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The Effect of Metformin Therapy for Preventing Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Meta-Analysis

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ABSTRACT

Objective This study was to analyze the efficacy of metformin intervention in preventing gestational diabetes mellitus (GDM).

Methods A systematic review and meta-analysis of clinical trials or observational studies of metformin intervention in preventing symptoms of GDM during pregnancy were performed. Medline, Embase, and Cochrane Library were searched through to now. The main evaluated primary outcomes were incident of GDM, miscarriage, preterm delivery, and neonatal mortality. The evaluated secondary outcomes were mean difference of gestational age at birth and birth weight between metformin group and control group.

Results We included 6 studies including 3 randomized clinical trials (RCTs), 2 observational studies, and 1 non-RCT in our meta-analysis. A total of 643 patients were enrolled for a follow-up study with continued metformin therapy (n = 341) or not (n = 302) during pregnancy. Metformin therapy reduced the proportion of patients developing GDM (log Odds Ratio: -1.27; 95 %CI: -2.24 to -0.30) but had no significant effect on reducing the proportion of abortion, preterm delivery, and neonatal death in pregnant women with polycystic ovary syndrome (PCOS). Also, it did not cause a significant difference in gestational age at birth and birth weight in metformin group versus control/placebo group.

Conclusions Metformin was associated with less frequent GDM development than control diets, suggesting that it is the appropriate intervention to be prescribed to prevent GDM in patients with PCOS.

Introduction

Gestational diabetes mellitus (GDM), a commonly-seen condition characterized by glucose intolerance, was reported to affect pregnancy and represent 90 % of all cases of diabetes mellitus diagnosed during pregnancy in the United States[1]. The incidence of GDM has been rising in the past decades which call upon a need for successful monitoring and treatment for patients. The significance of gestational diabetes in women remains elusive, some investigators believe that gestational diabetes is a diagnosis rather than a disease. It has been reported that maternal diabetes increases the risk of perinatal morbidity and mortality, as well as maternal morbidity[2]. Diagnosis and management of GDM bring beneficial effects on maternal and neonatal outcomes. Early intervention based on screening out risk factors[3], such as high blood pressure, prediabetes, a family history of GDM, increasing age or BMI, that leads to the development of GDM has been a key strategy in relevant prevention or treatment[4, 5]. Specifically, polycystic ovarian syndrome (PCOS), one of the most common endocrinopathies in women of reproductive age and was found to be associated with hyperinsulinemia and insulin resistance, could further aggravate during pregnancy and is predisposed to developing GDM[6].

Several studies have shown that prenatal lifestyle intervention aimed at modifying physical activity and diet among women with pregnant overweight or obesity may help to attenuate pregnancy-related adverse maternal and neonatal outcomes caused by glucose intolerance[7, 8]. However, whether pharmacological interventions took effect on reducing the development of GDM and improving pregnancy outcomes remains a controversy. Oral medication therapy is a treatment modality for GDM and in some circumstances could serve as the first-line therapy when dietary interventions fail. Insulin treatments are added as an adjunct therapy when oral medications fail to establish glucose control[9]. Despite oral medications are thought as effective and safe methods, they are not recommended by the FDA due to the risk of fears of teratogenicity and life-threatening neonatal hypoglycemia[10, 11]. Typical oral medications for GDM included metformin, glyburide, insulins, and their analogues[12], among which Metformin, a biguanide, oral hypoglycemic, insulin-sensitizing drug that improves tissue sensitivity to insulin, while decreasing insulin levels, and inhibiting hepatic glucose production, has been widely used for treating metabolic and endocrinal abnormalities and for effective ovulation in PCOS[13]. It reduces luteinizing hormone (LH), sex hormone binding globulin and ovarian androgen and also correct hyperinsulinemia[14]. In this study, we performed an extensive literature review of different available clinical studies, published in recent years, concerning pharmacological therapy for women with PCOS, dealing with safety and efficacy, for both fetal and maternal morbidity consequences; as well as failure and success in establishing appropriate metabolic and glucose control. By means of systematic review, our study provided available evidence to compare and determine the effective pharmacological intervention.

Methods

Literature Search

We manually searched 3 electronic databases [Medline, Embase, Cochrane Library (CENTRAL)]. The search strategy used the following general keywords, adapted to each above database: "gestational diabetes" or "glucose intolerance" and the appropriate terms for clinical trials evaluating effects of pharmacological interventions on GDM, such as "treatment" or "Metformin" or "polycystic ovary syndrome". All potentially eligible studies were considered for review, limited to the English language. Manual searching was also performed in the reference lists of included articles or from recent reviews correlated to the above keywords.

Inclusion and Exclusion Criteria

We included clinical trials or perspective cohort studies that aimed to assess the effect of the pharmacological intervention on reducing the risk of an incident of gestational diabetes. Maternal outcomes that we interested in include HbA1c level in the third trimester, an incident of severe maternal hypoglycemia, pre-eclampsia, total weight gain during pregnancy, cesarean section, treatment failure, fasting and postprandial blood glucose and induction of labor. Fetal outcomes were the gestational age at delivery, preterm birth, birth weight, macrosomia (> 4000 g), large for gestational age newborn (birth weight > 90th centile), small for gestational age newborn (birth weight < 10th centile), any neonatal hypoglycemia, and perinatal mortality. Articles with detailed information on the maternal and fetal outcomes and pharmacological approaches for the study participants with risk factors of GDM were included in our systematic review. The exclusion criteria include non-English written articles, animal study, missing information in the outcome of interests, patients with severe comorbidities, a subanalysis of primary study, and non-clinical study.

Study selection and validity assessment

The information of selected studies such as year of publication, abstract, authors' name, a total sample size of the clinical trials, study design, trial duration, medical and demographic characteristics of study participants (e. g., age, BMI, previous history of GDM) were carefully reviewed by two independent investigators. Studies not satisfying inclusion criteria were excluded.

Data extraction and statistical analyses

Relative risks and their 95 % CIs were pooled from each study. Descriptive data were presented as mean and/or range if available. The absolute difference for continuous variables such as weight gain at the baseline level and the endpoint of the study were calculated for the further analysis.

The heterogeneity among the studies was evaluated by Cochran Q test, and a P for trend less than 0.10 was considered statistically significant. The I^2 test was also performed to evaluate the magnitude of heterogeneity. Fixed effect model was presumably unless substantial heterogeneity ($I^2 > 50\,\%$) was found and alternatively a random effect model was used. Sensitivity analysis was conducted by the leave-one-out method. Possible publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error. Funnel plot asymmetry was evaluated by Begg and Egger Regression tests, and a significant publication bias was considered if the P value was < 0.10. All statistical analyses were performed using R studio with functional packages such as rmeta, metafor, or meta. Significance was set at P value < 0.05.

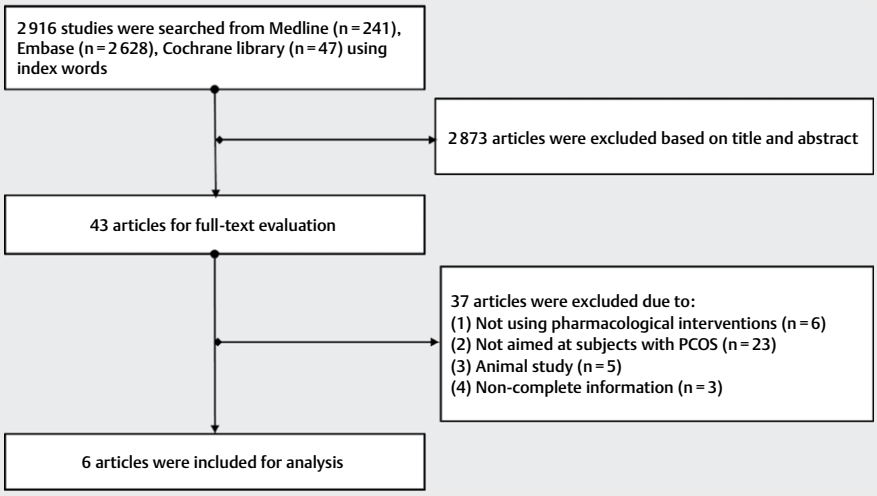
Results

Literature Search

We identified total 2916 articles from the Medline (n = 241), Cochrane Library (n = 47), and Embase database (n = 2628), of which 2873 articles were removed after reading the titles or abstracts and 43 articles were left for full-text evaluation. After review of the above 43 articles by two independent investigators, 37 articles were excluded for not satisfying inclusion criteria: 6 were removed for using lifestyle or dietary interventions, 23 were removed for not using clinical trials, 5 were removed for non-human study, and 3 were removed for containing missing information when extracting necessary data (▶ **Fig. 1**).

Study Characteristics

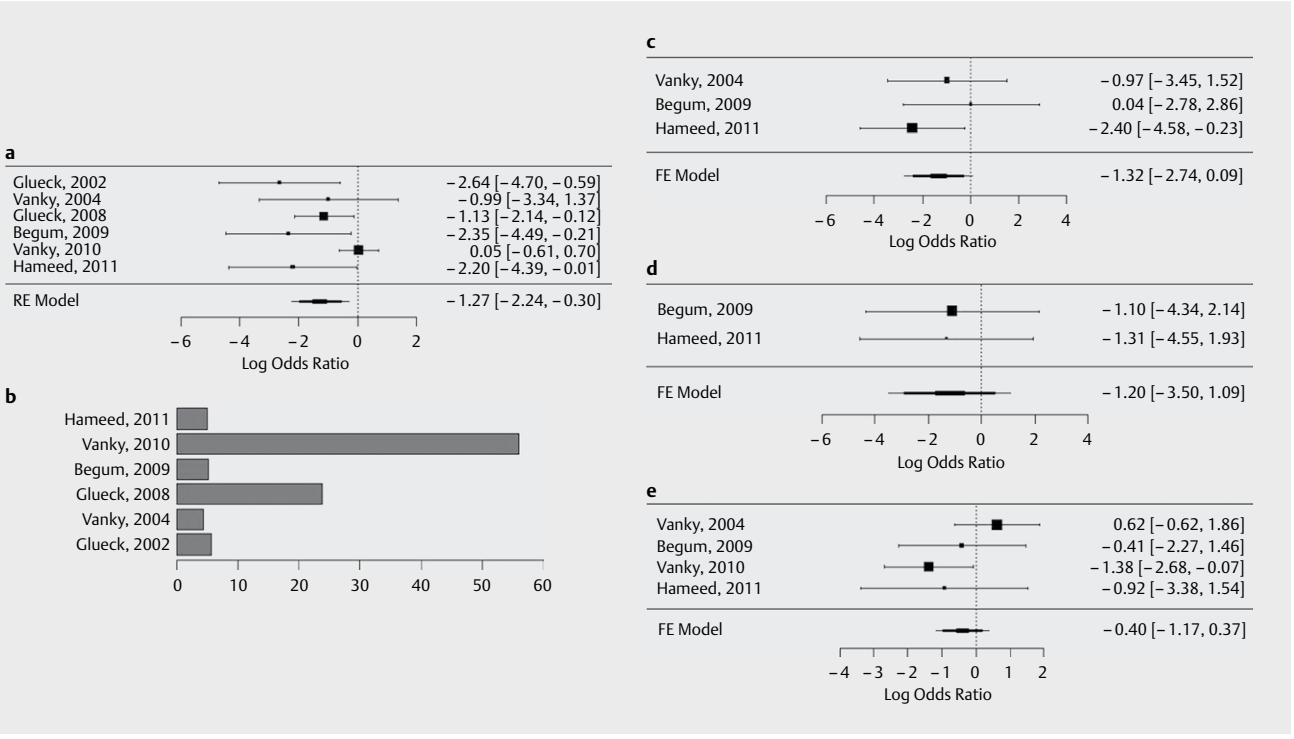
The study characteristics of the 6 selected studies [13, 15–19] were summarized in ▶ **Table 1**, of which two studies were cohort studies and the other 5 were clinical trials that all aimed at investigat-



▶ **Fig. 1** Consort diagram of literature search for evaluating the effect of pharmacological interventions on subjects with risk factors of GDM.

▶ **Table 1** Characteristics of selected studies aimed at investigating the effect of metformin on subjects with PCOS.

Author, year	Study Design	Treatment Arms	Sample Characteristics	Outcomes
Glueck, 2002	Cohort study on subjects with PCOS	Treatment (n = 33): metformin therapy; control (n = 39): without metformin therapy	Treatment: mean age (years) = 30 ± 3.7; Median BMI = 33.5 kg/m^2; mean fasting glucose level = 98 mg/dL; Non-white = 3.03 %; control: mean age = 37.9 ± 8.6; Median BMI = 33.6 kg/m^2; mean fasting glucose level = 89 mg/dL; Non-white = 5.12 %	Maternal outcomes: Incident of GDM, Weight, BMI, Insulin, Insulin Resistance, and Insulin Secretion. Fetal outcomes: gestational Age, Weight, and Height In Neonates
Vanky, 2004	A prospective, randomized, double-blind, placebo-controlled pilot study on subjects with PCOS	Treatment (n = 18): Metformin and lifestyle counseling; Control (n = 22): Placebo	Mean age (years) = 28.6 ± 4.2; mean BMI = 30.6 ± 7.3 kg/m^2; mean gestational age at inclusion: 56 ± 16 days; mean blood pressure = 118/75 mmHg	Primary outcome: changes in serum levels of dehydroepiandrosterone sulphate, androstenedione, testosterone, sex hormone-binding globulin, and free testosterone index. Secondary outcome measures were pregnancy complications and outcome
Glueck, 2008	Perspective cohort study on subjects with PCOS	Treatment (n = 95): metformin diet; Control (n = 47): without metformin	Mean age (years) = 32.3 ± 4.9; Median BMI = 32.7 kg/m^2; median fasting serum insulin was 16.4 mU/mL	Development of GDM, pregnancy on Weight, insulin, and HOMA Insulin Resistance
Begum, 2009	Perspective cohort study on subjects with PCOS	Treatment (n = 29): metformin therapy; Control (n = 30): without metformin therapy	Treatment: Mean age (years) = 28.14 ± 2.92; mean fasting insulin (μ IU/mL) = 20.62 ± 8.72; mean BMI = 28.21 ± 2.37; Control: Mean age = 26.13 ± 3.62; mean fasting insulin (μ IU/mL) = 18.84 ± 5.64; mean BMI = 27.97 ± 2.49	Main outcome measures were abortion rate, development of GDM, live birth rate, congenital anomaly, macrosomia and condition of newborn at birth
Vanky, 2010	Randomized, placebo-controlled, double-blind, multicenter study on subjects with PCOS	Treatment (n = 135): metformin; Control (n = 138): Placebo	Treatment: mean age (SD) = 29.6 (4.4); mean BMI (SD) = 29.5 (7.0); mean gestational length at inclusion (d) = 74 days; Control: mean age (SD) = 29.2 (4.4); mean BMI (SD) = 28.5 (7.2); mean gestational length = 75 days	Primary outcomes: prevalence of preeclampsia, preterm delivery and GDM; Secondary outcomes: weight, blood pressure, heart rate, and mode and length of delivery
Hameed, 2011	Non randomized, controlled clinical trial with PCOS	Treatment (n = 31): metformin diet; Control (n = 26): without metformin	Treatment: Age (years) = 30.2 ± 3.87; mean BMI = 29.22 ± 2.31; Control: Age (years) = 28.12 ± 4.35; mean BMI = 28.35 ± 1.97	Maternal outcomes: insulin resistance, incidence of GDM, the need for insulin therapy and incidence of preeclampsia. Fetal outcomes: incidence of spontaneous miscarriage, preterm birth, fetal growth abnormalities, suspected fetal asphyxia at birth, fetal anomalies and neonatal mortality



▶ **Fig. 2** Primary Analysis of the effect of metformin therapy on incident of GDM, neonatal mortality, and preterm birth: **a** Primary Analysis. **b** Study Contribution. **c** Meta-analysis for Abortion, **d** neonatal death, **e** Preterm Delivery.

ing the effect of metformin on preventing the incident of GDM for pregnant women with PCOS. Total 643 women with a confirmed diagnosis of PCOS were enrolled for a follow-up study with continued metformin therapy (n = 341) or not (n = 302) during pregnancy. The study populations were around 30 year-old and had an average BMI of 30 kg/m^2. Maternal outcomes such as Incident of GDM, changes in Weight, BMI, Insulin Resistance, and Insulin Secretion and fetal outcomes such as incidence of spontaneous miscarriage, preterm birth, fetal growth abnormalities, suspected fetal asphyxia at birth, fetal anomalies and neonatal mortality were reported in each study.

Primary Analysis

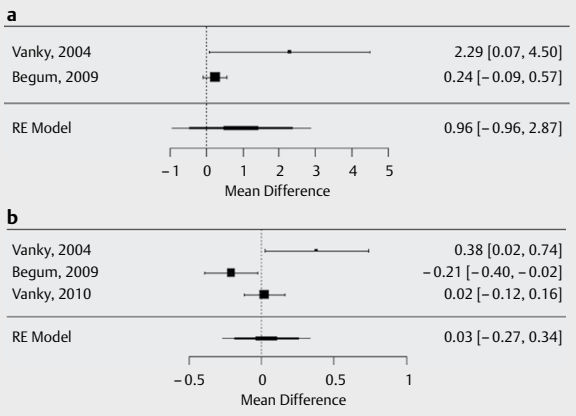
Our primary interest is how metformin therapy alters the risk of developing GDM and abortion in women with PCOS and neonatal mortality or preterm birth. Using Cochran Q test and random effect model, we found a trend of significant heterogeneity (I^2 = 60.43, p < 0.05) for the incident of GDM. The pooled logarithm odds ratio for the 6 studies was -1.27 (95 %CI: -2.24 to -0.30), suggesting metformin therapy significantly reduced the incident of GDM out of total pregnancies (▶ **Fig. 2a**). To further determine the percentage of each study contributed to an overall summary of the estimated odds ratio, we calculated study population based on the variance of each estimated logarithm odds ratio (▶ **Fig. 2b**). As indicated by the result, the results published by Glueck et al. in 2008 and Vanky et al. in 2010 had study contribution of 23.77 % and 55.84 % which were significantly higher than other publications. Similarly, through employing Cochran Q test and fixed effect model, we found the logarithm odds ratio for abortion, neonatal death, and preterm delivery was -1.32 (95 %CI: -2.74-0.09), -1.20 (95 %CI: -3.5-1.09), and -0.40 (95 %CI: -1.17-0.37) (▶ **Fig. 2c-e**). As indicated by the result of tests of heterogeneity, metformin therapy tended to have no significant effect on the fetal outcomes including abortion (I^2: 0.13 %, p > 0.05), neonatal mortality (I^2: 0.00 %, p > 0.05), and preterm delivery (I^2: 42.52 %, p > 0.05).

Secondary Analyses

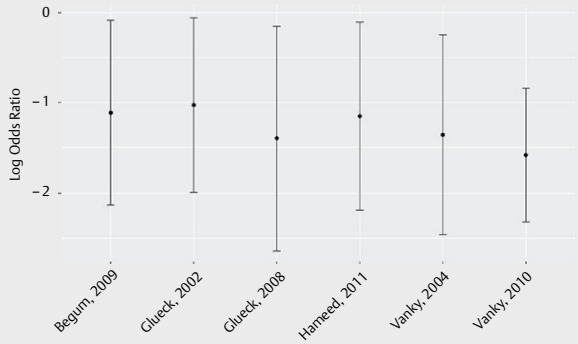
To further investigate how metformin intervention effects on gestational age at birth (weeks) and birth weight (kg), we calculated and pooled mean difference between metformin group and control group. As indicated by the result by employing random effect model, the pooled mean difference of gestational age at birth between metformin group and control group was 0.96 (95 %CI: -0.96-2.87) (▶ **Fig. 3a**) and there was considerate heterogeneity between the selected two studies (I^2: 68.91 %, p = 0.0729). Similarly, we found the pooled mean difference of birth weight between metformin group and control group was 0.03 (95 %CI: -0.27-0.34) (▶ **Fig. 3b**) and there was significant heterogeneity among the selected three studies (I^2: 84.24 %, p < 0.05). Thus, we concluded that metformin did not cause a significant difference in gestational age at birth and birth weight in patients with PCOS.

Sensitivity Analysis

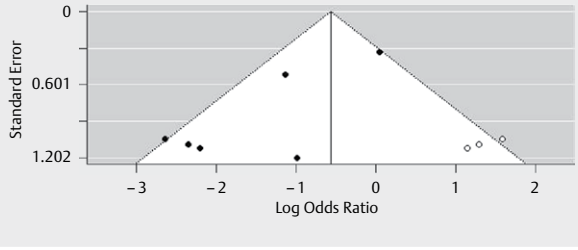
To perform sensitivity analysis, we re-calculate pooled log odds ratio by removing one study to derive leave-one-out diagnostics. As indicated by the result (▶ **Fig. 4**), each study contributed to the significant differences in log odds ratio for an incident of GDM before and after being removed (p < 0.05). Noticeably, the paper pub-



▶ **Fig. 3** Forest plot of the mean difference of gestational age at birth and birth weight between metformin group and control group: **a** Gestational age at birth. **b** Birth weight.



▶ **Fig. 4** Sensitivity analysis of the selected studies for contributing to the estimates of the incident of GDM.



▶ **Fig. 5** Funnel Plot for assessing publication bias that measured the effect of metformin therapy on developing GDM.

lished by Vanky et al. in 2010 remarkably reduced the magnitude of heterogeneity (I^2) to 0.626 %, suggesting a high sensitivity.

Publication Bias

Here, we measured publication bias by judging asymmetry in the funnel plot. By employing a trim-and-fill method, 3 missing null studies from the meta-analysis were added to the funnel plot (▶ **Fig. 5**). According to the result of regression test for funnel plot asymmetry by using mixed-effects meta-regression model, there is no obvious relationship between the study precision and measured effect of metformin intervention on the incident of GDM ($p = 0.689$).

Discussion

The systematic review of metformin intervention in patients with PCOS included total 643 study participants from 2 observational studies, 3 randomized clinical trials, and 1 non-randomized clinical trial. We were able to perform a meta-analysis on primary outcomes of interest (i. e., development of GDM, an incident of abortion, preterm delivery, and neonatal mortality) and secondary outcomes of interests (i. e., gestational age at birth and birth weight). Our study provided detailed analysis on the effect of metformin therapy in reducing risk of different types of adverse events for patients with PCOS. In summary, we found that metformin therapy significantly reduced the risk of developing GDM while not having a significant effect on the incident of miscarriage, preterm delivery, and neonatal death. Also, we found there was no significant difference in gestational age at birth and birth weight between metformin therapy and placebo/control group. The magnitude of heterogeneity among studies when measuring pooled odds ratio for the development of GDM was relatively high and the publication bias was not significant. Noticeably, there was no significant association between study precision and an estimate of the odds ratio of developing GDM.

PCOS is an endocrinopathy that associated with significant morbidity (e. g., amenorrhea, oligomenorrhea, hirsutism, obesity, infertility, anovulation, and acne) in women[20]. Having PCOS and being a pregnant posed additional risk for developing GDM which is associated with high perinatal mortality and morbidity for the fetus and both short- and long-term complications for the mother [21]. Several studies note a significantly elevated prevalence of GDM among PCOS versus non-PCOS women[22]. A significant number of PCOS patients are hyperinsulinemic[23, 24]. By correcting insulin resistance, PCOS patients would have reduced or corrected level of plasma androgen, which suggested a crucial role of insulin resistance in the pathogenesis of PCOS[25].

Metformin, an antidiabetic drug that increases the glucose uptake by peripheral tissues, is used in inducing ovulation during early pregnancy of PCOS patients[26]. Based on previous studies, Metformin inhibits hepatic gluconeogenesis and reduces fatty acid oxidation[27]. Also, it has a positive effect on the endothelium and adipose tissue independent of its action on insulin and glucose levels[28]. The mechanism of metformin was not fully explained. Some studies suggested that it involved in AMP-activated protein kinase[26]. In 1994, Velazquez and colleagues reported in an observational study a significant improvement in menstrual regularity and reduction in circulating androgen levels[29] after the treatment of metformin therapy. An early pilot study suggested that the continuation of metformin throughout pregnancy reduced the risk of GDM among PCOS women, which subsequently led to a wide discussion on whether the metformin intake in pregnancy is of benefit to women with PCOS[29]. Thus, Metformin may reduce the incident of GDM via a mechanism of directly regulating AMP-activated protein kinase, level of circulating androgen, and fatty

acid oxidation to inhibit gluconeogenesis. The indirect effect of Metformin on preventing other adverse events may not be significant, which is consistent with our finding that Metformin has no obvious effect in preventing miscarriage, preterm delivery, and neonatal death.

In our selected studies included for meta-analysis, two observational studies were from Glueck and colleagues. They reported a prevalence of GDM of 7 % among pregnant PCOS women who continued taking metformin throughout pregnancy compared with 30 % among those who did not in their 2002 study. Subsequently, they included a relatively larger sample size compared with the previous study and reported similar results [17, 18]. Nevertheless, the studies were observational, therefore their publication may have to low quality of evidence and should be considered carefully. Furthermore, it is not known whether the beneficial effect of metformin and weight loss prior to conception had contributed to the reduction of GDM risk. The other 4 clinical trials emerging on the benefits of administering metformin to all pregnant women at high risk of gestational diabetes clarified the effect of Metformin in preventing GDM. Their results were considered as a high quality of evidence.

A possible limitation of our systematic review could be related to selection bias and a limited amount of selected studies (n = 6). As shown in the trim-and-fill method, 3 non-significant studies were estimated to be missing and not included. Regarding our results, the metformin therapy in preventing gestational age at birth and neonatal mortality, missing information was found in 4 studies and therefore only 2 studies were pooled for summarizing effect estimates, which may limit their value in measuring the effect of metformin therapy in patients with PCOS. Another potential weakness of our systematic review was the inability of measuring valuable estimates such as weight gain, changes in insulin resistance, and so on because, in the included studies, the outcomes evaluated were not always the same, were not uniformly standardized, or were even not available. Also, the adherence of metformin interventions was barely assessed or reported in four trials. All these aspects reinforce the need to perform well-designed RCTs on the effects of metformin intervention on preventing GDM in patients with PCOS.

In conclusion, we demonstrated that in patients with PCOS, the use of metformin intervention was associated with less frequent GDM development and did not differentiate birth weight, gestational age at birth, the proportion of miscarriage, preterm delivery and neonatal mortality than the control. Therefore, the presently available evidence suggests that metformin may be recommended for usage in order to prevent GDM in patients with PCOS.

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Conflict of Interest

We confirm that we have no any financial or non-financial conflict of interest.

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