Systematic Review and Meta-Analysis

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Association between polycystic ovary syndrome and the risk of pregnancy complications

A PRISMA-compliant systematic review and meta-analysis

Hai-Feng Yu, MS[a], Hong-Su Chen, MS[b], Da-Pang Rao, MS[a], Jian Gong, MS[c,*]

Abstract

Background: Polycystic ovary syndrome (PCOS) is inconsistently associated with increased risk of adverse pregnancy outcomes. The purpose of this meta-analysis was to summarize the evidence regarding the strength of the association between pregnancy in women with PCOS and pregnancy complications.

Methods: We systematically searched PubMed, EmBase, and the Cochrane Library to identify observational studies up to January 2016. The primary focus was pregnancy outcomes, including gestational diabetes mellitus (GDM), preeclampsia, pregnancy-induced hypertension (PIH), preterm delivery, cesarean delivery, oligohydramnios, and polyhydramnios. Effect estimates were pooled using the random-effects model. The analysis was further stratified by factors that could affect these associations.

Results: We included 40 observational studies that reported data on a total of 17,816 pregnancies with PCOS and 123,756 pregnancies without PCOS. Overall, PCOS in pregnancy was associated with greater risk of GDM, preeclampsia, PIH, preterm delivery, cesarean delivery, miscarriage, hypoglycemia, and perinatal death. However, PCOS in pregnancy had little or no effect on oligohydramnios, polyhydramnios, large-for-gestational age (LGA), small-for-gestational-age (SGA), fetal growth restriction (FGR), preterm premature membrane rupture, fasting blood glucose (FBG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, total cholesterol, congenital malformation, macrosomia, and respiratory distress syndrome. Subgroup analysis suggested that these associations might be influenced by study design and pre-BMI.

Conclusion: PCOS in pregnancy is associated with a significantly increased risk of adverse pregnancy, fetal, and neonatal outcomes.

Abbreviations: CI = confidence interval, FBG = fasting blood glucose, GDM = gestational diabetes mellitus, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LGA = large-for-gestational age, PCOS = polycystic ovary syndrome, PIH = pregnancy-induced hypertension, SGA = small-for-gestational-age.

Keywords: meta-analysis, polycystic ovary syndrome, pregnancy complications, risk, systematic review

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a reported prevalence between 6% and 15%.[1,2] The disease is characterized by ovulation disorders, androgen excess, and polycystic ovarian morphology.[2,3] Moreover, PCOS is a primary risk factor for adverse pregnancy outcomes.[4,5] A meta-analysis conducted by Kjerulff et al[6] indicated that pregnancy in PCOS patients was associated with increased risk of gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preeclampsia, preterm delivery, and small-for-gestational-age (SGA); however, there was no significant impact on the risk of cesarean delivery, operative vaginal delivery, and large-for-gestational age (LGA). However, data on the impact of PCOS in pregnancy on subsequent fetal and neonatal outcomes are both limited and inconclusive. A meta-analysis by Qin et al[7] showed that PCOS in pregnancy led to increased risk of GDM, PIH, preeclampsia, preterm delivery, and cesarean delivery had negative effects on birth weight, and increased the risk of admission to the NICU. Toulis et al[8] evaluated the association between PCOS in pregnancy and the risk of GDM, and reported similar outcomes. An inherent limitation of the previous studies was that most fetal and neonatal outcomes could not be assessed. Furthermore, the possibility that the association between PCOS in pregnancy and adverse pregnancy, fetal, and neonatal outcomes may differ according to factors such as study design, mean age, and prebody mass index (pre-BMI) remains controversial.

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Ethics: An ethics statement was not required for this work.

Key message: The meta-analysis is to summarize the evidence regarding the strength of association between pregnancy women with polycystic ovary syndrome (PCOS) and pregnancy complications. PCOS in pregnancy is associated with a significantly increased risk of adverse pregnancy, fetal or neonatal outcomes.

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[a] Department of Urosurgery, [b] Department of Cardiothoracic Surgery, [c] Medical Laboratory Center, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China.

[*] Correspondence: Jian Gong, Medical Laboratory Center, The Second Affiliated Hospital & Yuying Children's, Hospital of Wenzhou Medical University, Wenzhou 325027, China (e-mail: gongjian_2016@sina.com).

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Several observational studies indicated that PCOS in pregnancy did not influence pregnancy outcomes.[9–19] Conversely, the results of other studies showed that women with PCOS were more likely to experience adverse pregnancy outcomes.[20–48] Furthermore, several other studies have suggested that women with PCOS may have increased risk of adverse fetal and neonatal outcomes.[12,16,20,21,27,40] Clearly, the relationship between PCOS in pregnancy and adverse pregnancy, fetal, and neonatal outcomes among women of reproductive age has not been definitively determined. Thus, we attempted a large-scale analysis of the available evidence to more clearly ascertain the association between PCOS in pregnancy and adverse pregnancy, fetal, and neonatal outcomes. We then compared these associations among women with different baseline characteristics.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement and Checklist.[49] Ethics approval was not necessary for this study, as only deidentified pooled data from individual studies were analyzed. Any observational study that examined the relationship between PCOS in pregnancy and the risk of adverse pregnancy, fetal, and neonatal outcomes was eligible for inclusion in our study, and no restrictions were placed on language or publication status (published or in press). Three electronic databases, PubMed, EmBase, and the Cochrane Library, were searched to identify studies up to January 2016 and the following search terms were used: ("Polycystic ovary syndrome" OR "PCOS" OR "hyperandrogenic anovulation" OR "Stein–Leventhal syndrome") AND ("gestational diabetes mellitus" OR "pregnancy-induced hypertension" OR "preeclampsia" OR "cesarean delivery rates" OR "operative vaginal delivery Rates" OR "preterm delivery" OR "small-for-gestational-age infants" OR "large-for-gestational-age infants" OR "maternal complications" OR "neonatal complications") AND ("pregnant" OR "pregnancy"). We also conducted manual searches of the reference lists of all relevant original and review articles to identify additional eligible studies. The title, study design, characteristics of participants, exposure, control, and outcome variables of these studies were considered to determine relevance.

Search strategy and study identified were independently performed by 2 authors (H-FY, H-SC) using a standardized approach, and any inconsistency was settled by group discussion until a consensus was reached. The inclusion criteria were delineated as follows: an observational study design was mandatory, whether prospective or retrospective; the study needed to explore the relationship between PCOS in pregnancy and the risk of adverse pregnancy, fetal, and neonatal outcomes; and the study needed to have reported effect estimates and 95% confidence intervals (CIs), or number of interesting outcomes and sample size in each group for comparisons of PCOS in pregnancy and normal pregnancy. Editorials, reviews, and letters to the editor were excluded.

2.2. Data collection and quality assessment

The data collected included characteristics of the study and participants, and outcomes of interest. The study and participant characteristics included first author's name, publication year, country, study design, number of PCOS, number of control, age at baseline, and pre-BMI. The outcomes included GDM, preeclampsia, PIH, preterm delivery, cesarean delivery, oligohydramnios, polyhydramnios, LGA, SGA, fetal growth restriction, miscarriage, preterm premature rupture membrane, fasting blood glucose (FBG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, total cholesterol, diastolic blood pressure, systolic blood pressure, congenital malformation, hypoglycemia, macrosomia, perinatal death, and respiratory distress syndrome.

The Newcastle–Ottawa Scale, which is very comprehensive and has been partially validated for evaluating the quality of observational studies,[50] is based on the following 3 subscales: selection (4 items), comparability (1 item), and outcome (3 items). A "star system" ranging from 0 to 9 has been developed for assessment (Table S1, http://links.lww.com/MD/B305). Data collection and quality assessment were independently performed by 2 authors (H-FY, D-PR). Information was then examined and adjudicated independently by an additional author (JG) who referred to the original studies.

2.3. Statistical analysis

We examined the relationship between PCOS in pregnancy and risk of adverse pregnancy, fetal, and neonatal outcomes on the basis of the effect estimate and its 95% CI as published in each study. We used the random-effects model to calculate summary relative risks (RRs) or mean difference (MD) and 95% CIs for PCOS in pregnancy versus pregnancy without PCOS.[51,52] Furthermore, the relative risk ratios (RRRs) and their 95% CIs were estimated using specific RRs and 95% CIs after stratifying the study design, mean age, and pre-BMI. Heterogeneity between studies was evaluated using the Q statistic, and P values less than 0.10 were indicative of significant heterogeneity.[53,54] Subgroup analyses were conducted for the pregnancy, fetal, and neonatal outcomes, using more than 5 datasets included on the basis of study design, mean age, and pre-BMI. Sensitivity analyses were also conducted by removing each individual study from the meta-analysis in order to assess the influence of a single study on the meta-analysis.[55] The Egger and Begg tests were used to

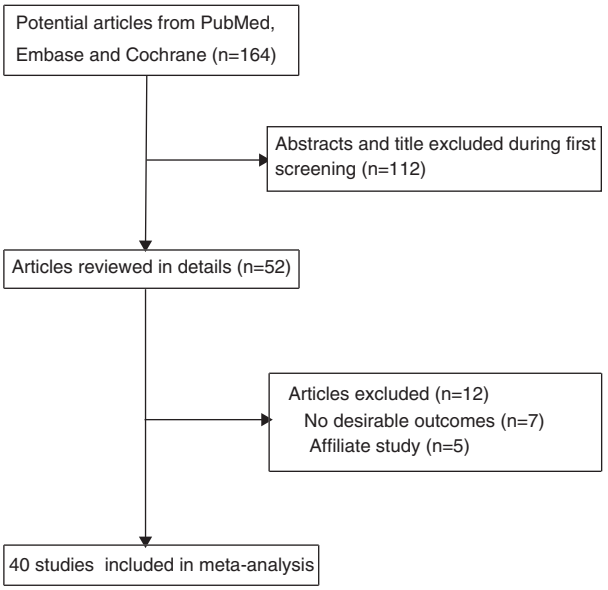

Figure 1. Flow diagram of the literature search and trials selection process.

statistically assess publication bias for pregnancy, fetal, and neonatal outcomes.[56,57] All reported *P* values are 2-sided, and *P* values less than 0.05 were considered statistically significant for all included studies. Statistical analyses were conducted by using STATA software (version 10.0; Stata Corporation, College Station, TX).

3. Results

A total of 164 articles were identified during the initial electronic search, 112 of which were excluded because of duplication and irrelevance. A total of 52 potentially eligible studies were selected. Among these, 7 were ruled out for lack of desirable outcomes and another 5 were also excluded because they were different publications of the same studies (Fig. 1). A manual search of the reference lists of these studies did not yield any new eligible studies. The general characteristics of the included studies are presented in Table 1.

Of the 40 included studies (for a total of 17,816 PCOS in pregnancy and 123,756 pregnancies without PCOS), 15 studies had a prospective design,[10,11,16,20–22,25,26,31,32,35,38,42–44] while the remaining 25[9,12–15,17–19,23,24,27–30,33,34,36,37,39–41,45–48] had a retrospective design. The baseline participant age was 25.9 to 32.8 years, while pre-BMI ranged from 20.8 to 29.7 in each individual study. Study quality was assessed using the NOS scale (Table S1, http://links.lww.com/MD/B305) and studies with scores greater than 6 were considered to be of high quality.[50] Overall, 3 studies had a score of 9,[9,16,42] 25 studies had a score of 8,[10,11,13–15,17,18,20,22,23,25,27–29,31–34,38–41,44,45,47] 7 studies had a score of 7,[12,19,21,24,26,37,46] and the remaining 5 studies had a score of 6[30,35,36,43,48] (Table S1, http://links.lww.com/MD/B305).

A total of 29 studies reported an association between PCOS in pregnancy and the risk of GDM. The summary showed that PCOS in pregnancy was associated with increased risk of GDM (RR: 2.78; 95% CI: 2.27–3.40; $P < 0.001$; Fig. 2A), and

Table 1

Baseline characteristic of studies included in the systematic review and meta-analysis.

Study	Publication years	Country	Study design	Case	Control	Age at baseline	Pre-BMI
Aktun et al[20]	2015	Turkey	Prospective	150	160	30.1	22.1
Li et al[21]	2011	China	Prospective	61	122	NA	21.2
Koster et al[22]	2015	Netherland	Prospective	73	209	31.5	NA
Sawada et al[9]	2015	Japan	Retrospective	49	49	31.8	24.3
Fridström et al[23]	1999	Sweden	Retrospective	33	66	32.7	23.6
Radon et al[24]	1999	US	Retrospective	22	66	31.4	28.2
Sir-Petermann et al[10]	2007	Chile	Prospective	48	51	27.3	26.2
Hu et al[11]	2007	UK	Prospective	22	22	31.6	24.31
Al-Ojaimi et al[25]	2006	Bahrain	Prospective	134	479	28.5	29.7
Palomba et al[26]	2014	Italy	Prospective	150	150	27.6	27.2
Reyes-Muñoz et al[27]	2012	Mexico	Retrospective	52	52	29.1	27.5
Altieri et al[28]	2010	Italy	Retrospective	15	159	32.8	23.1
de Vrieset al[29]	1998	Netherland	Retrospective	81	81	29.8	NA
Yan et al[12]	2011	China	Retrospective	631	1423	NA	NA
Urman et al[30]	1997	Turkey	Retrospective	47	100	27.9	24.0
Wang et al[31]	2013	China	Prospective	220	594	29.6	20.8
Palomba et al[32]	2012	Italy	Prospective	42	84	28.4	27.5
Kollmann et al[33]	2015	Austria	Retrospective	177	708	29.9	22.9
Foroozanfard et al[34]	2014	Iran	Retrospective	130	131	29.1	27.9
Pan et al[35]	2015	China	Prospective	3109	31090	29.06	NA
Aziz et al[36]	2013	UK	Retrospective	258	24594	NA	NA
West et al[37]	2014	Finland	Retrospective	153	3340	31.0	NA
Haakova et al[13]	2003	Czech Republic	Retrospective	66	66	29.4	23.4
Sir-Petermann et al[38]	2005	Chile	Prospective	47	180	25.9	26.5
Lo et al[39]	2006	US	Retrospective	11035	55175	30.8	NA
Turhan et al[40]	2003	Turkey	Retrospective	38	136	26.8	25.3
Diamant et al[41]	1982	Israel	Retrospective	70	71	31.0	NA
Bjercke et al[42]	2002	Norway	Prospective	52	335	32.5	22.5
Lesser et al[14]	1997	US	Retrospective	24	44	31.2	25.2
Li et al[43]	2010	China	Prospective	34	70	31.5	23.6
Maliqueo et al[44]	2009	Chile	Prospective	30	34	NA	NA
Mikola et al[45]	2001	Finland	Retrospective	80	712	29.5	23.3
Laven et al[15]	2002	Netherland	Retrospective	76	95	NA	NA
Palomba et al[16]	2010	Italy	Prospective	93	73	30.0	24.1
Vollenhoven et al[17]	2000	Australia	Retrospective	60	60	NA	26.8
Weerakiet et al[46]	2004	Thailand	Retrospective	47	264	31.3	22.4
Wortsman[18]	1991	US	Retrospective	53	2306	NA	NA
Cardenas[19]	2006	Mexico	Retrospective	31	78	NA	NA
Kashyap and Claman[47]	2000	Canada	Retrospective	22	27	NA	NA
Foroozanfard et al[48]	2013	Iran	Retrospective	301	300	NA	NA

BMI = body mass index, NA = not available.

substantial heterogeneity was observed ($P < 0.001$). As a result, a sensitivity analysis was performed, and after each study was sequentially excluded, the conclusion was not affected. Similarly, the pooled analysis results for preeclampsia and PIH indicated that the comparison of the PCOS in pregnancy versus pregnancies without PCOS showed a harmful impact (pre-eclampsia: RR: 2.79; 95% CI: 2.29–3.38; $P < 0.001$; without evidence of heterogeneity; Fig. 2B) (PIH: RR: 2.46; 95% CI: 1.95–3.09; $P < 0.001$; Fig. 2C). Heterogeneity was detected in the magnitude of the effect across the studies for PIH ($P = 0.024$), although after sequential exclusion of each study, the conclusion was not affected by the exclusion of any specific study.

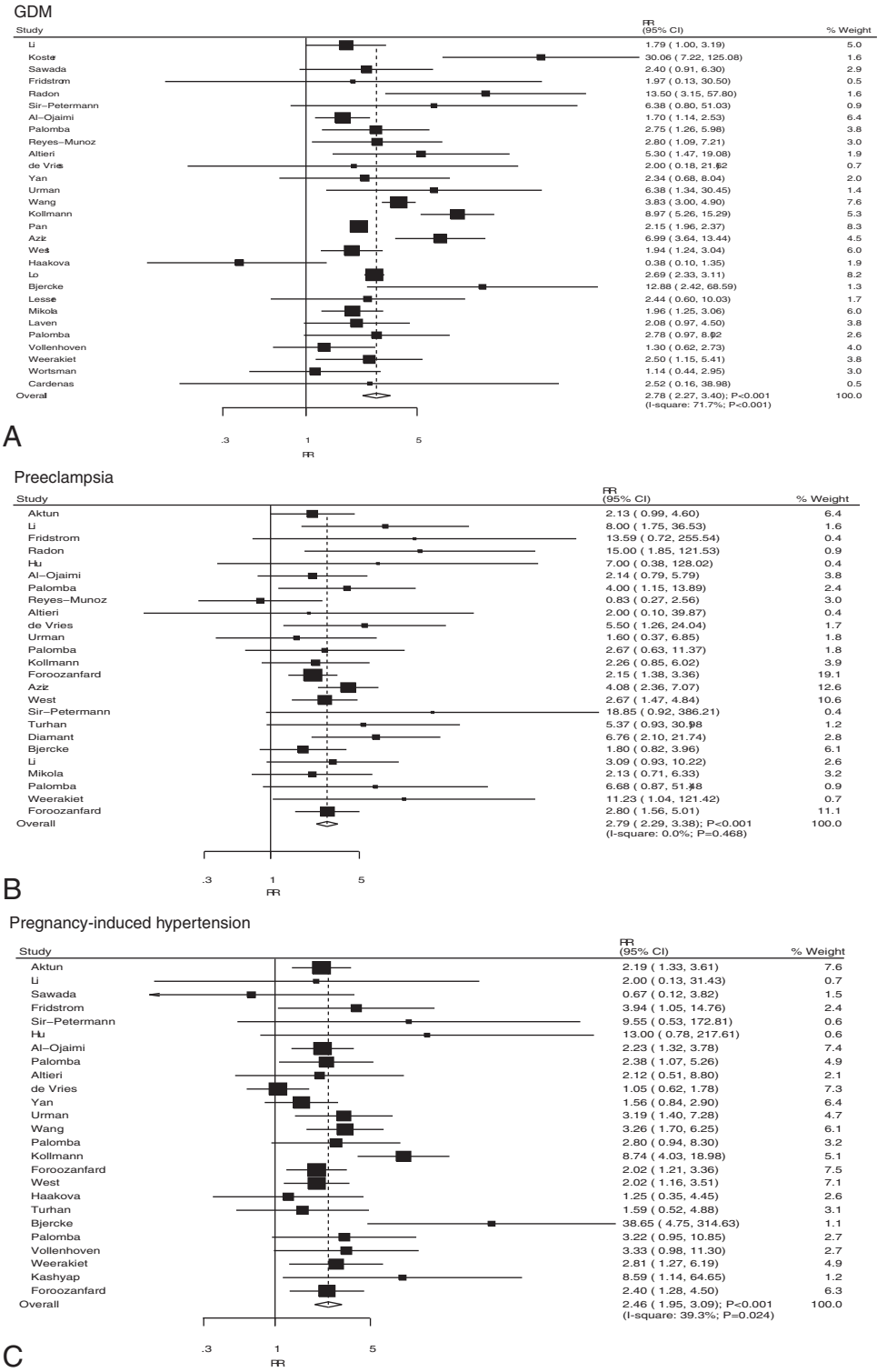

Figure 2. Association between PCOS in pregnancy and the risk of GDM (A), preeclampsia (B), and PIH (C). GDM = gestational diabetes mellitus, PCOS = polycystic ovary syndrome, PIH = pregnancy-induced hypertension.

A total of 20 studies reported an association between PCOS in pregnancy and the risk of preterm delivery. We noted that PCOS in pregnancy was associated with increased risk of preterm delivery (RR: 1.52; 95% CI: 1.22–1.90; $P < 0.001$; Fig. 3A). Although substantial heterogeneity was observed in the magnitude of the effect across the studies ($P = 0.015$), after sequential exclusion of each study from all of the pooled analyses, the conclusion was not affected by the exclusion of any specific study. Similarly, the summary RR also indicated that PCOS in pregnancy might affect the incidence of cesarean delivery (RR:

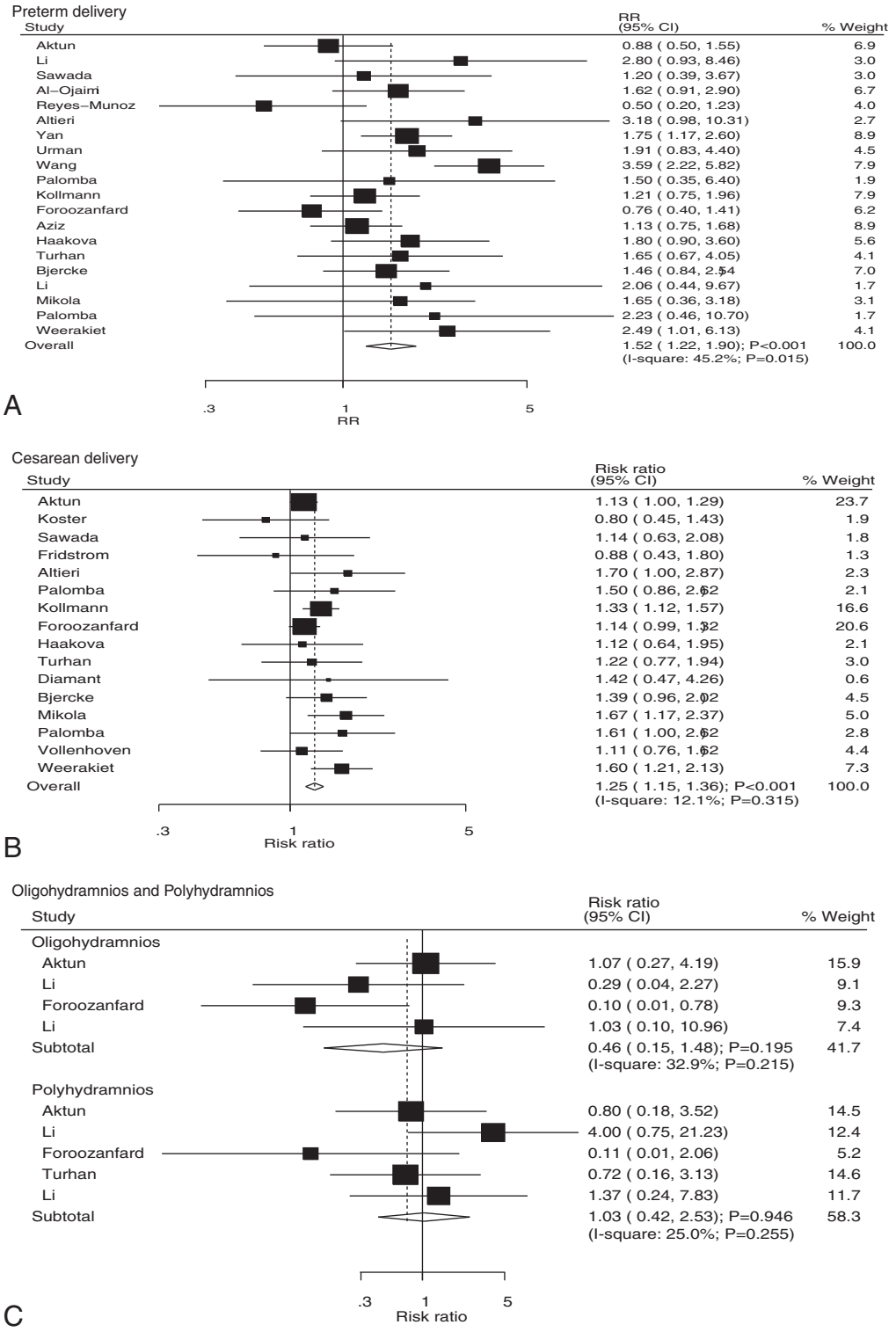

Figure 3. Association between polycystic ovary syndrome (PCOS) in pregnancy and the risk of preterm delivery (A), cesarean delivery (B), or oligohydramnios and polyhydramnios (C).

1.25; 95% CI: 1.15–1.36; $P < 0.001$; Fig. 3B). Finally, there was no significant association between PCOS in pregnancy and risk of oligohydramnios (RR: 0.46; 95% CI: 0.15–1.48; $P = 0.195$; Fig. 3C) and polyhydramnios (RR: 1.03; 95% CI: 0.42–2.53; $P = 0.946$; Fig. 3C). Unimportant heterogeneity was detected for these 3 outcomes, and the outcomes were reliable.

The number of studies pertaining to the outcomes of LGA and SGA was 11 and 10, respectively. The summary RR showed that PCOS in pregnancy was not associated with risk of LGA (RR: 1.14; 95% CI: 0.93–1.39; $P = 0.201$; Fig. 4) or SGA (RR: 1.45; 95% CI: 0.96–2.20; $P = 0.081$; Fig. 4). Similarly, there was no significant association between PCOS in pregnancy and risk of fetal growth restriction (FGR, RR: 2.02; 95% CI: 0.71–5.74; $P = 0.187$; Fig. 4), or preterm premature membrane rupture (RR: 0.81; 95% CI: 0.22–2.97; $P = 0.754$; Fig. 4), whereas PCOS in pregnancy was associated with increased risk of miscarriage (RR: 2.87; 95% CI: 1.65–4.98; $P < 0.001$; Fig. 4).

The summary MD for the association between PCOS in pregnancy and levels of cardiovascular risk factors was also performed. As presented in Fig. 5, we noted that PCOS in pregnancy has no significant impact on FBG (MD: 0.17; 95% CI: −0.01–0.36; $P = 0.061$), HDL (MD: −0.17; 95% CI: −0.38–0.03; $P = 0.090$), LDL (MD: 0.41; 95% CI: −0.55–1.37; $P = 0.403$), triglycerides (MD: 0.26; 95% CI: −0.27–0.79; $P = 0.333$), and total cholesterol (MD: 0.12; 95% CI: −0.04–0.27; $P = 0.146$).

The association between PCOS in pregnancy and the risk of fetal and neonatal outcomes is presented in Fig. 6. We found that PCOS in pregnancy was associated with increased risk of hypoglycemia (RR: 2.85; 95% CI: 1.93–4.22; $P < 0.001$) and perinatal death (RR: 1.83; 95% CI: 1.06–3.16; $P = 0.029$); however, there were no significant associations between PCOS in pregnancy and congenital malformation (RR: 0.94; 95% CI: 0.36–2.42; $P = 0.894$), macrosomia (RR: 1.25; 95% CI: 1.00–1.57; $P = 0.055$), or respiratory distress syndrome (RR: 1.24; 95% CI: 0.80–1.93; $P = 0.336$).

Heterogeneity testing for the analysis showed a value of $P < 0.10$ for most of the outcomes. Therefore, we conducted subgroup analyses for GDM, preeclampsia, PIH, preterm delivery, cesarean delivery, LGA, SGA, congenital malformation, and macrosomia to minimize heterogeneity among the included studies (Table 2). For the most part, results of the subgroup analyses were consistent with

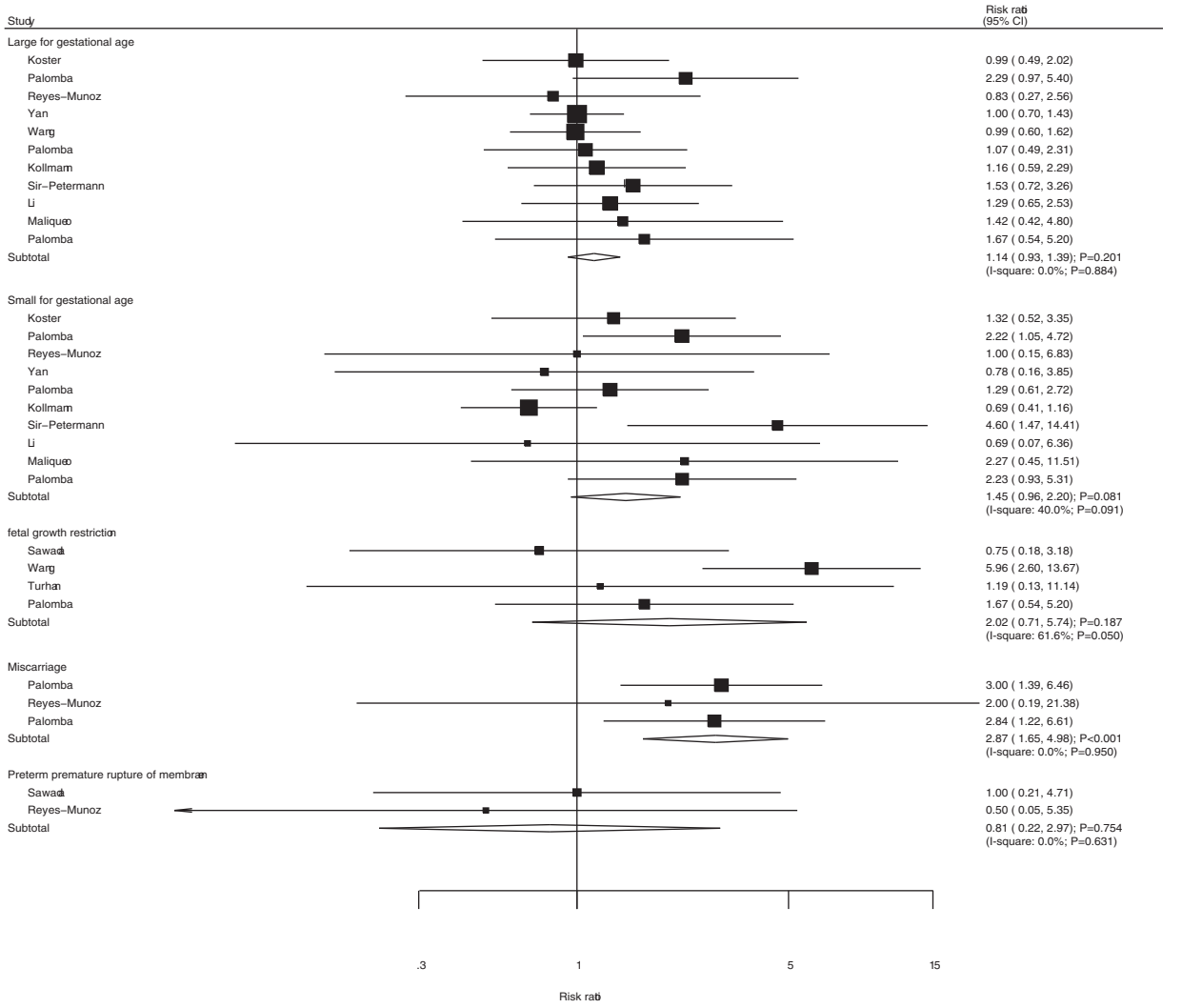

Figure 4. Association between PCOS in pregnancy and the risk of LGA, SGA, FGR, preterm premature rupture of membrane, and miscarriage. FGR = fetal growth restriction, LGA = large-for-gestational age, PCOS = polycystic ovary syndrome, SGA = small-for-gestational-age.

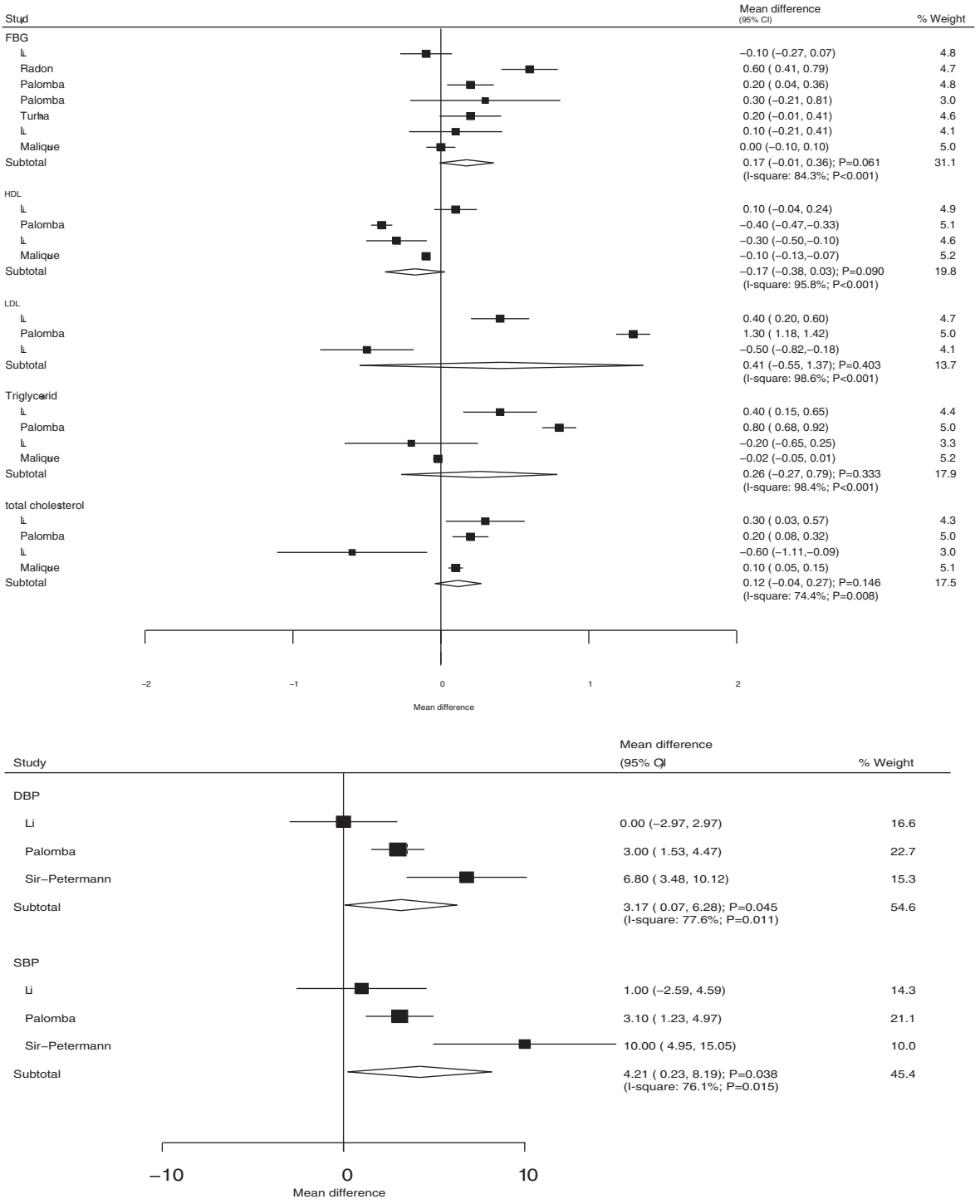

Figure 5. Association between PCOS in pregnancy and the levels of FBG, HDL, LDL, triglyceride, and total cholesterol. FBG = fasting blood glucose, HDL = high density lipoprotein, LDL = low density lipoprotein, PCOS = polycystic ovary syndrome.

the overall analysis, though several inconsistent conclusions were also observed. First, PCOS in pregnancy was not associated with preterm delivery in pregnancies with a pre-BMI greater than 25 (RR: 1.07; 95% CI: 0.66–1.73; $P = 0.780$). Second, PCOS in pregnancy was associated with increased risk of SGA in studies with a prospective design (RR: 1.86; 95% CI: 1.27–2.71; $P = 0.001$), and pregnancies with pre-BMI greater than 25 (RR: 1.97; 95% CI: 1.13–3.46; $P = 0.018$). Third, the RRR showed a statistically significant association between PCOS in pregnancy and the risk of SGA in studies with prospective designs when compared to studies with retrospective designs (RRR: 2.35; 95% CI: 1.30–4.25; $P = 0.005$); Finally, there was no evidence of a factor-specific difference in the RR for pregnancy, fetal, and neonatal outcomes among participants with PCOS compared to those without PCOS.

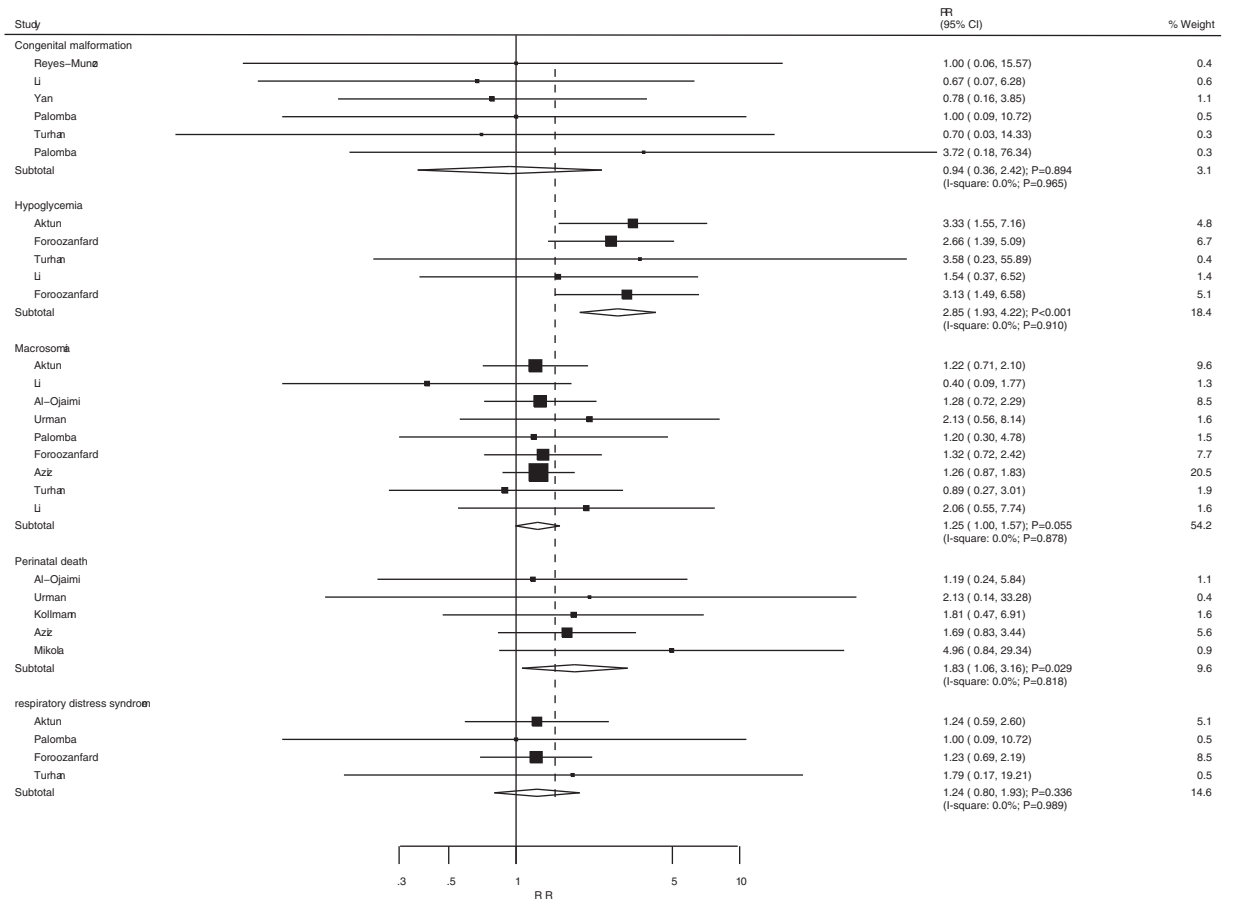

Figure 6. Association between polycystic ovary syndrome (PCOS) in pregnancy and the risk of hypoglycemia, perinatal death, pregnancy and congenital malformation, macrosomia, and respiratory distress syndrome.

The Egger[56] and Begg test[57] results showed no evidence of publication bias for GDM (*P* value for Egger: 0.193; *P* value for Begg: 0.320), preterm delivery (*P* value for Egger: 0.660; *P* value for Begg: 0.456), cesarean delivery (*P* value for Egger: 0.302; *P* value for Begg: 0.620), oligohydramnios (*P* value for Egger: 0.663; *P* value for Begg: 0.308), polyhydramnios (*P* value for Egger: 0.423; *P* value for Begg: 1.000), LGA (*P* value for Egger: 0.373; *P* value for Begg: 0.436), SGA (*P* value for Egger: 0.846; *P* value for Begg: 0.858), FGR (*P* value for Egger: 0.888; *P* value for Begg: 1.000), miscarriage (*P* value for Egger: 0.552; *P* value for Begg: 0.296), congenital malformation (*P* value for Egger: 0.566; *P* value for Begg: 0.734), hypoglycemia (*P* value for Egger: 0.646; *P* value for Begg: 1.000), macrosomia (*P* value for Egger: 0.711; *P* value for Begg: 1.000), perinatal death (*P* value for Egger: 0.547; *P* value for Begg: 0.462), and respiratory distress syndrome (*P* value for Egger: 0.706; *P* value for Begg: 0.308). However, a significant publication bias for both preeclampsia (*P* value for Egger: 0.021; *P* value for Begg: 0.016) and PIH (*P* value for Egger: 0.049; *P* value for Begg: 0.038) was detected (Table 3). The conclusions were not changed after adjustment for the publication bias by using the trim and fill method.[58]

4. Discussion

Our current study was based on observational studies and we explored all possible correlations between PCOS and the risk of adverse pregnancy, fetal, and neonatal outcomes. This large and comprehensive quantitative study included 17,816 pregnancies with PCOS and 123,756 pregnancies without PCOS from 40 observational studies with a broad range of populations. The findings from our current meta-analysis suggested that PCOS in pregnancy was associated with increased risk of GDM, preeclampsia, PIH, preterm delivery, cesarean delivery, miscarriage, hypoglycemia, and perinatal death. However, there was no significant difference between pregnancies with and without PCOS in terms of oligohydramnios, polyhydramnios, LGA, SGA, FGR, preterm premature membrane rupture, FBG, HDL, LDL, triglyceride, total cholesterol, congenital malformation, macrosomia, and respiratory distress syndrome.

In this study, we noted that PCOS in pregnancy increases the risk of GDM, preeclampsia, PIH, preterm delivery, cesarean delivery, miscarriage, hypoglycemia, and perinatal death. Several prior studies reported similar conclusions regarding the potentially harmful impact of PCOS in pregnancy. Radon et al[24] concluded that women with PCOS are at increased risk of glucose intolerance and preeclampsia during pregnancy, and Kashyap and Claman[47] suggested a much higher incidence of PIH (31.8%) in pregnancy with PCOS versus pregnancy without PCOS (3.7%). The findings of Kollmann et al[33] suggested that PCOS in pregnancy was associated with an increased risk of maternal complications, without a significant impact in terms of neonatal complications. The pathophysiological mechanisms for these relationships are not thoroughly

Table 2

Subgroup analysis of pregnancy, fetal, and neonatal outcomes.

Outcomes	Group	RR and 95%CI	*P*	*P* value for heterogeneity	RRR	*P* value for interaction test
GDM	Study design					
	Prospective	2.96 (2.06–4.25)	<0.001	<0.001	1.10 (0.69–1.75)	0.700
	Retrospective	2.70 (2.01–3.63)	<0.001	<0.001		
	Mean age					
	>30	3.44 (2.34–5.05)	<0.001	0.014	1.26 (0.75–2.13)	0.379
	<30	2.72 (1.91–3.88)	<0.001	<0.001		
	Pre-BMI					
	>25	2.44 (1.53–3.88)	<0.001	0.091	0.81 (0.43–1.51)	0.499
	<25	3.03 (1.99–4.62)	<0.001	<0.001		
Preeclampsia	Study design					
	Prospective	2.73 (1.87–3.97)	<0.001	0.663	0.95 (0.60–1.52)	0.834
	Retrospective	2.87 (2.18–3.79)	<0.001	0.250		
	Mean age					
	>30	2.97 (2.11–4.18)	<0.001	0.456	1.31 (0.83–2.06)	0.245
	<30	2.27 (1.69–3.06)	<0.001	0.588		
	Pre-BMI					
	>25	2.57 (1.56–4.24)	<0.001	0.194	1.00 (0.54–1.86)	1.000
	<25	2.57 (1.78–3.69)	<0.001	0.726		
PIH	Study design					
	Prospective	2.71 (2.02–3.65)	<0.001	0.364	1.19 (0.78–1.84)	0.420
	Retrospective	2.27 (1.66–3.10)	<0.001	0.014		
	Mean age					
	>30	2.62 (1.73–3.97)	<0.001	0.167	1.07 (0.61–1.88)	0.803
	<30	2.44 (1.68–3.54)	<0.001	0.007		
	Pre-BMI					
	>25	2.25 (1.67–3.02)	<0.001	0.913	0.70 (0.43–1.15)	0.161
	<25	3.20 (2.16–4.74)	<0.001	0.053		
Preterm delivery	Study design					
	Prospective	1.80 (1.18–2.74)	0.006	0.030	1.31 (0.81–2.13)	0.269
	Retrospective	1.37 (1.08–1.74)	0.010	0.147		
	Mean age					
	>30	1.47 (1.04–2.08)	0.030	0.352	1.00 (0.60–1.67)	1.000
	<30	1.47 (1.01–2.14)	0.043	0.004		
	Pre-BMI					
	>25	1.07 (0.66–1.73)	0.780	0.142	0.60 (0.34–1.05)	0.075
	<25	1.78 (1.34–2.37)	<0.001	0.071		
Cesarean delivery	Study design					
	Prospective	1.22 (1.02–1.46)	0.031	0.247	0.95 (0.78–1.17)	0.642
	Retrospective	1.28 (1.16–1.40)	<0.001	0.400		
	Mean age					
	>30	1.28 (1.09–1.50)	0.002	0.190	1.02 (0.84–1.23)	0.874
	<30	1.26 (1.13–1.41)	<0.001	0.351		
	Pre-BMI					
	>25	1.16 (1.02–1.31)	0.021	0.795	0.87 (0.73–1.04)	0.122
	<25	1.33 (1.18–1.50)	<0.001	0.194		
LGA	Study design					
	Prospective	1.23 (0.94–1.61)	0.131	0.696	1.18 (0.79–1.76)	0.410
	Retrospective	1.04 (0.77–1.39)	0.809	0.909		
	Mean age					
	>30	1.21 (0.77–1.89)	0.412	0.725	1.00 (0.59–1.70)	1.000
	<30	1.21 (0.91–1.60)	0.193	0.713		
	Pre-BMI					
	>25	1.39 (0.91–2.12)	0.128	0.456	1.20 (0.71–2.04)	0.503
	<25	1.16 (0.84–1.59)	0.361	0.911		
SGA	Study design					
	Prospective	1.86 (1.27–2.71)	0.001	0.415	2.35 (1.30–4.25)	0.005
	Retrospective	0.79 (0.50–1.24)	0.302	0.590		
	Mean age					
	>30	1.63 (0.88–3.00)	0.119	0.530	1.05 (0.44–2.51)	0.910
	<30	1.55 (0.84–2.88)	0.165	0.025		
	Pre-BMI					
	>25	1.97 (1.13–3.46)	0.018	0.270	1.63 (0.63–4.23)	0.317
	<25	1.21 (0.56–2.63)	0.630	0.100		

(*continued*)

Table 2

(continued).

Outcomes	Group	RR and 95%CI	*P*	*P* value for heterogeneity	RRR	*P* value for interaction test
Congenital malformation	Study design					
	Prospective	1.14 (0.27–4.78)	0.858	0.660	1.41 (0.21–9.48)	0.726
	Retrospective	0.81 (0.23–2.83)	0.738	0.984		
	Mean age					
	>30	3.72 (0.18–76.34)	0.394		4.09 (0.14–121.23)	0.416
	<30	0.91 (0.20–4.26)	0.907	0.981		
	Pre-BMI					
	>25	0.91 (0.20–4.26)	0.907	0.981	0.74 (0.07–7.90)	0.803
	<25	1.23 (0.20–7.43)	0.823	0.367		
Macrosomia	Study design					
	Prospective	1.21 (0.85–1.73)	0.294	0.595	0.95 (0.59–1.50)	0.813
	Retrospective	1.28 (0.95–1.73)	0.105	0.820		
	Mean age					
	>30	1.32 (0.80–2.17)	0.284	0.472	1.02 (0.55–1.90)	0.942
	<30	1.29 (0.90–1.87)	0.166	0.922		
	Pre-BMI					
	>25	1.24 (0.85–1.82)	0.261	0.951	0.99 (0.52–1.90)	0.981
	<25	1.25 (0.74–2.11)	0.403	0.332		

BMI = body mass index, CI = confidence interval, GDM = gestational diabetes mellitus, LGA = large-for-gestational age, PIH = pregnancy-induced hypertension, RR = relative risk, RRR = relative risk ratio, SGA = small-for-gestational-age.

illustrated. A possible explanation could be the increased risk of multiple pregnancies and nulliparity,[45] and the interplay of estrone, hyperinsulinemia, and the subsequent diabetic or hypertensive predispositions.[59] Additionally, we noted that PCOS in pregnancy had no significant impact on the risk of oligohydramnios and polyhydramnios. However, due in part to several outcomes was reported in only a few trials and these conclusions might be due to change. In addition, in most of the studies designed with pregnancy outcomes and fetal or neonatal outcomes as the primary endpoints, their sample sizes did not allow adequate power to detect potential clinical differences in oligohydramnios and polyhydramnios. Therefore, future large-scale prospective studies should be performed to verify these associations.

Most of our findings were in agreement with previous meta-analyses,[6–8] though there were several inconsistent outcomes. A previous meta-analysis indicated that PCOS in pregnancy might harmfully impact SGA, but has no significant impact on cesarean delivery, whereas the opposite conclusions were gleaned from our current meta-analysis. The possible reason for this could be that several recently completed large-scale studies suggested an association between PCOS in pregnancy and increased risk of cesarean delivery.[20,33,34] Furthermore, since PCOS in pregnancy can involve elevated androgen concentration levels, the increased fetal exposure to androgens might affect fetal and neonatal outcomes. Kollmann et al[33] conducted a retrospective matched cohort study and concluded after adjusting for BMI and age that PCOS in pregnancy had no significant effect on subsequent SGA. Hence, although PCOS in pregnancy might be a risk factor for SGA, the strength of the association was weakened by potential confounders.

Table 3

Publication bias for the relationship between PCOS in pregnancy and pregnancy, fetal, and neonatal outcomes.

Outcomes	*P* value for Egger	*P* value for Begg
GDM	0.193	0.320
Preeclampsia	0.021	0.016
PIH	0.049	0.038
Preterm delivery	0.660	0.456
Cesarean delivery	0.302	0.620
Oligohydramnios	0.663	0.308
Polyhydramnios	0.423	1.000
LGA	0.373	0.436
SGA	0.846	0.858
FGR	0.888	1.000
Miscarriage	0.552	0.296
Congenital malformation	0.566	0.734
Hypoglycemia	0.646	1.000
Macrosomia	0.711	1.000
Perinatal death	0.547	0.462
Respiratory distress syndrome	0.706	0.308

FGR = fetal growth restriction, GDM = gestational diabetes mellitus, LGA = large-for-gestational age, PIH = pregnancy-induced hypertension, PCOS = polycystic ovary syndrome, SGA = small-for-gestational-age.

There was no significant difference between pregnancies with PCOS and pregnancies without PCOS and cardiovascular risk factor levels. However, several of the included studies reported inconsistent results. Palomba et al[26] and Radon et al[24] indicated that PCOS in pregnancy was in fact associated with higher level of FBG; Li et al[21] and Palomba et al[26] indicated that PCOS in pregnancy was associated with decreased levels of HDL. Most studies reported lipid profiles with high heterogeneity, and the influences may be mostly attributable to potential confounders. Furthermore, while insulin resistance in pregnancy occurs to protect the fetus, in pregnancy with PCOS, it may cause a pathologic alteration, which could induce an overexpression of metabolic pathways and cause subsequent adverse pregnancy, fetal, and neonatal outcomes.

Subgroup analysis indicated that these associations might differ when stratified by study design and pre-BMI. The reason for this could be that prospective studies eliminate selection and recall bias. Furthermore, PCOS in pregnancy was associated with increased risk of GDM, which can itself lead to adverse pregnancy, fetal, and neonatal outcomes. This higher risk for glucose metabolism impairment was also influenced by pre-BMI levels.[60] Finally, although several interesting determinations could be made, these conclusions may be unreliable since the studies included in the subsets were smaller overall. Therefore, we sought to give a relative result and to provide a synthetic and comprehensive review.

A few strengths of our study should be highlighted. First, the large sample size allowed us to quantitatively assess the association of PCOS in pregnancy with the risk of adverse pregnancy, fetal, and neonatal outcomes, and thus our findings are potentially more robust than those of any individual study. Second, these relationships were also calculated and stratified by study design, mean age, and pre-BMI, which could elucidate the association between PCOS in pregnancy and the risk of adverse pregnancy, fetal, and neonatal outcomes in specific subpopulations.

The limitations of our study are as follows: the effect estimate in individual study with different adjusted factors, and these factors might have contributed an important role in the development of adverse pregnancy, fetal, and neonatal outcomes; publication bias is an inevitable problem given that all of included studies are published articles; and the analysis used pooled data (individual data were not available), which restricted us from performing a more detailed, relevant analysis and obtaining more comprehensive results.

The results of this study suggested that PCOS in pregnancy might impact the risk of GDM, preeclampsia, PIH, preterm delivery, cesarean delivery, miscarriage, hypoglycemia, and perinatal death. Subgroup analysis suggested that study design and pre-BMI might affect these associations, which should be evaluated in a future study. Furthermore, future studies should focus on specific populations, including human assisted reproductive technologies and pregnancies with particular characteristics.

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