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Effect of metformin treatment during pregnancy on women with PCOS: a systematic review and meta-analysis

Abstract

Purpose: Some previous studies have found that continued metformin use is beneficial in the management of polycystic ovary syndrome (PCOS) in pregnant women. A systemic review and meta-analysis were needed to more fully assess the effects of metformin on pregnant PCOS patients.

Methods: The literature was fully searched using MEDLINE, EMBASE, SCOPUS, and COCHRANE for continued metformin use during pregnancy in women with PCOS. A systematic review and meta-analysis were performed to evaluate the comprehensive effects of continued metformin treatment on pregnancy-related outcomes in these women.

Results: Eleven eligible studies out of 127 relevant publications were included in meta-analysis. The rates of early pregnancy loss and preterm delivery were found to be significantly decreased in metformin-treated PCOS women. A non-significant difference was found in fetal abnormality and fetal birth weight between the metformin-treated and the non-treated groups. The incidence of gestational diabetes mellitus (GDM) and hypertension/preeclampsia were not significantly different in the two groups, probably because of inconsistent results in the subgroup analysis.

Conclusions: Our results showed that continued use during of metformin, during pregnancy in women with PCOS, had no effect on incidence of fetal abnormalities or fetal birth weight. The effects of metformin on GDM and hypertension/preeclampsia should be determined through high-quality randomized controlled trials.

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of anovulatory infertility in women of reproductive age. Estimates of prevalence vary between 3% and 11%, depending on the diagnostic criteria used and the population studied, with a rate of 6.5–6.8% in European Caucasian women [1, 2]. Until now, two main diagnostic criteria have been proposed: the National Institute of Health (NIH)/National Institute of Child Health and Human Development (NICHD) criteria proposed in April 1990 [3], and European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) criteria proposed in May 2003 [4]. The extreme variability of the diagnostic criteria notwithstanding, the main clinical features related to this syndrome, albeit not pathognomonic, are menstrual disorders, anovulatory infertility and signs of hyperandrogenism [4, 5]. The pathogenesis of PCOS is still unclear, and a complex group of genetic and environmental factors may be involved. Factors including obesity, insulin resistance, prenatal androgen excess during early gestation, birth weight, precocious pubarche, dietary intake, lifestyle, and stress may act on the genetic substrate. Most women with PCOS also exhibit features of the metabolism syndrome, including insulin resistance, obesity and dyslipidemia [6-8]. Insulin resistance (IR) with compensatory hyperinsulinemia is most likely a cornerstone of the pathogenesis of PCOS, and the recognition of the importance of IR has led to a much better understanding of the syndrome and associated short- and long-term complications. IR in women with PCOS appears in both obese and non-obese women [9].

Metformin is a biguanide oral anti-diabetic drug that improves the insulin sensitivity of tissue, reducing insulin concentration, as well as inhibiting hepatic glucose production without affecting normal glucose levels; hence, there is a mechanistic rationale to use metformin to treat the hyperinsulinemia associated with PCOS. Metformin reduces luteinizing hormone (LH), sex hormone-binding globulins and ovarian androgens and also correct hyperinsulinemia when used in patients with PCOS; therefore, metformin is considered a first-line drug in the administration of PCOS, for its safety and effectiveness [10]. Some studies revealed that metformin may increase ovulation rate; consequently, many PCOS patients conceive while taking this medication. Metformin is a category B drug for use during pregnancy (absence of teratogenic effect based on animal data) and the safety and efficacy of metformin treatment in PCOS, especially in pregnant women with PCOS, had not been established.

Many women with PCOS have difficulty conceiving naturally due to the ovulatory disturbances associated with their medical condition. In addition, PCOS patients who are fortunate enough to become pregnant, either naturally or through assisted reproduction technology, are still at an increased risk for pregnancy complications. A meta-analysis was performed to investigate the pregnancy outcomes between PCOS women and control subjects and revealed that pregnancies in PCOS patients are characterized by a higher incidence of complications, including early pregnancy loss (EPL), gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preeclampsia (PE), preterm delivery (PD) and neonatal admission to intensive care units [11]. In recent years, the use of metformin in PCOS patients during pregnancies has become increasingly popular. As there are no guidelines for metformin administration in PCOS patients during pregnancy, the duration of treatment is selected by physicians based on their clinical experience. The efficacy and safety of metformin in pregnant women with PCOS have been controversial and unconfirmed [12]. The actual value of using

metformin treatment in PCOS women is still a matter of discussion because conflicting data exists in the literature on its true therapeutic effect. A meta-analysis was conducted to examine pregnancy outcomes after metformin using in the first-trimester of pregnant women with PCOS [13]. Only malformations due to the use of metformin during first trimester were analyzed, due to the limited data. Some studies in the past decade have investigated the effect of metformin treatment on women with PCOS throughout their pregnancies. In order to present an evidence-based analysis for clinical practice, this systematic review and meta-analysis was carried out to evaluate the effect of continued metformin treatment on pregnancy outcomes in women with PCOS.

Materials and Methods

The protocol design followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Data Sources and Search Strategy

MEDLINE, EMBASE, SCOPUS and COCHRANE Central Register were systematically searched in July 2013 with the following terms: metformin, polycystic ovary syndrome (PCOS) and pregnancy. The reference lists of retrieved articles were also hand-searched. There were no language restrictions. Two reviewers (Shengbing Li and Xingrong Tan)

independently screened all the abstracts that examined the pregnancy outcomes of women with PCOS with continued metformin treatment during their pregnancies. The filtered abstracts were further searched for the corresponding full texts, and the inclusion criteria applied.

Study Selection Criteria

Published studies that investigated the effect of continued metformin treatment on pregnancy-related outcomes in women with PCOS were considered. The diagnosis of PCOS was fully described. The treatment and control group was well matched in each study. The treatment groups consisted of women with PCOS who used metformin throughout pregnancy. Control group was defined women with PCOS who did not use metformin during pregnancy, or who discontinued metformin use after they became pregnant. Each study provided detailed information on pregnancy outcomes in different groups, including GDM and pregnancy induced hypertension/ preeclampsia (PIH/PE), early pregnancy loss (EPL), preterm delivery (PD), fetal abnormality (FA) and fetal birth weight (FBW). There was no restriction of the use of other ovulation induction drugs, such as clomiphene citrate and gonadotrophins, which were usually used as part of a combination therapy. These studies were approved by local ethics committee, and all participants gave their informed consent for participation and follow-up.

The following studies were excluded from the review and analysis: 1) no control group; 2) no data available; 3) non-matched control study; and 4) overlapped data or study population.

Two of the authors (Ying Chang and Shengbing Li) independently identified and reviewed each relevant paper. Reviewers resolved disagreements about study inclusion or exclusion by consensus and by referring to the original reports.

Data extraction

Two investigators (Shengbing Li and Xingrong Tan) independently extracted data after assessing all studies and after reaching a consensus for eligible studies using a standardized data extraction form. The following information was obtained from each study: first author, journal and year of publication, study design, defined study groups and corresponding intervention measures, number of both cases and control, diagnostic criteria of PCOS, index of pregnancy outcome and detailed data.

Statistical analysis

Heterogeneity between the results of different studies was examined by chi-square-based Q statistic and I^2 value. Heterogeneity was considered significant at a P value of <0.10 in Q -test or $I^2 > 50\%$ [15, 16]. For dichotomous data, the results for each study were expressed as odds ratio (OR) with 95% confidence intervals (CI). Continuous data were combined by using the weighted mean difference (WMD) with 95% CI. Data were combined using fixed-effects (Mantel-Haenszel) or random-effects (DerSimonian and Laird) model according to the result of heterogeneity test in meta-analysis. In the absence of between-study heterogeneity, the two methods provide identical results. Random effects were more appropriate when heterogeneity is discovered. P value ≤ 0.05 and 95% CI not containing 1.00 (OR) or 0 (WMD) were considered to be statistically significant. Subgroup analysis was carried out according to the characteristic of the study design of included studies. Qualitative analysis was conducted to assess the comparisons that could not be pooled by meta-analysis. The publication bias was assessed by the combination of Begg's test, Egger's test and fail-safe number for $P=0.05$ ($Nf_{0.05}$) [17-20].

Data were analyzed by RevMan 5.2 (the Cochrane collaboration; www.cochrane.co.uk), intercooled Stata 9.2 (StataCorp LP, www.stata.com) and MS Excel 2003 (Microsoft Corporation). All P -values are two-tailed.

Results

Search results and eligible studies

One hundred twenty-seven literature studies were searched and returned. Fourteen eligible literature studies [21-31] met the study selection criteria (Figure 1). The characteristics of the included studies are presented in Tables 1 and 2. Three studies [21-23] were randomized. The pregnancy outcomes, including GDM, PIH/PE, EPL, PD, fetal abnormality (FA), fetal birth weight (FBW), were considered in the analysis.

Gestation diabetes mellitus (GDM)

Seven studies [21-25, 27, 30] provided the data of GDM in patients with PCOS with or without metformin treatment. Subgroup analyses were performed in three randomized studies [21-23]. In the subgroup analysis, heterogeneity was detected (Table 3). The random effect model was employed, and the pooled OR (95% CI) was 0.75 (0.16, 3.42, $P=0.71$). In the subgroup analysis of non-randomized studies, heterogeneity was absent (Table 3). Fixed effect model was

TABLE 1. General information of included studies in the meta-analysis

First author and publication year	Study characteristics	Management in grouped population and sample size (n)		Metformin administration prior to conception	Other treatments for PCOS	Study limitation
Vanky, 2010 [19]	Randomized placebo-controlled double-blind multi-center	T	Pregnant women with PCOS treated with metformin (2000 mg/d) from first trimester to delivery (n = 135)	Yes	Not described	
		P	Pregnant women with PCOS treated with placebo (n = 138)	Washout period ≥ 7 day		
Begum, 2009	Randomized	T	Pregnant women with PCOS who continued treatment with metformin (1500–2500 mg/day) (n=29)	Yes	Ovulation inducing agents Clomiphene citrate (n = 15), letrozole, (n = 30), clomiphene citrate + gonadotropins (n = 60), and letrozole + gonadotropins (n = 45) were used along with metformin for 6–12 months.	Small number of cases
		P	Pregnant women with PCOS who discontinued Metformin at 8 weeks of pregnancy (n = 30)			
Vanky, 2004	Randomized placebo-controlled double-blind	T	Pregnant women with PCOS treated with metformin (1700 mg/d) (n = 17)	8/17, washout period ≥ 2 day	Not described	Small number of cases
		P	Pregnant women with PCOS treated with placebo (n = 21)	11/21, washout period ≥ 2 day		
Khattab, 2011	Prospective cohort	T	Continued taking metformin (1000–2000 mg/d) throughout pregnancy (n=200)	Yes (taking metformin for 3–6 months before they become pregnant and participated in the study)	Not described	Non-randomized
		P	Discontinued using metformin at the time of conception or at 8 weeks of pregnancy (n=160)			
Hameed, 2011	Prospective cohort	T	Women with PCOS conceived while taking Metformin (1000-2500 mg/d) with or without other ovulation inducing agents and continued metformin (1000-1500 mg/d) during pregnancy (n=31)	Yes	Clomiphene citrate and/or gonadotrophins	Non-randomized, small number of cases
		P	Women with PCOS conceived without taking metformin and did not take it during pregnancy (n=26)	No		
Nawaz, 2008 [§] , 2010	Prospective cohort	T	Women with PCOS who conceived while taking Metformin(1500mg/d) and continued throughout pregnancy (n=45 [§] , 119)	Yes	The other 49 (41.1%) needed additional medication, including clomiphene citrate or gonadotrophins, for induction of ovulation.	Non-randomized
		P	Women with PCOS stopped metformin in first trimester after confirmation of pregnancy or conceived spontaneously without the use of metformin (n=32 [§] , 78)	Not described	44 patients required induction of ovulation with clomiphene or gonadotrophins in addition to the use of metformin.	
Khattab, 2006	Prospective cohort	T	PCOS patients became pregnant while taking metformin, and continued taking metformin at a dose of 1000–2000 mg daily throughout pregnancy (n=120)	Yes	Not described	Non-randomized
		P	PCOS women discontinued metformin use at the time of conception or during pregnancy (n=80)	Yes		
Jakubowicz, 2002	Retrospective ^Ω Case-control	T	Pregnant women with PCOS treated with metformin (1000-2000mg/d) from conception to delivery (n=65)	Yes	Clomiphene citrate (41.5%) or hCG (9.2%)	Non-randomized, retrospective
		P	Pregnant women with PCOS not treated with metformin either at the time of conception or during pregnancy (n = 31)	Not described	Clomiphene citrate (29.0%) or hCG (9.7%)	
Glueck, 2002	Prospective Retrospective cohort	T	Pregnant women with PCOS treated with metformin 2250 mg/d from conception to delivery (n=33)	Yes	Not described	Non-randomized, retrospective
		P	Pregnant women with PCOS without taking metformin ^Ω n=39 ^Ω	No		
Glueck, 2001	Prospective Retrospective cohort	T	Women conceived while receiving metformin, 1.5 to 2.55 g/day and continued to receive metformin throughout pregnancy ^Ω n=19 ^Ω	Yes	Not described	Non-randomized, retrospective
		P	Pregnant women with PCOS not treated with metformin ^Ω n=125 ^Ω	No		

T: PCOS patients treated with metformin throughout pregnancy; P: PCOS patients without metformin during pregnancy

TABLE 2. Data from the studies included in this meta-analysis

First Author and publication year	Groups and Sample size (n)		BMI (kg/m ²)	New GDM* (n/N)	PIH/PE* (n/N)	Early pregnancy loss*(n/N)	Preterm delivery* (n/N)	Fetal abnormality* (n/N)	Mean body weight (g)
Vanky, 2010 [19]	T	135	29.5±7.0	22/125	10/135	-	5/135	-	3550±568
	P	138	28.5±7.2	21/124	5/135	-	11/135	-	3527±615
Begum, 2009	T	29	28.1±2.9	1/29	-	1/29	2/29	-	2790±143
	P	30	26.1±3.6	9/30	-	1/30	3/30	-	3000±499
Vanky et al, 2004	T	17	32.1±6.1	6/15	3/17	-	0/17	3/17	3595±420
	P	21	29.3±8.0	3/15	2/21	-	5/21	4/21	3215±1048
Khattab, 2011	T	200	30.1±1.5	8/200	6/200	-	-	-	-
	P	160	29.6±1.6	32/160	13/160	-	-	-	-
Hameed, 2011	T	31	29.2±2.3	1/31	1/31	1/31	1/31	0/31	-
	P	26	28.4±2.0	6/26	2/26	7/26	2/26	1/26	-
Nawaz, 2008 [§] , 2010	T	119	32±4.6	12/119	20/119	9/119	2/41 [§]	0/45 [§]	2880±950 [§]
	P	78	33.2±5.2	35/78	35/78	23/78	5/26 [§]	0/32 [§]	2900±1100 [§]
Khattab, 2006	T	120	28.1±1.5	-	-	14/120	-	1/120	-
	P	80	27.6±1.6	-	-	29/80	-	0/80	-
Jakubowicz, 2002	T	65	27.1±1.7	-	-	6/68	8/68	1/62	-
	P	31	26.9±0.4	-	-	13/31	6/31	0/18	-
Glueck, 2002	T	33	-	1/33	-	-	-	0/33	-
	P	39	-	14/60	-	-	-	0/60	-
Glueck, 2001	T	19	-	-	-	2/19	-	-	-
	P	125	-	-	-	103/265	-	-	-

Abbreviations: GDM: gestational diabetes mellitus; PIH: pregnancy induced hypertension; PE: preeclampsia.

* Sample size was calculated according to the actual pregnancies in each group and not the number of women investigated.

conducted, and the pooled OR (95% CI) was 0.14 (0.09, 0.24, $P<0.00001$). When all studies were included, heterogeneity was significant and the pooled OR (95% CI) was 0.28 (0.10, 0.75, $P=0.01$) (Figure 2). No publication bias was found by Begg's and Egger test in these analyses (Table 3). And the $Nfs_{0.05}$ was larger than the number of studies (Table 3).

Pregnancy induced hypertension (PIH) / Preeclampsia (PE)

Two randomized studies [21, 23] and three non-randomized studies [24, 25, 27] were included in meta-analysis of PIH/PE. Heterogeneity was detected when all studies were included (Table 3). In the randomized studies subgroup, the pooled

OR (95% CI) was 2.07 (0.80, 5.38), $P=0.14$. In the non-randomized studies subgroup, the pooled OR (95% CI) was 0.28 (0.17, 0.48), $P<0.00001$. Random effect model was employed when all studies were included and the pooled OR (95% CI) was 0.62 (0.23, 1.67), $P=0.35$ (Figure 3). No publication bias was found by Begg's and Egger test in any of the analyses (Table 3) and the $Nfs_{0.05}$ was larger than the number of studies included in the corresponding analysis (Table 3).

TABLE 3. Pregnancy outcome by continued metformin treatment in women with PCOS

Index	Subgroups	Heterogeneity test		Overall effect				$Nfs_{0.05}$	Publication bias test		
		P_{het}	I^2	Effect model	OR/WMD	95%CI	P		Begg's test P	Egger test bias P and its 95%CI	
New GDM	Randomized	0.03	70%	R	0.75	(0.16, 3.42)	0.71	-	0.60	0.73	(-38.32, 35.72)
	Non-randomized	0.96	0%	F	0.14	(0.09, 0.24)	<0.00001	82.20	0.50	0.31	(-1.81, 0.95)
	All studies	<0.00001	80%	R	0.28	(0.10, 0.75)	0.01	202.11	0.65	0.67	(-5.99, 4.18)
PIH/PE	Randomized	0.98	0%	F	2.07	(0.80, 5.38)	0.14	-	0.32	-	-
	Non-randomized	0.82	0%	F	0.28	(0.17, 0.48)	<0.00001	16.31	0.60	0.45	(-6.34, 7.62)
	All studies	0.01	70%	R	0.62	(0.23, 1.67)	0.35	-	0.33	0.33	(-3.78, 8.10)
EPL	Randomized	-	-	-	1.04	(0.06, 17.38)	0.98	-	-	-	-
	Non-randomized	0.89	0%	F	0.19	(0.12, 0.30)	<0.00001	103.27	0.10	-2.67	0.42
	All studies	0.78	0%	F	0.20	(0.12, 0.31)	<0.00001	103.58	0.85	0.90	(-2.09, 2.30)
PD	Randomized	0.50	0%	F	0.38	(0.16, 0.90)	0.03	3.35	0.60	0.69	(-9.11, 8.38)
	Non-randomized	0.30	18%	F	0.29	(0.13, 0.67)	0.004	8.01	0.12	0.01*	(-4.26, -2.77)*
	All studies	0.56	0%	F	0.33	(0.18, 0.60)	0.0003	28.10	0.75	0.23	(-3.10, 1.02)
FA	Randomized	-	-	-	0.91	(0.17, 4.77)	0.91	-	-	-	-
	Non-randomized	0.69	0	F	0.78	(0.14, 4.27)	0.78	-	0.58	-466.23	412.03
	All studies	0.86	0%	F	0.85	(0.26, 2.78)	0.78	-	0.50	0.86	(-4.40, 4.02)
FBW	Randomized	0.03	71%	R	-10.49	(-251.44, 230.46)	0.93	-	0.60	0.72	(-41.87, 45.09)
	Non-randomized	-	-	-	-20.00	(-491.48, 451.48)	0.93	-	-	-	-
	All studies	0.08	56%	R	-19.93	(-217.22, 177.36)	0.84	-	0.50	0.66	(-7.13, 9.05)

Abbreviations: GDM: gestational diabetes mellitus; PIH: pregnancy induced hypertension; PE: preeclampsia; EPL: Early pregnancy loss; PD: Preterm delivery; FA: Fetal abnormality; FBW: fetal birth weight; OR: odds ratio; WMD: weighted mean difference; $Nfs_{0.05}$: fail-safe number for $P=0.05$;

* Significant publication bias so not suitable for evaluation.

Early pregnancy loss (EPL)

The data of EPL was provided from five non-randomized studies [25, 27-29, 31] and one randomized study [22]. Heterogeneity in these studies was negligible, and the pooled OR (95% CI) was 0.20 (0.12, 0.31, $P<0.001$) (Figure 4). No publication bias was found by the Begg's and Egger test, and the $Nfs_{0.05}$ was larger than the number of studies included in the corresponding analysis (Table 3).

Preterm delivery (PD)

Three randomized [21-23] and three non-randomized studies [25, 26, 29] investigated PD. There was no heterogeneity in either analysis. In subgroup analysis for randomized studies, the pooled OR (95% CI) was 0.38 (0.16, 0.90, $P=0.03$); however, for non-randomized studies, the pooled OR (95% CI) was 0.29 (0.13, 0.67, $P=0.004$). For all studies, the pooled OR (95% CI) was 0.33 (0.18, 0.60, $P=0.0003$) (Figure 5). Publication bias was found in the subgroup analysis of non-randomized study. The $Nfs_{0.05}$ was larger than the number of studies in the corresponding analysis (Table 3).

FIGURE 1. Flowchart of search strategy and results.

Fetal abnormality (FA)

Five non-randomized studies [25, 26, 28-30] and one randomized study assessed FA [23]. Homogeneity was found in all three analyses. The pooled OR (95% CI) was 0.85(0.26, 2.78, $P=0.78$) (Available from author on request). No publication bias was found by the Begg's and Egger test (Table 3).

Fetal birth weight (FBW)

FBW was investigated by three randomized studies [21-23] and one non-randomized study [26]. The random effect model was used in this analysis. The pooled WMD (95% CI) was -19.93 (-217.22, 177.36, $P=0.84$) (Available from author on request). No publication bias was found by the Begg's and Egger test.

Discussion

In the current meta-analysis, we demonstrated that the rates of early pregnancy loss and preterm delivery were significantly decreased in metformin-treated women with PCOS. A non-significant difference was found in fetal abnormalities and fetal birth weight between metformin-treated and non-treated groups. The incidence of GDM and

hypertension/preeclampsia were not significantly different between the two groups.

Metformin has been widely used for the treatment of type 2 diabetes mellitus (T2DM) for more than 60 years. Interests in the therapeutic use of metformin have been sparked by the recognition of its pleiotropic actions on several tissues, namely liver, skeletal muscles, adipose tissue, endothelium and the ovary, which are affected by IR and/or hyperinsulinemia.

An intriguing aspect of metformin is the reproductive effects of treatment in women with PCOS. Metformin may act upon the ovary, either directly or indirectly, by inhibiting the effects of insulin excess on steroidogenesis and follicular growth. In theca cells, metformin may inhibit 17, 20-lyase (17 α -hydroxylase, CYP17) activity, either through direct action or indirectly through the reduction of insulin levels and the subsequent suppression of insulin-induced phosphatidylinositol-3 kinase (PI3K) activity. By reducing insulin levels, metformin may inhibit LH receptor expression as well as StAR protein (StAR), 3 β -hydroxysteroid dehydrogenase (HSD3-b) and P450 side-chain cleavage (CYP11A1 or P450scc) activity in granulosa cells. In addition, metformin-induced AMP-activated protein kinase (AMPK) activation may not only decrease StAR, HSD3-b, and CYP11A1 activity in granulosa cells, but also enhance antioxidant defenses in ovarian tissue. These mechanisms may

FIGURE 2. Meta-analysis of the odds ratio for gestational diabetes mellitus in the compared groups-forest plot.

FIGURE 3. Meta-analysis of the odds ratio for pregnancy induced hypertension/ preeclampsia in a compared groups-forest plot.

FIGURE 4. Meta-analysis of the odds ratio for early pregnancy loss in a compared groups-forest plot.

FIGURE 5. Meta-analysis of the odds ratio for preterm delivery in a compared groups-forest plot.

contribute to the inhibition of sex steroid overproduction and of premature luteinization, and consequently attenuate androgen excess and improve ovulation [32-37].

The capacity of metformin to attenuate both IR and androgen excess has motivated the investigation of metformin's role in the management of reproductive failure in women with PCOS. Metformin monotherapy, as compared with a placebo, has been shown to improve ovulation rates in women with PCOS in randomized control trials (RCT), cohort studies or uncontrolled descriptive studies [38-42]. Moreover, some studies have found higher or similar ovulation and pregnancy rates following metformin treatment as compared to the clomiphene citrate (CC) [43-45], while the addition of metformin to CC monotherapy was reported to further enhance ovulation rate in a meta-analysis [46]. Addition of metformin may also decrease the risk of multiple pregnancies in women with PCOS [47]. In addition, metformin co-administration during gonadotrophin ovulation induction or in *vitro* fertilization (IVF) may reduce the risk of ovarian hyperstimulation syndrome (OHSS), by reduction of serum levels of vascular endothelial growth factor (VEGF) [48, 49]. In addition to difficulty in conceiving, women with PCOS are at increased risk for early miscarriage. Other gestational complications, mainly GDM and PIH/PE as well as neonatal complications, are also more prevalent in PCOS women [11]. IR and hyperinsulinemia may contribute to the propensity of women with PCOS to adverse events. Considering the impact of IR on the physiology of pregnancy, continued metformin treatment in women with PCOS may be beneficial.

There were several other potential mechanisms of metformin, including increased glycolipin levels, decreased PAI-1 levels and AMPK activation, which were revealed to play a role in improving the pregnancy outcome in women with PCOS [50-52]. It is important to note that the beneficial role of metformin in pregnancy may be accomplished through a continuation of effects that starts from preconception and lasts throughout pregnancy.

Recently, two meta-analyses were published [53, 54] and some important deficiencies have been noted: 1) some studies were missing; 2) the control and treated groups were not matched; and, 3) duplicate data were used in these analyses; therefore, their results are not reliable. Importantly, according to the PRISMA guidelines and available data, our meta-analysis is standard and presents reliable results for the effects of continued metformin treatment during pregnancy on women with PCOS. We found that EPL and PD were significantly decreased in metformin-treated PCOS patients; however, there was no difference in FA and FBW between

metformin-treated patients and control subjects. In the subgroup analysis for GDM and PIH/PE, the results were paradoxical; therefore, the effects of continued metformin treatment on GDM and PIH/PE in pregnant women with PCOS were not confirmed.

There were several potential limitations of our meta-analysis and our results should, therefore, be interpreted with caution. First, this meta-analysis was based on a relative paucity of quality data. Only three of the 11 studies were randomized and some results were based on a relatively small sample size. Second, not all the pregnancy and neonatal complications were involved in this meta-analysis, so the overall effect of continued metformin use on PCOS pregnancy cannot be concluded. Third, the dosage of metformin was not considered due to the absence of data. Fourth, the co-administrations of diet and lifestyle intervention, CC, gonadotrophins and IVF in some PCOS patients may be confounders to metformin's effect. Fifth, the effect of pretreatment of pregnancy and other possible endocrine or genetic influence related to PCOS were not considered in this analysis. In addition, sensitivity analysis cannot be carried out due to the poor quality of the data. To generate stronger data, more studies with multi-center, randomized placebo-controlled, double-blind protocol should be carried out, with special emphasis on the effect of metformin dosage, the combined therapy and other possible confounder factors.

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