI	GWG, PTB, BW, SGA, Macrosomia, LGA
Reyes-Munoz 2012 [16]	Mexico	Retrospective cohort	Moderate	N= 52; age= 29.1; BMI= 27.5 kg/m^2; GDM= 14; HDP= 5	N= 52; age= 29; BMI=27.5 kg/m^2; GDM= 5; HDP= 6	Age, BMI, Parity	GWG, PTB, BW, SGA, LGA
Yamamoto 2012 [60]	USA	Retrospective cohort	Low	N= 908; age= 31.3; BMI= NP; GDM= 21; HDP= 23	N= 992; age= -; BMI= NP; GDM= NP; HDP= 74		PTB

Boutzios 2013 [61]	Greece	Prospective cohort	Low	N= 41; age= 31.4; BMI= 25.2 kg/m^2; GDM= 0; HDP= 0	N= 110; age= 32.3; BMI= 24.2 kg/m^2; GDM= 2; HDP= 0		BW, SGA, LGA
Wang 2013 [62]	China	Prospective cohort	Low	N= 144; age= 30.8; BMI= 23.0 kg/m^2; GDM= 79; HDP= 15	N= 594; age= 29.1; BMI= 20.0 kg/m^2; GDM= 85; HDP= 19		IUGR, PTB, LGA
Elkholi 2014 [63]	Egypt	Prospective cohort	Moderate	N= 200; age= 23.4; BMI= 31.7 kg/m^2; GDM= 10; HDP= 14	N= 200; age= 23.2; BMI= 31.8 kg/m^2; GDM= 14; HDP= 18	Age, BMI, SES	IUGR, PTB, BW, Macrosomia
Foroozanfard 2014 [64]	Iran	Retrospective cohort	Low	N= 130; age= 28.8; BMI= 28.0 kg/m^2; GDM= 130; HDP= 83	N= 131; age= 29.3; BMI= 27.7 kg/m^2; GDM= 131; HDP= 40		PTB, BW, Macrosomia
Naver 2014 [65]	Denmark	Prospective cohort	High	N= 459; age= 31.6; BMI= 22.9 kg/m^2; GDM= 11; HDP= 30	N= 5409; age= 30.7; BMI= 23.4 kg/m^2; GDM= 57; HDP= 25		PTB, BW, SGA, LGA
Palomba 2014 [66]	Italy	Prospective cohort	Low	N= 150; age= 27.8; BMI= 27.3 kg/m^2; GDM= 22; HDP= 31	N= 150; age= 27.4; BMI= 27.0 kg/m^2; GDM= 8; HDP= 11	Age, BMI	IUGR, PTB, BW, SGA, LGA
Doherty 2015 [67]	Australia	Retrospective cohort	Low	N= 2566; age= NP; BMI= NP; GDM= 253; HDP= 298	N= 25660; age= NP; BMI= NP; GDM= 1144; HDP= 1852	Age	PTB, SGA, Macrosomia
Kollmann 2015 [68]	Austria	Retrospective cohort	Moderate	N= 177; age= 29.6; BMI= 24.3 kg/m^2; GDM= 39; HDP= 25	N= 708; age= 30; BMI= 22.5 kg/m^2; GDM= 18; HDP= 20		PTB, SGA, LGA
Koster 2015 [69]	Netherlands	Prospective cohort	Low	N= 73; age= 31.1; BMI= 26 kg/m^2; GDM= 21; HDP= 10	N= 209; age= 31.7; BMI= NP; GDM= 2; HDP= 10		BW, SGA, LGA
Lovvik 2015 [39]	Sweden	Retrospective cohort	Low	N= 223; age= NP; BMI= NP; GDM= NP; HDP= 29	N= 20742; age= NP; BMI= NP; GDM= NP; HDP= 2183		PTB
Mumm 2015 [3]	Denmark	Prospective cohort	Low	N= 157; age= 29; BMI= 26.1 kg/m^2; GDM= 10; HDP= 13	N= 1037; age= 29; BMI= 23.3 kg/m^2; GDM= 22; HDP= 47		PTB, SGA, LGA
Sawada 2015 [19]	Japan	Retrospective cohort	Low	N= 49; age= 31.7; BMI= 24.4 kg/m^2; GDM= 12; HDP= 2	N= 49; age= 31.9; BMI= 24.2 kg/m^2; GDM= 5; HDP= 3	Age, BMI, Parity	IUGR, PTB, BW
Wan 2015 [70]	China	Retrospective cohort	Low	N= 24; age= 31.4; BMI= 22.8 kg/m^2; GDM= 7; HDP= 4	N= 224; age= 31.1; BMI= 21.4 kg/m^2; GDM= 68; HDP= 14	Age	IUGR, BW

Aktun 2016 [18]	Turkey	Prospective cohort	Low	N= 150; age= 29.3; BMI= 22.9 kg/m^2; GDM= 57	N= 160; age= 30.8; BMI= 21.4 kg/m^2; GDM= 160; HDP= 28	GWG, PTB, Macrosomia
Sterling 2016 [71]	Canada	Retrospective cohort	Low	N= 71; age= 33; BMI= 24.6; GDM= 11; HDP= 14	N= 323; age= 35; BMI= 23.6; GDM= 16; HDP= 21	PTB, SGA, Macrosomia, LGA
Xiao 2016 [72]	China	Retrospective cohort	Low	N= 352; age= 29.7; BMI= NP; GDM= 64; HDP= NP	N= 2037; age= 28.6; BMI= NP; GDM= 278; HDP= NP	PTB, BW, SGA, Macrosomia, LGA
Klevedal 2017 [73]	Sweden	Retrospective cohort	Low	N= 37; age= 27; BMI= 28.7 kg/m^2; GDM= 1; HDP= 4	N= 126; age= 29.5; BMI= 23.4 kg/m^2; GDM= 3; HDP= 5	IUGR, PTB, Macrosomia

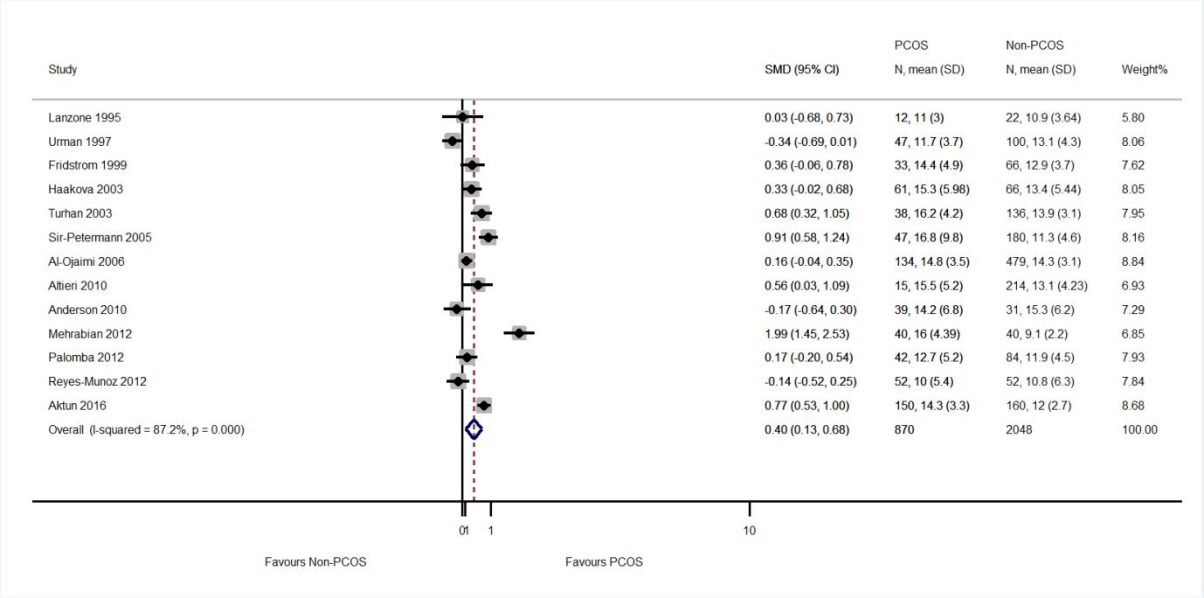
BMI: body mass index; BW: birth weight; GWG: gestational weigh gain; IUGR: intra-uterine growth restriction; LGA: large for gestational age; NP: not provided in PCOS vs. controls; PTB: preterm birth; SES: socioeconomic status; SGA: small for gestational age.

BMI was measured pre-conception for 19 studies,[16,17,19,42,43,46-49,51,53,54,56,59,61-64,70] early pregnancy for 4 studies,[15,18,45,66] and also late pregnancy for 3 studies.[15,17,54] Compared to women without PCOS, women with PCOS had significantly higher pre-conception BMI (SMD: 0.49 kg/m^2, 95% CI: 0.24, 0.75; I^2= 91.8%).

Thirteen studies measured GWG.[15-18,41-43,47-49,53,54,59] Of these, only 1 study mentioned the initial and last time points for weight measurements [49] 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: 0.40 kg, 95% CI: 0.13, 0.68; I^2= 87.2%) (Figure 2). There was no study on GWG in which women were taking metformin during pregnancy.

Of these, 674 and 2004 pregnancies were affected by GDM in women with and without PCOS, respectively.

Figure 2: Meta-analyses for gestational weight gain in women with and without PCOS



SMD: standardised mean difference; CI: confidence interval

On sub-group analysis (Table 2), this higher GWG in PCOS was maintained for studies from Europe and Asia and poor and good quality studies. The degree of GWG was greater in Asian, and good quality studies.

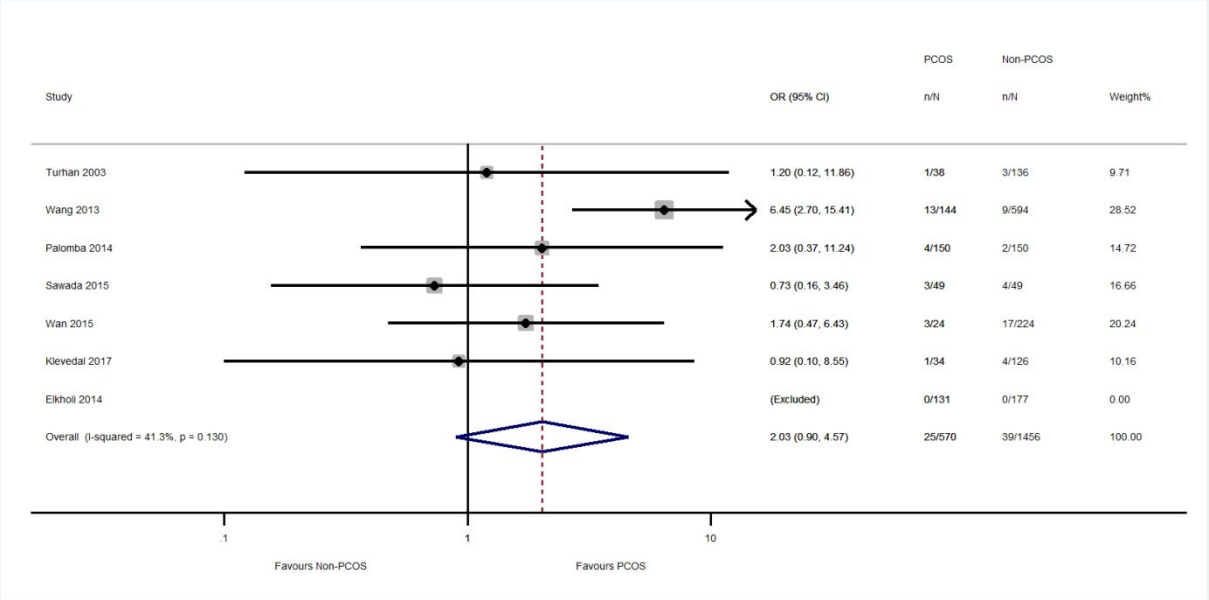
Table 2-Sub-group analysis of gestational weight gain

Sub-group		No. Studies	SMD (95%CI)	I^2
Phenotype	Ovulatory	0		
	Anovulatory	7	0.36 (-0.23, 0.95)	91.8%
	Hyperandrogenic	4	0.37 (-0.68, 1.42)	94.5%
	Non-hyperandrogenic	0		
Geographic continent	Europe	5	0.30 (0.11, 0.50)	0.0%
	Americas	3	0.21 (-0.53, 0.96)	90.8%
	Asia	5	0.62 (0.07, 1.17)	94.2%
	Australia & New Zealand	0		
	Africa	0		
BMI	Matched	4	0.72 (-0.08, 1.51)	93.8%
	BMI<30 (kg/m^2)	4	0.72 (-0.08, 1.51)	93.8%
	BMI≥30 (kg/m^2)	0		
Conception mode	Spontaneous	0		
	ART	0		
Complications	GDM	1	0.17 (-0.20, 0.54)	.%
	Non-GDM	2	0.91 (-1.21, 3.03)	97.1%
	Non-HDP	2	0.91 (-1.21, 3.03)	97.1%
Study quality	Poor quality	6	0.36 (0.03, 0.69)	78.7%
	Fair quality	2	-0.25 (-0.51, 0.01)	0.0%
	Good quality	5	0.74 (0.25, 1.23)	88.4%

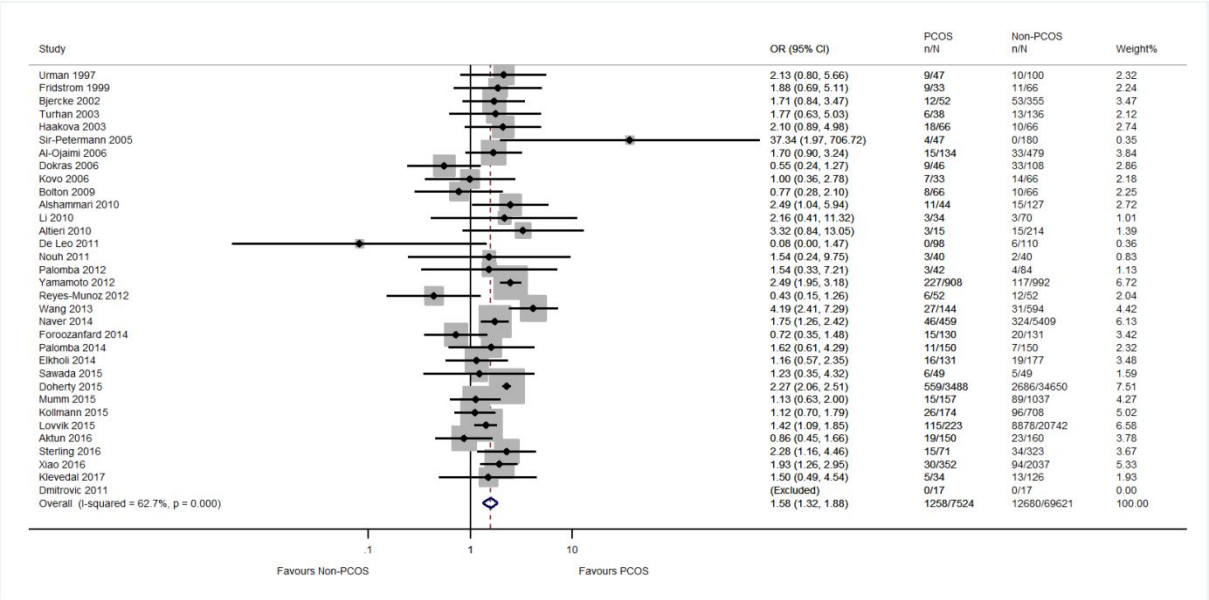
Figure 3$_{(A-E)}$ shows pooled and individual ORs for infant outcomes.

Figure 3: Meta-analyses for intra-uterine growth restriction, preterm birth, birth weight, small for gestational age, and large for gestational age in women with and without PCOS

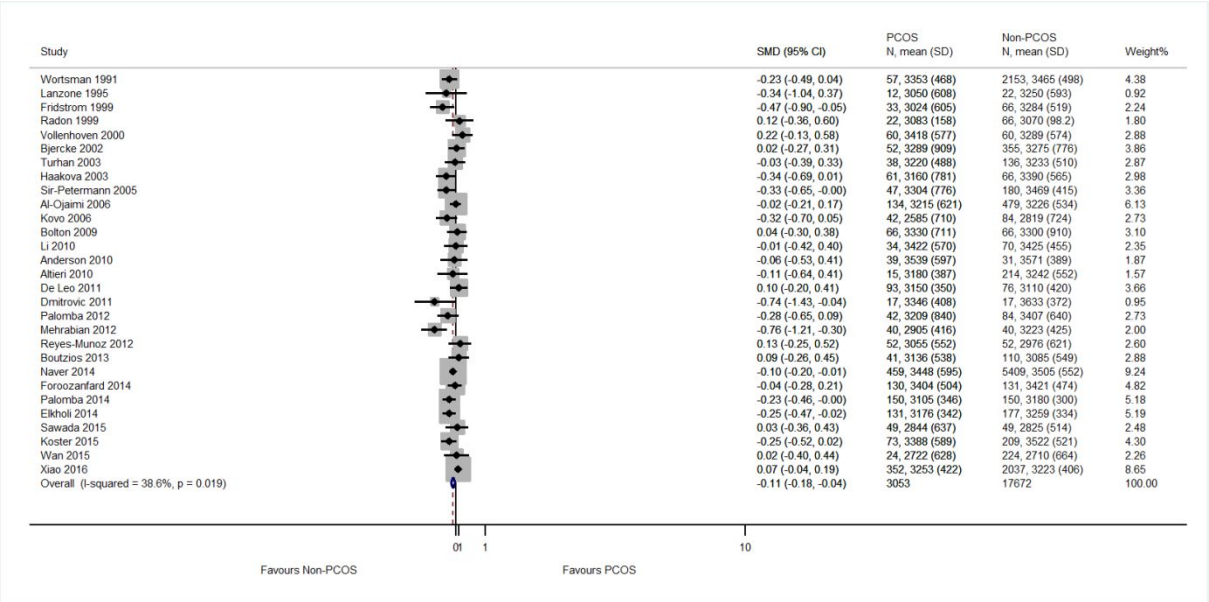
A: Intra-uterine growth restriction



B: Preterm birth

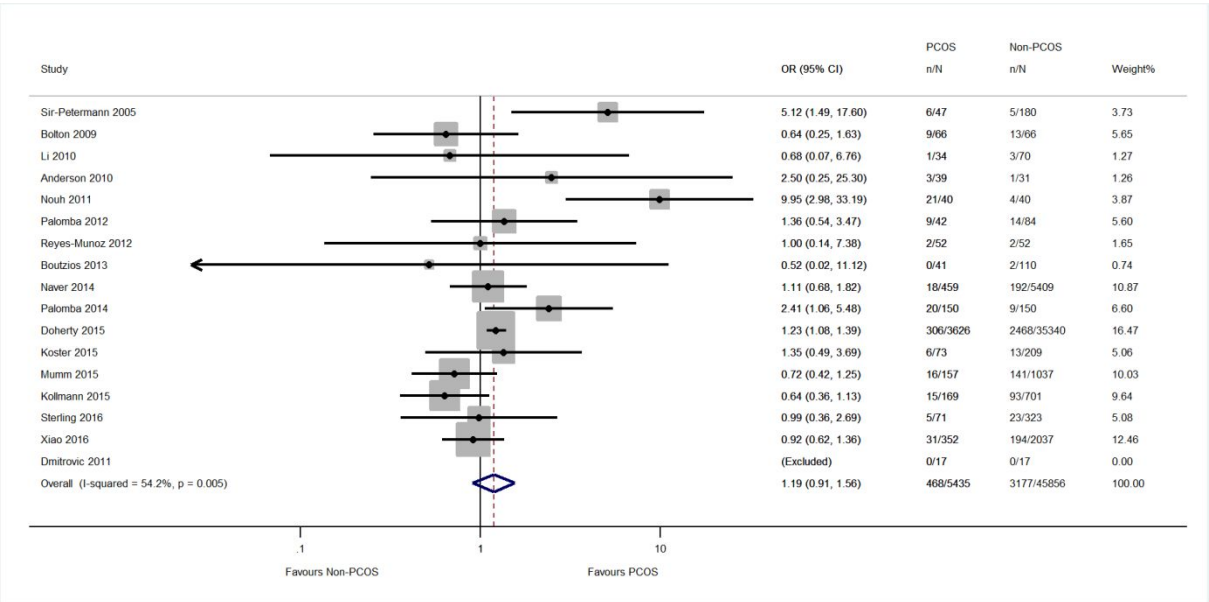


C: Birth weight

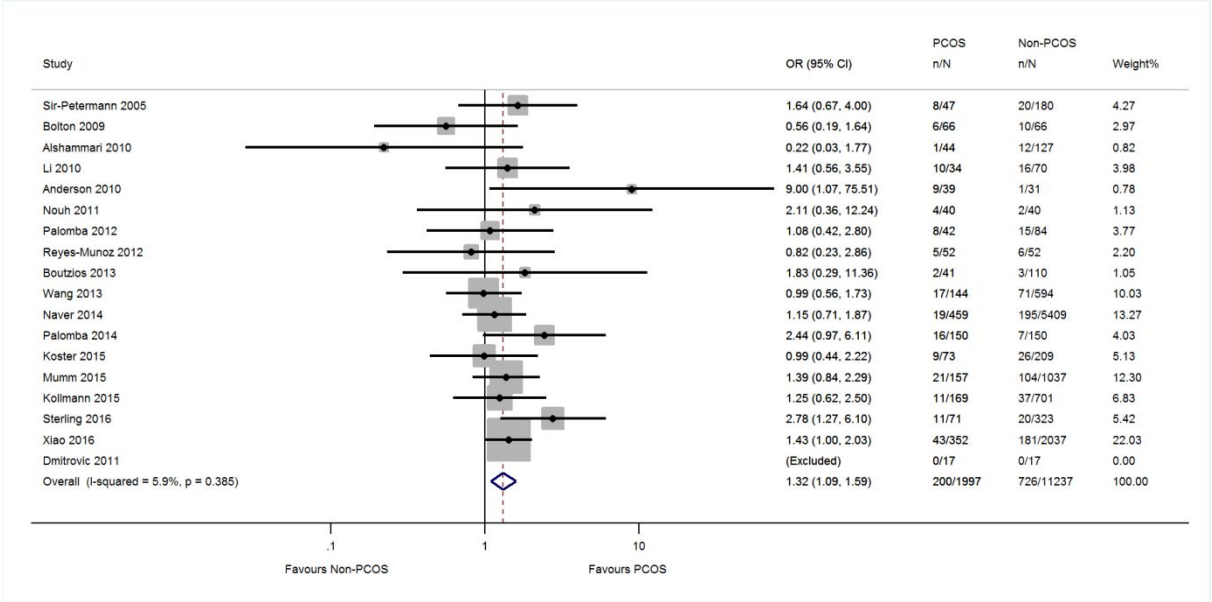


SMD: standardised mean difference; CI: confidence interval

D: Small for gestational age



E: Large for gestational age



Infant outcomes:

Intra-uterine growth restriction- Seven studies assessed IUGR in 570 women with and 1456 without PCOS. The definition of IUGR was foetal growth indices <10th percentile for gestational age[62,63] and foetal weight <-1.5 SD for the SD of the same gestational age.[19] The definition was not provided by the other 4 studies.[20,48,70,73] On meta-analysis, the prevalence of IUGR was similar between women with and without PCOS (OR: 2.03, 95% CI: 0.90, 4.57; I^2= 41.3%) (Figure 3$_A$). There was no study in which women were taking metformin during pregnancy and no study with self-reported PCOS diagnosis. The certainty of evidence for IUGR was low due to small sample size and lack of consideration of important risk factors.

Table 3a-Sub-group analysis of intra-uterine growth restriction

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	0		
	Anovulatory	1	1.74 (0.47, 6.43)	.%
	Hyperandrogenic	0		
	Non-hyperandrogenic	0		
Geographic continent	Europe	3	1.51 (0.39, 5.88)	0.0%
	Americas	0		
	Asia	4	2.11 (0.70, 6.36)	59.8%
	Australia & New Zealand	0		
	Africa	0		
BMI	Matched	3	1.16 (0.37, 3.67)	0.0%
	BMI<30 (kg/m^2)	1	2.03 (0.37, 11.24)	.%
	BMI≥30 (kg/m^2)	0		
Conception mode	Spontaneous	0		
	ART	1	1.74 (0.47, 6.43)	.%
Study quality	Poor quality	1	1.20 (0.12, 11.86)	.%
	Fair quality	0		
	Good quality	5	2.09 (0.84, 5.19)	50.3%

Preterm birth- Thirty-three studies composed of a total of 77145 infants assessed PTB among 7524 and 69621 infants born to women with and without PCOS, respectively. Of these, 12 studies defined PTB as birth prior to 37 weeks of gestation[16,18,38,47,49,55,60,62,63,71,73] and 1 study defined PTB as spontaneous onset of birth and or rupture of membranes prior to 37 weeks of gestation.[39] Women with PCOS had a higher prevalence of PTB (OR: 1.58, 95% CI: 1.32, 1.88; I^2= 62.7%) (Figure 3$_B$). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher rate of PTB in PCOS (OR:

1.62, 95% CI: 1.35, 1.94, I^2= 63%). The exclusion of one study with self-reported PCOS diagnosis, did not significantly impact the odds of PTB (OR: 1.55, 95% CI: 1.30, 1.86; I^2= 63.8%). The certainty of evidence for PTB was very low due to significant overall heterogeneity, not being primary outcome of most of included studies and lack of consideration of important risk factors.

On sub-group meta-analysis (Table 3_b), this higher prevalence of PTB in PCOS was maintained in women with anovulatory and hyperandrogenic phenotypes, studies from Europe, Asia, Australia and New Zealand and fair and good quality studies. The rate of PTB was the greatest in women from Australia and New Zealand. The higher rate of PTB was maintained in singleton pregnancies (OR: 1.48, 95% CI: 1.11, 1.97; I^2= 64.0%).

Table 3b-Sub-group analysis of preterm birth

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	0.94 (0.32, 2.76)	0.0%
	Anovulatory	9	1.50 (1.03, 2.17)	79.9%
	Hyperandrogenic	8	1.45 (1.01, 2.08)	77.1%
	Non-hyperandrogenic	2	0.81 (0.42, 1.54)	0.0%
Geographic continent	Europe	13	1.46 (1.25, 1.71)	0.0%
	Americas	6	1.48 (0.64, 3.43)	83.2%
	Asia	11	1.65 (1.16, 2.36)	55.5%
	Australia & New Zealand	1	2.27 (2.06, 2.51)	.%
	Africa	2	1.20 (0.62, 2.32)	0.0%
BMI	Matched	7	1.25 (0.70, 2.25)	35.7%
	BMI<30 (kg/m^2)	4	1.60 (0.87, 2.96)	0.0%
	BMI≥30 (kg/m^2)	3	1.03 (0.57, 1.86)	41.9%
Conception mode	Spontaneous	1	1.54 (0.24, 9.75)	.%
	ART	2	1.15 (0.28, 4.63)	85.3%
Complications	GDM	4	1.47, 0.70, 2.88)	41.3%
	Non-GDM	0		
	Non- HDP	0		
Study quality	Poor quality	7	1.54 (0.82, 2.88)	44.7%
	Fair quality	9	1.66 (1.23, 2.24)	58.9%
	Good quality	17	1.55 (1.20, 2.01)	64.8%

Birth weight- Twenty-nine studies reported BW among 3053 and 17672 infants born to mothers with and without PCOS. Compared to women without PCOS, women with PCOS gave birth to infants with significantly lower BW (SMD: -0.11 g, 95% CI: -0.18, -0.04; I^2= 38.6%) (Figure 3_C). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher BW in women with PCOS (SMD: -0.11 g, 95%

CI: -0.19, -0.04, I^2= 40.5%). There was no study in which PCOS diagnosis was self-reported. The certainty of evidence for BW was very low due to high risk of bias and not being primary outcome in most of included studies and lack of consideration of important risk factors.

On sub-group meta-analysis (Table 3c), the significantly lower BW in PCOS was retained for infants born to mothers with anovulatory phenotypes, mothers from Europe and Africa, on BMI-matched, BMI<30 kg/m^2 and BMI>30 kg/m^2 studies. The decrement in BW was greatest in anovulatory PCOS phenotype. The lower BW in PCOS was not maintained in singleton pregnancies (SMD: -0.09, 95% CI: -0.20, 0.02; I^2= 52.3%).

Table 3c-Sub-group analysis of birth weight

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	0		
	Anovulatory	11	-0.19 (-0.37, -0.01)	52.9%
	Hyperandrogenic	8	-0.16 (-0.41, 0.08)	59.7%
	Non-hyperandrogenic	0		
Geographic continent	Europe	12	-0.13 (-0.21, -0.04)	10.4%
	Americas	6	-0.11 (-0.34, 0.13);	34.0%
	Asia	9	-0.07 (-0.20, 0.07)	47.8%
	Australia & New Zealand	1	0.22 (-0.14, 0.58);	.%
	Africa	1	-0.25 (-0.47, -0.02)	.%
BMI	Matched	8	-0.18 (-0.35, -0.001)	57.0%
	BMI<30 (kg/m^2)	2	-0.24 (-0.44, -0.05)	0.0%
	BMI≥30 (kg/m^2)	1	-0.25 (-0.47, -0.02)	.%
Conception mode	Spontaneous	1	0.09 (-0.27, 0.45)	.%
	ART	1	0.02 (-0.40, 0.44)	.%
Complications	GDM	3	-0.09 (-0.27, 0.09)	0.0%
	Non-GDM	2	-0.41 (-1.09, 0.27)	76.9%
	Non-HDP	3	-0.33 (-0.78, 0.12)	72.2%
Study quality	Poor quality	10	-0.10 (-0.20, 0.008)	6.0%
	Fair quality	7	-0.10 (-0.25, 0.05)	47.2%
	Good quality	12	-0.12 (-0.25, 0.008)	53.9%

Small for gestational age- Seventeen studies with a total of 51291 infants reported SGA prevalence in 5435 and 45856 infants born to mothers with and without PCOS. SGA was defined as BW below 10th percentile for mean weight for gestational age by 9 studies[3,16,52,54,55,68,69,71,72] and BW below 5th percentile for mean weight for gestational age.[17] The definition was not provided by the remaining 7 studies.[15,57,58,61,65-67] The prevalence of SGA was not significantly different in women with and without PCOS (OR: 1.19, 95% CI:

0.91, 1.56; I^2=54.2%) (Figure 3_D). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed similar rate of SGA in women with and without PCOS (OR: 1.24, 95% CI: 0.94, 1.63, I^2= 55.0%). There was no study in which PCOS diagnosis was self-reported. The certainty of evidence for SGA was low due to not being primary outcome in most of included studies and lack of consideration of important risk factors.

On sub-group meta-analyses (Table 3_d), the rate of SGA in PCOS was significantly higher among those from Australia and New Zealand and Africa, BMI-matched studies, studies limited to BMI<30 kg/m^2 and fair quality studies. The prevalence of SGA was similar in singleton pregnancies (OR: 1.09, 95% CI: 0.74, 1.60; I^2= 54.4%).

Table 3d-Sub-group analysis of small for gestational age

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	2.19 (0.44, 10.94)	76.8%
	Anovulatory	7	1.06 (0.61, 1.84)	68.3%
	Hyperandrogenic	7	1.25 (0.64, 2.42)	74.8%
	Non-hyperandrogenic	2	0.72 (0.38, 1.37)	0.0%
Geographic continent	Europe	8	0.98 (0.71, 1.360)	30.2%
	Americas	5	1.88 (0.75, 4.70)	34.2%
	Asia	2	0.91 (0.62, 1.35)	0.0%
	Australia & New Zealand	1	1.23 (1.08, 1.39)	.%
	Africa	1	9.95 (2.98, 33.19)	.%
BMI	Matched	5	2.91 (1.37, 6.19)	53.5%
	BMI<30 (kg/m^2)	3	2.99 (1.07, 8.35)	70.0%
	BMI≥30 (kg/m^2)	0		
Conception mode	Spontaneous	2	3.22 (0.19, 54.13)	68.0%
	ART	1	0.99 (0.36, 2.70)	.%
Complications	GDM	2	1.24 (0.52, 2.94)	0.0%
	Non-GDM	1	2.50 (0.25, 25.30)	.%
	Non-HDP	3	1.41 (0.22, 8.95)	0.0%
Study quality	Poor quality	4	1.54 (0.45, 5.24)	60.4%
	Fair quality	4	1.22 (1.08, 1.38)	0.0%
	Good quality	9	1.24 (0.78, 1.95)	65.5%

Large for gestational age- Eighteen studies assessed LGA in 1997 and 11237 infants born to mothers with and without PCOS, respectively. The LGA birth was defined as BW above 90th percentile for mean weight for the same gestational age in ten studies,[16,17,38,52,54,55,68,69,71,72] as BW above 2 SD for gestational age and sex in 1 study [3] and as BW above 4000 g in 1 study.[62] Overall, the rate of LGA was significantly higher in women with PCOS compared to those

without PCOS (OR: 1.32, 95% CI: 1.09, 1.59; I^2= 5.9%) (Figure 3_E). Sensitivity analysis for exclusion of studies where women were taking metformin during pregnancy showed higher LGA in PCOS (OR: 1.37, 95% CI: 1.15, 1.64, I^2= 0.0%). The exclusion of one study with self-reported PCOS diagnosis did not significantly impact the odds of LGA (OR: 1.34, 95% CI: 1.12, 1.60; I^2= 0.0%). However macrosomia, reported by 13 studies, was not significantly different in women with and without PCOS (OR: 1.08, 95% CI: 0.98, 1.18; I^2= 0.0%). The certainty of evidence for LGA was low due to not being primary outcome in most of included studies and lack of consideration of important risk factors.

On sub-group meta-analysis (Table 3_e), women with hyperandrogenic phenotypes of PCOS showed higher rate of LGA birth. LGA birth was also significantly higher in post ART and non-GDM affected pregnancies and in good quality studies. The odds of LGA in PCOS was the greatest for those who had received infertility treatment. The higher rate of LGA was maintained in singleton pregnancies (OR: 1.37, 95% CI: 1.11, 1.70; I^2= 0.0%).

Table 3e-Sub-group analysis of large for gestational age

Sub-group		No. Studies	OR (95%CI)	I^2
Phenotype	Ovulatory	3	1.94 (0.87, 4.30)	0.0%
	Anovulatory	6	1.37 (0.93, 2.01)	0.0%
	Hyperandrogenic	6	1.63 (1.08, 2.49)	0.0%
	Non-hyperandrogenic	2	0.82 (0.35, 1.93)	0.0%
Geographic continent	Europe	8	1.23 (0.95, 1.59)	0.0%
	Americas	5	2.01 (1.00, 4.04)	37.0%
	Asia	4	1.20 (0.82, 1.75)	25.1%
	Australia & New Zealand	0		
	Africa	1	2.11 (0.36, 12.24)	.%
BMI	Matched	5	1.52 (0.95, 2.43)	0.0%
	BMI<30 (kg/m^2)	3	1.70 (0.92, 3.15)	0.0%
	BMI≥30 (kg/m^2)	0		
Conception mode	Spontaneous	2	1.97 (0.56, 6.99)	0.0%
	ART	1	2.78 (1.27, 6.10)	.%
Complications	GDM	3	1.00 (0.47, 2.15)	24.3%
	Non-GDM	1	9.00 (1.07, 75.511)	.%
	Non-HDP	3	3.70 (0.75, 18.33)	24.2%
Study quality	Poor quality	4	1.41 (0.64, 3.12)	48.9%
	Fair quality	4	0.93 (0.49, 1.75)	20.4%
	Good quality	10	1.40 (1.14, 1.72)	0.0%

Meta-regression

While studies on BW and LGA were not significantly heterogeneous ($I^2 \leq 50\%$), we observed significant heterogeneity ($I^2 > 50\%$) for PTB and SGA for which meta-regression analyses were

performed to investigate the source of heterogeneity (Table 4). On meta-regression, age was not associated with PTB (P=0.081), and SGA (P=0.057). For SGA, the between-study variance (tau^2) was 0.11, where no covariates were not considered. Although the coefficient marginally non-significant (P=0.057), tau^2 for age was 0 indicating that 100% of heterogeniety in studies on SGA is likely explained by age. BMI was not associated with PTB (P=0.155). There was no association between GWG and PTB (P=0.188). Multiple pregnancy could not also explain the observed heterogeneity in PTB (P=0.065) and SGA (P=0.797). For PTB, the between-study variance (tau^2) was 0.11, where no covariates were taken into account. Although the coefficient marginally non-significant (P=0.065), tau^2 for multipe pregnancy was 0.07 suggesting that 36.36% of heterogeniety in studies on PTB could be attributable to multiple pregnancy.

There was insufficient data to investigate the association of BMI and GWG with SGA birth. Maternal gestational disorders including GDM and HDP were not associated with PTB and SGA birth. There was insufficient data or no observations to perform meta-regression on socioeconomic status, acne, hirsutism, blood pressure, WBC, CRP, glucose and insulin homeostasis, reproductive hormones, smoking status, and parity.

Table 4- Univariate meta-regression analysis of possible confounders on maternal and infant outcomes in women with and without PCOS.

	No. studies	Coefficient (95% CI)	p-value	tau^2
PTB				
Age (years)	22	6.39 (-0.859, 13.63)	0.081	0.06
BMI (kg/m^2)	21	2.36 (-0.98, 5.71)	0.155	0.10
GWG (kg)	10	2.72 (-1.64, 7.07)	0.188	0.20
Multiple pregnancy	21	0.05 (-0.003, 0.10)	0.065	0.07
GDM	28	0.03 (-0.04, 0.09)	0.398	0.15
HDP	27	0.09 (-0.06, 0.24)	0.223	0.13
SGA				
Age (years)	11	-10.50 (-21.36, 0.37)	0.057	0
Multiple pregnancy	10	0.49 (-3.74, 4.72)	0.797	0.15
GDM	13	0.02 (-0.02, 0.06)	0.284	0.07
HDP	11	0.19 (-0.03, 0.42)	0.084	0.21

Discussion

In this systematic review, meta-analysis, and meta-regression in 70763 women, we report for the first time women with PCOS had a higher GWG. In PCOS, pregnancy was associated with higher prevalence of PTB and LGA birth, and lower BW. On sub-group analysis, participant characteristics including PCOS phenotypes, geographic continent, conception mode and study quality were variably associated with GWG and infant outcomes. However, GWG, PTB and LGA were not associated with PCOS status on BMI–matched studies.

We confirmed that women with PCOS have a higher pre-conception BMI which is consistent with previous literature on PCOS in general.[12] This is the first meta-analysis that we are aware of, examining the association of GWG in PCOS. We report that women with PCOS have higher GWG, which is consistent with prior reports of higher longitudinal weight gain in PCOS.[13,74] Our findings here of higher BMI and GWG in PCOS is supported by prior findings in the general population of higher GWG being associated with higher baseline BMI.[14] For women with PCOS, these may be related to abnormal appetite regulation, energy expenditure, psychological function,[75] and higher energy intake[76]. Importantly, these findings may also result from participants not being selected from a truly representative population.[77]

There are significant potential health implications of these findings with higher BMI and GWG being associated with worsened infant outcomes.[11] The implications may also extend to the longer-term burden of obesity and related diseases with women with higher GWG being more likely to retain weight, and potentially have a greater likelihood of weight-related concerns, post pregnancy.[78]

We confirm prior reports of a higher rate of PTB in PCOS.[6-9] However, we note that only one study clearly stated that PTB was related to the spontaneous onset of labour.[39] Risk factors contributing to PTB include obesity, infertility treatment, over distension of uterus (by multiple pregnancy, polyhydramnios or macrosomia), hypertensive disorders, inflammation,

smoking, and extreme maternal age.[22,60] We report that the higher rate of PTB in PCOS was not maintained on BMI-matched studies and post ART pregnancies. Given that women with higher BMI are more likely to receive infertility treatments,[50] this suggests that the increased rate of PTB in PCOS may be related to obesity. Conversely, the significant increased prevalence for PTB was retained in singleton pregnancies which likely relates to a larger baby or polyhydramnios contributing to PTB in PCOS independent of multiple pregnancy. Previous studies reported higher risk for HDP in PCOS, which indicate labour induction when being life threatening for mother or foetus.[6-9,60] However, we did not observe an association between the HDP ratio and PTB suggesting that despite having higher rate of HDP, women with PCOS may experience mild forms of HDPs. There was insufficient data to explore associations with inflammation, smoking, and maternal age extremes in PTB. The potential health implications of increased PTB are considerable given that PTB is associated with lower BW and higher risk for admission to NICU.[8]

We report here, lower BW and higher rate of LGA in PCOS. Despite being statistically significant, the lower BW (0.11 g) lacks clinical significance. It is possible that the placenta alterations may occur in PCOS which are associated with foetal growth restriction.[69] Nevertheless, here, the lower BW is likely attributable to the higher PTB in PCOS. Due to the nature of a meta-analysis, we cannot correct for confounders and evaluate the impact of PCOS independently on these factors. Women are recommended to gain 0.22-0.51 kg/week over the second and third trimester to achieve appropriate foetal growth.[79] It is therefore logical for premature infants with shorter gestations to have lower BW. On the other hand, maternal obesity, excessive GWG, diabetes mellitus, GDM, multi-parity, age, and ethnicity are known risk factors for LGA in the general population.[10,23,80] We report here that the higher rate of LGA in PCOS was not maintained for ovulatory, anovulatory and non-hyperandrogenic phenotypes, across geographic continents, on BMI-matched studies, GDM

affected pregnancies and for spontaneous conception. Given the higher pre-conception BMI, GWG and GDM in PCOS, these could play an important role in the higher rate of LGA. The effect of adiposity may be either directly[10] or through increasing the risk of GDM.[6] Here, while LGA was similar in GDM affected pregnancies, it was significantly higher in a non-GDM affected study with a higher BMI.[54] This highlights the role of adiposity on LGA. However the higher LGA was maintained for post ART pregnancies. This might be due to higher GDM and or adiposity in this sub-group.[23,80] Excessive GWG has been reported to be a stronger predictor for LGA than BMI.[81] Despite this, women with PCOS from Europe and Asia with a higher GWG showed similar prevalence of LGA. This suggests that geographic continent is likely to be the most important risk factor for LGA.

In this meta-analysis, the prevalence of outcomes did not significantly change on exclusion of studies using metformin during pregnancy which is consistent with prior literature on PTB and BW.[82] While a prior RCT reported women with PCOS who continued taking metformin during pregnancy had lower GWG,[82] we had no data to explore this in the current study. We also explored the contribution of study level features to the reported maternal obesity and infant outcomes. Higher PTB and LGA were confirmed in good quality studies highlighting the validity of observed results. However the overall certainty of literature for all outcomes was low to very low highlighting the absence or deficiency of credible evidence for infant outcomes in PCOS.[26]

Compared to previous meta-analyses,[6-9] ours is strengthened by assessing outcome-specific certainty of evidence using the GRADE system, sub-group meta-analyses for a range of potential confounders, meta-regression to allow exploration of potential sources of heterogeneity and exclusion of studies reporting outcomes in multiple number of pregnancies for further methodological consistency. We note limitations included lack of non-English written studies. Observational studies were included for which the risk of bias could not be

completely eliminated and their protocols widely varied in terms of outcomes of interest and important risk factors. PCOS was defined differently across included studies which limited the number of studies for sub-group analyses by some PCOS phenotypes. We were also unable to perform sub-group meta-analysis by the IOM GWG recommendations due to lack of data. The definition of some pregnancy outcomes was either not reported or inconsistently reported. The geographic continent where the study was conducted was considered instead of ethnicity as ethnicity was not consistently reported across included studies. There were few studies reporting outcomes by specific BMI categories which made us unable to perform sub-group analyses for some of the outcomes. There was only one study reporting outcomes in multiple pregnancies which made us unable to perform sub-group analyses for all outcomes. We were unable to perform sub-group meta-analysis in HDP affected pregnancies due to lack of data. Meta-regression could not be performed for the majority of potential confounders due to the lack of sufficient observations.

We report here that women with PCOS had a higher pre-conception BMI and report for the first time that they also have a higher GWG compared to women without PCOS. They were more likely to give birth to a premature and LGA infant. The association between PCOS and BMI, GWG, PTB or BW varied by factors such as geographic continent, PCOS phenotypes, BMI categories, conception modes, singleton and multiple pregnancies, and study type and quality. It is therefore important to avoid iatrogenic multiple pregnancy in PCOS as worsened infant outcomes seem to be already higher in PCOS, even in singleton pregnancies. Higher GWG, PTB and LGA were explained by obesity on BMI-matched studies. These results emphasise the influence of geographic continent, study type, and quality on BMI and GWG in pregnancy in PCOS and on geographic continent, obesity and PCOS phenotypes on infant outcomes in PCOS. Future well designed community-based studies with appropriate sample sizes should assess the contribution of the PCOS per se to infant outcomes with consideration

of the important role of adiposity, geographic continent, and well-defined PCOS status. This will help to target high risk groups for timely screening and management for prevention of adverse infant outcomes.

Conflict of interests: Authors declare that there is no competing interest.

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Figure legends list:

Figure 1- PRISMA flowchart of study selection

Figure 2: Meta-analyses for gestational weight gain in women with and without PCOS

Figure 3: Meta-analyses for intra-uterine growth restriction, preterm birth, birth weight, small for gestational age, and large for gestational age in women with and without PCOS

A: Intra-uterine growth restriction

B: Preterm birth

C: Birth weight

D: Small for gestational age

E: Large for gestational age