Metformin for the prevention of hypertensive disorders of pregnancy in women with gestational diabetes and obesity: a systematic review and meta-analysis

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Short title: Metformin prevents preeclampsia

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ABSTRACT

Objectives: Metformin has been reported to reduce the risk of preeclampsia. It is also known to influence soluble fms-like tyrosine kinase-1 (sFlt-1) levels, which correlate significantly with the gestation of onset and severity of preeclampsia. The main aim of this systematic review and meta-analysis was to determine whether metformin use is associated with the incidence of hypertensive disorders of pregnancy (HDP).

Methods: MEDLINE (1947 – September 2017), Scopus (1970 – September 2017) and the Cochrane Library (since inception - September 2017) were searched for relevant citations in English language. Randomized controlled trials on metformin use, reporting the incidence of preeclampsia or pregnancy induced hypertension were included. Studies on populations with a high probability of metformin use prior to randomization (type II diabetes or polycystic ovary syndrome) were excluded. Random-effects models with Mantel-Haenszel were used for subgroup analyses. Moreover, a Bayesian random-effects meta-regression was used to synthesize the evidence.

Results: In total, 3337 citations matched the search criteria. After evaluating the abstracts and full text review, 15 studies were included in the review. Metformin use was associated with a reduced risk of pregnancy induced hypertension when compared to insulin (RR: 0.56, 95% CI: 0.37-0.85, $I^{\wedge 2}$=0, 1260 women) and a non-significantly reduced risk of preeclampsia (RR: 0.83, 95% CI: 0.60-1.14, $I^{\wedge 2}$=0%, 1724 women). When compared to placebo, metformin use was associated with a non-significant reduction of preeclampsia (RR: 0.74, 95% CI: 0.09-6.28, $I^{\wedge 2}$=86%, 840 women). Metformin use was also

associated with a non-significant reduction of any HDP (RR: 0.71, 95% CI: 0.41-1.25, I^2=0, 556 women) when compared to glyburide. When studies were combined with Bayesian random-effects meta-regression using treatment type as a covariate, the posterior probabilities of metformin having a beneficial effect for the prevention of preeclampsia, pregnancy induced hypertension and any HDP were 92.7%, 92.8% and 99.2%, respectively when compared to any other treatment or placebo.

Conclusions: There is a high probability that metformin use is associated with a reduced HDP incidence when compared to other treatments and placebo. The small number of studies included in the analysis, the low quality of evidence and the clinical heterogeneity preclude the generalization of these results to broader populations. Given the clinical importance of this topic and the magnitude of effect observed in this meta-analysis, further prospective trials are urgently needed.

INTRODUCTION

Preeclampsia is a leading cause of maternal mortality and morbidity which imposes a substantial burden on the healthcare system.[1] Significant efforts have been devoted to developing clinically useful screening methods and prevention strategies for preeclampsia. Although the recommended approach to screening for preeclampsia is blood pressure monitoring, the ASPRE trial has shown that it is possible to predict the development of early-onset preeclampsia with good precision using a combination of maternal factors and biomarkers in the first trimester of pregnancy.[2,3] Early prediction is quite important as aspirin, the only proven prevention method for preeclampsia, has a dose- and time-dependent effect.[4] Early prediction and additional interventions could boost the beneficial effects of aspirin.[5] However, only 12% of all preeclampsia cases are early-onset and prediction models show poorer precision for late-onset disease.[3,6] Furthermore, aspirin failed to show a clinically meaningful effect on the development of late-onset preeclampsia where the majority of the disease burden lies.[7] Therefore, a prevention method targeting both early- and late-onset preeclampsia is highly desirable.

Metformin is a biguanide that prevents gluconeogenesis in liver and increases the sensitivity of the peripheral tissue to insulin. The use of metformin in obstetrics is gaining pace as it has been shown to be efficacious in the treatment of gestational diabetes and possibly in the prevention of preeclampsia.[8-10] A plausible mechanism by which metformin, an anti-diabetic agent, might prevent preeclampsia is suggested by an in-vivo study by

Brownfoot *et al*., which demonstrated that metformin reduces soluble fms-like tyrosine kinase-1 (sFlt-1) levels which correlate significantly with the preeclampsia onset and severity.[11,12] It has also been suggested that metformin may prevent preeclampsia by improving cardiovascular function and limiting gestational weight gain.[13] Regardless of the underlying mechanism, the clinical implications are very important if metformin is proven effective in preventing late-onset preeclampsia. However, a randomized trial investigating the effects of metformin on the development of preeclampsia as the primary outcome is yet to be conducted. The main aim of this systematic review and meta-analysis was to determine whether metformin prevents hypertensive disorders of pregnancy.

METHODS

Protocol, eligibility criteria, information sources, and search

This review was performed according to a protocol designed a priori and recommended for systematic reviews and meta-analysis.[14-18] MEDLINE (1947 – September 2017), Scopus (1970 – September 2017) and the Cochrane Library (since inception - September 2017) including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched electronically on September 2017 utilizing combinations of the relevant MeSH terms, keywords, and word variants for “metformin”, “pregnancy”, “preeclampsia”, “hypertension”, “randomized”, “gestational hypertension”. The search was restricted to studies in English language. Reference lists of relevant articles and reviews were hand searched for additional reports. The PRISMA guidelines were followed.[16] The study was registered with the PROSPERO database (Registration number CRD42017080369).

Study selection, data collection and data items

Studies were assessed according to the following criteria: population, outcome, type of hypertensive disorder, gestational weight gain and gestational age at initiation of metformin therapy. Randomized controlled trials reporting the incidence of preeclampsia or pregnancy induced hypertension were included. Studies in which metformin treatment was received prior to randomization were

excluded. All abstracts were independently reviewed by two authors (EK, ES). Agreement about potential relevance was reached by consensus, and full-text copies of those papers were obtained. The same two reviewers independently extracted data regarding the study characteristics and outcomes. Inconsistencies were discussed by the reviewers and consensus reached. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. Randomized controlled trials were included while cohort studies, case control studies, case series, case reports, conference abstracts, and editorials were excluded. Studies were included in which data on pregnancy outcomes, including the incidence of preeclampsia and gestational hypertension could be extracted.

Risk of bias, summary measures and synthesis of the results

The risk of bias in the included studies was assessed using the Cochrane risk of bias tool.[17] The quality of the evidence was assessed using the GRADE approach developed by the Grading of Recommendations, Assessment, Development and Evaluations Working Group. Data on the type of intervention, gestational age at randomization, gestational age and the incidence of hypertensive disorders, with corresponding participant numbers were extracted from each included study. Analysis of the extracted data was performed with RStudio (Version 1.0.136, RStudio, Inc). For binary outcomes, a random-effects model with Mantel-Haenszel method were used for pooling of studies. Relative risks were obtained for binary outcomes. The variance between the studies was

tested using the I squared statistic. When the number of included studies was adequate, publication bias was explored using funnel plots asymmetry tests (i.e. Egger test).[19,20] Due to low number of studies in each subgroup analysis, a Bayesian meta-regression or meta-analysis were employed to synthesize the evidence regarding metformin use and hypertensive disorders of pregnancy using the comparator (insulin, glyburide, placebo) as a covariate. A normal distribution (N~0,10.000) for the mean effect estimates and a uniform distribution (U~0,5) for the variance estimates were used as vague priors for Bayesian random effects meta-regression. Posterior probabilities of intervention having a protective effect against the hypertensive disorders of pregnancy were calculated. A fixed effects method for Bayesian analysis was used when posterior density plots for heterogeneity showed minimal between study variation (<1 SD). Convergence diagnostics were made with Gelman-Rubin statistic and traceplots. All Bayesian computations were performed using Markov Chain Monte-Carlo (MCMC) sampler in R. MCMC sampling was run for each analysis for 3.000.000 iterations after discarding the first 50000.

RESULTS

Study selection, characteristics and risk of bias

In total, 3337 citations matched the search criteria and three additional studies were identified via manual search (Figure 1). After removing duplicate and irrelevant studies, 52 were retrieved for full text review. Studies were excluded due to the outcome reported being not relevant (n=15), study design not matching our protocol (n=13) or overlapping populations (n=4). Another study

was excluded due to unacceptably high risk of bias[21] and 4 studies with metformin use prior to randomization[22-25], leaving 15 studies to be included in the meta-analysis. The methodological characteristics of the included studies are shown in Table 1. The participants' characteristics varied among the studies, which included women with gestational diabetes mellitus (13 studies) and obese women (2 studies). Metformin was

compared to insulin (8 studies), placebo (2 studies) and glyburide (5 studies).[10,26-39] The mean gestational age at randomization and the risk characteristics differed greatly among the studies (Table 1). The planned metformin dose, received metformin dose, additional treatment, and the compliance also varied among the studies, contributing to the observed clinical heterogeneity (Table 2). A summary of the qualitative evaluation of the included studies according to the Cochrane risk of bias tool is presented in Table 3. All trials were considered to be at low risk of blinding bias due to low probability of blinding affecting the occurrence of preeclampsia or pregnancy induced hypertension.

Synthesis of results

Studies were grouped according to the comparator treatment and analyzed for different outcomes. Metformin use was associated with a reduced risk of pregnancy induced hypertension when compared to insulin (RR: 0.56, 95% CI: 0.37-0.85) (Table4) in women with GDM. Although, the risk estimate for preeclampsia (RR: 0.83, 95% CI: 0.60-1.14) was lower with metformin use when compared to insulin, the difference didn't reach statistical significance

(Table 4, Supplementary Figure 1). According to Bayesian random-effects meta-analysis, the posterior probabilities of metformin having a beneficial effect for the prevention of preeclampsia, pregnancy induced hypertension and any HDP were 93.5%, 86.7% and 97.7%, respectively (Table 4).

Metformin use was associated with a non-significant reduction of preeclampsia (RR: 0.66, 95% CI: 0.11-3.82), pregnancy induced hypertension (RR: 0.79, 95% CI: 0.42-1.49) and any HDP (RR: 0.71, 95% CI: 0.41-1.25) when compared to glyburide in women with GDM (Table 1, Supplementary Figure 2). According to Bayesian random-effects meta-analysis, the posterior probabilities of metformin having a beneficial effect for the prevention of preeclampsia, pregnancy induced hypertension and any HDP were 50.7%, 50.0% and 74.3%, respectively (Table 4).

When compared to placebo, metformin use was associated with a non-significant reduction of preeclampsia in obese women (RR: 0.74, 95% CI: 0.09-6.28) (Table 4, Supplementary Figure 3). The number of studies included in this analysis was low (n=2) with high statistical heterogeneity (I^2=86%). According to Bayesian random-effects meta-analysis, the posterior probabilities of metformin having a beneficial effect for the prevention of preeclampsia, pregnancy induced hypertension and any HDP were 46.0%, 43.4% and 43.2%, respectively (Table 4). Due to low number of studies and methodological similarities between the studies, a fixed-effects model analysis was also performed. The risk of preeclampsia was lower with metformin use in the fixed effects model (RR: 0.51, 95%CI: 0.26-0.98) with high statistical heterogeneity

(I^2=86%). The posterior probability (fixed-effects Bayesian) for beneficial effect was 99.4% (OR: 0.54, 95% credible intervals: 0.25-0.95).

No studies compared metformin with placebo in women with GDM and also there were no studies comparing metformin with insulin in obese women as expected.

When the available evidence was combined with a Bayesian random-effects meta-regression using the treatment type as a covariate, the posterior probabilities of metformin having a beneficial effect for the prevention of preeclampsia, pregnancy induced hypertension and any HDP were 92.7% (OR: 0.72 95% credible intervals: 0.42-1.16), 92.8% (OR: 0.74, 95% credible intervals: 0.43-1.12) and 99.2%(OR: 0.71 95% credible intervals: 0.50-0.98), respectively when compared to other treatments (Figure 2). Between study variance in these analyses were small (Figure 2, Supplementary Figure 4).

The overall quality of evidence was low. Most analyses were downgraded one point for imprecision and at least one point for indirectness (Table 4, Supplementary Material). The publication bias wasn't formally investigated due to low number of studies in each subgroup analysis.

DISCUSSION

Summary of the main findings

In this meta-analysis of randomized trials, metformin reduced the risk of, pregnancy induced hypertension compared to insulin in women with GDM. Also, metformin use was associated with a high probability for the prevention of any HPD when compared to other treatments and placebo. The analyses were characterized by low number of included studies, significant clinical heterogeneity, and low quality of evidence.

Study strengths and limitations

We included all randomized trials in which metformin was compared to any treatment modality or placebo. The total number of studies included in the quantitative analysis was modest (n=15). Although we could not perform a subgroup analysis for early- and late-onset preeclampsia, metformin randomization was before 30 weeks' gestation in most of the studies included indicating that the summary effect we observed is likely due to the prevention of late-onset preeclampsia. Another limitation of this analysis was the clinical heterogeneity among the included studies. It is important to note that diagnostic criteria for the outcome measures differed between studies but the diagnostic criteria of preeclampsia and pregnancy induced hypertension are relatively similar among the available guidelines. Also, HDP was not the primary outcome measure in any of the included studies and metformin was not specifically tested for the prevention of HDP. This is an important confounder and the effect

observed in these studies could be due to other uncontrolled factors (i.e. gestational weight gain). We used both random and fixed effects models for studies comparing metformin with placebo which yielded conflicting results. The studies included in this analysis were quite similar in their design and execution, thus was characterized by low clinical heterogeneity but high statistical heterogeneity. However, it is unlikely the summary estimates presented by either method are good representations of the real effect. The Bayesian random-effects meta-analysis was in agreement with this assessment as the posterior estimates were dominated by the vague prior information (posterior probability ~50%), indicating the current evidence is too weak to draw firm conclusions for this subgroup. The majority of the evidence stemmed from studies comparing metformin with insulin in women with GDM. However, the magnitude of effect was relatively constant among other comparators but without statistical significance, which was probably due to insufficient number of included studies. Also, our review comprises two main population of pregnant women, i.e. women with GDM and obese women. The results we have obtained here is mainly applicable to such populations. Women with a high probability of metformin use prior to randomization (type II diabetes and polycystic ovary syndrome) were excluded in this meta-analysis and the results we have obtained cannot be applied to these populations.

Comparison with existing literature and research implications

Although the use of metformin in pregnant women dates back to 1979, it has recently become a popular treatment choice for gestational diabetes due to its

proven effectiveness, safety in pregnancy, ease of use and high compliance rate.[40] The effectiveness of metformin compared to insulin in managing gestational diabetes was demonstrated in a meta-analysis by Gui *et al.*[41] In a subgroup analysis Gui *et al.* have reported that the prevalence of preeclampsia was similar between the metformin and insulin groups (OR: 0.69 95% confidence internal: 0.42 to 1.12). However, this analysis included only three studies. Two previous meta-analyses by Feng *et al.* and Butalia *et al.* demonstrated a significant effect of metformin in reducing the incidence of preeclampsia in women with diabetes (RR: 0.70, 95% CI: 0.49 to 0.99, RR: 0.56, 95% CI: 0.37 to 0.85, respectively).[9,42] Again, these were subgroup analyses within studies aimed at assessing the effects of metformin during the treatment of diabetes during pregnancy. Notably, these meta-analyses did not report preeclampsia and pregnancy induced hypertension outcomes separately. A recent Cochrane review by Brown *et al*. reported a non-significant reduction in the risk of preeclampsia in women with gestational diabetes taking metformin, but a significantly reduced risk of gestational hypertension; this is in line with our findings.[43] In contrast to the findings of the Cochrane review, Alqudah *et al*. found a significant association between metformin use and reduced risk of preeclampsia when compared to insulin.[44] However, studies involving patients with type 2 diabetes were included in that review. Compared to previous reviews, we provide the Bayesian estimates in the form posterior probabilities. In general, metformin use was associated with a high probability for beneficial effect in the prevention of HDP. Bayesian analysis allows the probabilistic

interpretation of results and avoids the problems arising from null hypothesis testing (i.e. type I and II errors).

Obesity is a known risk factor for the development of pregnancy induced hypertension and preeclampsia. The trials which investigated increasing physical activity and limiting gestational weight gain during pregnancy have demonstrated a lower incidence of hypertensive disorders of pregnancy.[45,46] The preventive effects of physical activity could be due to an improvement in cardiovascular function and/or reduced gestational weight gain. Of note, metformin has been reported to have beneficial effects in those at-risk women.[42,47-49] Improved cardiovascular function and reduced gestational weight gain, in addition to its known stabilization of vasoactive mediators,[11] could be the underlying mechanisms of the beneficial effects of metformin. Weight gain is one of the factors that could contribute to clinical heterogeneity we observed in this analysis. Future studies on this topic should carefully investigate this factor and its association with late-onset preeclampsia in addition to metformin use.

Conclusions

Metformin is associated with a high probability of preventing of any HPD when compared to other treatments. The small number of the included studies and their clinical heterogeneity preclude the generalization of these results to broader populations. Therefore, randomized trials of metformin use for the prevention of preeclampsia are urgently needed.

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Figure legends

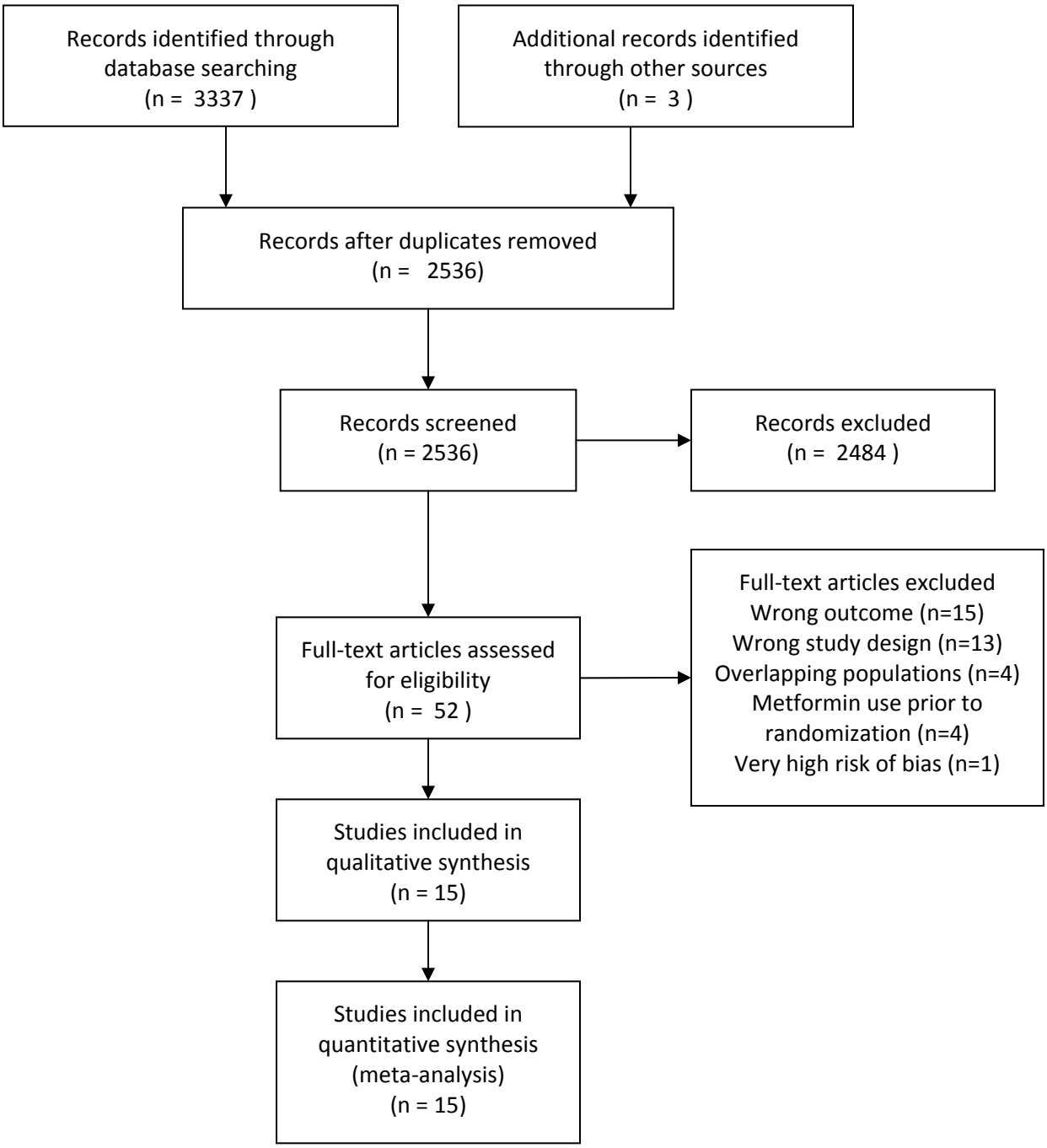
Figure 1. PRISMA flow diagram of study selection.

Identification

Screening

Eligibility

Included



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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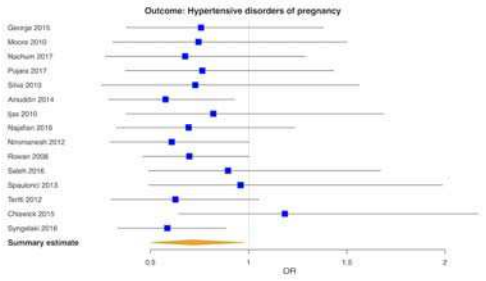
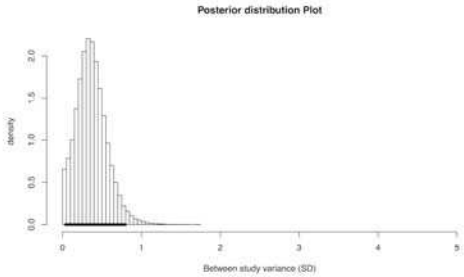
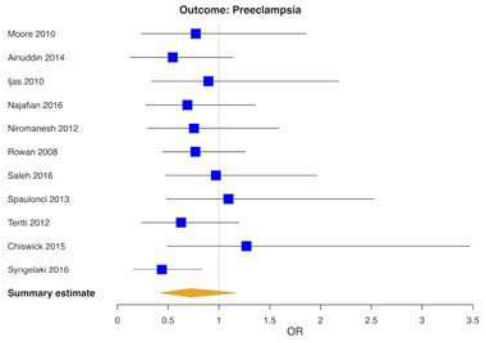
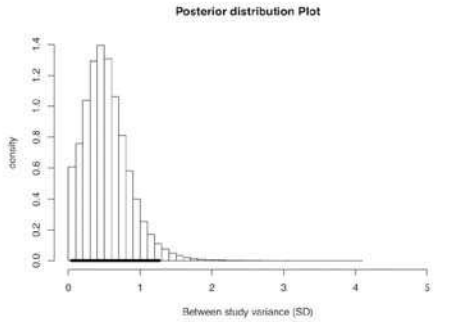
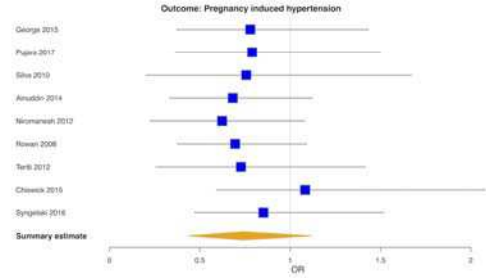
Figure 2. Results of Bayesian random-effects meta-regression using treatment type as the covariate. (Left) Forest plots of studies comparing metformin with any other treatment or placebo for the occurrence of pregnancy induced hypertension, preeclampsia or any hypertensive disorder of pregnancy. (Right) Posterior distribution plots of between study variance. Square boxes represent the mean effect estimate and black lines represent the 95% credible intervals for individual studies. The diamonds represent the summary effect estimates. Between study variance below 1 SD indicates low heterogeneity.

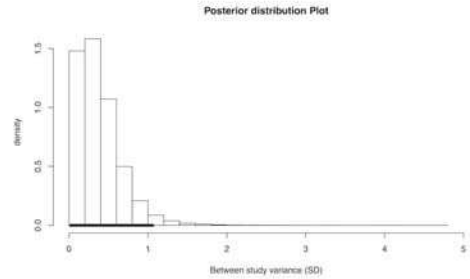












Supplementary Figure 1. Forest plot of studies comparing metformin versus insulin for the occurrence of pregnancy induced hypertension, preeclampsia or any hypertensive disorder of pregnancy.

Supplementary Figure 2. Forest plot of studies comparing metformin versus glyburide for the occurrence of pregnancy induced hypertension, preeclampsia or any hypertensive disorder of pregnancy.

Supplementary Figure 3. Forest plot of studies comparing metformin versus placebo for the occurrence of pregnancy induced hypertension, preeclampsia or any hypertensive disorder of pregnancy.

Supplementary Figure 4. Forest plot of studies comparing metformin versus other drugs or placebo for the occurrence of pregnancy induced hypertension, preeclampsia or any hypertensive disorder of pregnancy.

Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate. Heterogeneity (I^2) = diversity between studies.

Table 1. The characteristics of the studies included in this systematic review

Author	Comparator	Inclusion criteria	Exclusion criteria	No. of patients	GA at randomization (weeks)	GA at delivery (weeks)
Ainuddin 2015	Insulin	Women with GDM not responding to diet and exercise	Contraindication to metformin, fetal anomaly, type I or II diabetes, fetal growth restriction, positive glucose tolerance test before 26 weeks, ruptured membranes	150	29	37
Chiswick 2015	Placebo	Obese (BMI>30kg/m^2) women without overt diabetes	Non-Caucasian ethnicity, overt diabetes, GDM in previous pregnancy, GDM in current pregnancy before randomization, systemic disease, history of preeclampsia prior to 32 weeks,	434	14	39

			fetal growth restriction, sensitivity to metformin.			
George 2015	Glyburide	Women with GDM not responding to diet and exercise	Type I or II diabetes, currently on metformin, multiple pregnancy, fetal anomaly, renal or liver dysfunction, cardiorespiratory disease, malabsorption, sepsis, ruptured membranes, preeclampsia or gestational hypertension	159	29	38
Ijas 2011	Insulin	Women with GDM	Preeclampsia, essential hypertension, fetal growth restriction	97	30	39
Moore 2010	Glyburide	Women with GDM not responding to diet and exercise	Chronic hypertension, substance misuse, renal or hepatic disease	149	29	38

Nachum 2017	Glyburide	Women with GDM not responding to diet alone	Women without dating, pregestational diabetes, suspected fetal growth restriction, major fetal malformations	104	29	38
Niromanesh 2012	Insulin	Women with GDM not responding to diet alone	Systemic disease, substance abuse, overt diabetes, major fetal malformations	160	28	38
Rowan 2008	Insulin	Women with GDM not responding to diet and exercise	Contraindication to metformin, fetal anomaly, gestational hypertension, preeclampsia, fetal growth restriction, ruptured membranes	733	30	38
Spaulonci 2013	Insulin	Women with GDM not responding to diet and exercise	Lost to prenatal follow-up	92	32	38
Syngelaki	Placebo	Obese	History of GDM, major fetal defect,	400	15	91.5%

2016		(BMI>35kg/m^2) women without overt diabetes	kidney, liver or heart failure, hyperemesis gravidarum, sensitivity to metformin, metformin use at the time of screening, miscarriage before randomization.			term delivery
Tertti 2013	Insulin	Women with GDM not responding to diet alone	Cardiac or renal insufficiency, liver disease, metformin use within 3 months preceding index pregnancy or during pregnancy prior to randomization, self-reported fasting plasma glucose value >5.5mmol/L	227	30	39
Silva 2010	Glyburide	Women with GDM not responding to diet and exercise	Medication intolerance, fetal abdominal circumference above 97% or below 5%, lack of follow-up, fetal malformations	72	26	92.3% term delivery

Pujara 2017	Glyburide	Women with GDM not responding to diet and exercise	Smoking, assisted reproduction, overt diabetes, allergy to metformin, fetal anomaly, abdominal circumference above 97% or below 5%,intolerance to medication, lost to follow-up, multiple pregnancy, randomization delivery interval less than 2 weeks	72	25	38
Najafian 2017	Insulin	Women with GDM not responding to diet and exercise	Lack of patient satisfaction, overt diabetes, multiple pregnancy, systemic disease, lack of glycemic control under maximum dose of metformin	138	Not reported	Not reported
Saleh 2016	Insulin	Women with GDM not responding to	Overt diabetes, fetal anomaly, obstetric high risk conditions, liver or	137	28	38

		diet alone	kidney disease, intolerance to metformin			

GA: gestational age; GDM: gestational diabetes; BMI: body mass index

Table 2. The characteristic of metformin use in the studies included in this systematic review

Author and year	No. women requiring adjunct treatment, n (%)	Planned metformin dose	Compliance *	Received metformin dose
Ainuddin 2015	32 (42.7)	500 to 2500 mg	Not reported	Mean dose: 1950 mg (SD: 540mg) for metformin alone group and mean dose: 1910 mg (SD: 680mg) for metformin plus insulin group
Chiswick 2015	-	500 to 2500 mg	65.3%	A metformin dose of 2500mg and 2000mg were taken during 38% and 62% of all possible drug taking days, respectively.
George 2015	0 (0)	500 to 2500 mg	Not reported	The maximum daily dose was 500mg in 58.7%, 1000mg in 21.3% and >1000mg in 20.0% of participants
Ijas 2011	15 (31.9)	750 to 2250 mg	Not reported	Not reported

Moore 2010	26 (34.7)	500 to 2000 mg	Not reported	Not reported
Nachum 2017	9 (17%)	850 to 2250mg	Not reported	Not reported
Niromanesh 2012	11 (13.8)	1000 to 2500 mg	Not reported	Median:1500mg (IQR: 1000 to 2500mg)
Rowan 2008	168 (46.3)	500 to 2500 mg	69.4%	All but one participant received more than 1000mg with a median dose of 2500mg
Spaulonci 2013	12 (26.1)	1700 to 2550 mg	Not reported	The maximum daily dose was 1700mg in 29.8%, 2550mg in 42.6% of participants
Syngelaki 2016	-	1000 to 3000 mg	79.5%	The maximum daily dose was 3000mg in 63.5%, 2500mg in 14.2% and 2000 mg in 22.2% of participants
Tertti 2013	23 (20.9)	500 to 2000 mg	Not reported	Median:1500mg (IQR: 500 to 2000mg)
Silva 2010	8 (25.0)	500 to 2500 mg	Not reported	Mean:1284mg (SD: 535mg)
Pujara 2017	13(26.0%)	500 to 2500 mg	Not reported	Not reported
Najafian 2017	Not reported	500 to 2000 mg	Not reported	26% of patients was on 2000mg, 66% was on 1500mg, 5.9% was on 1000mg and 1% was on

				500mg
Saleh 2016	Not reported	500 to 3000mg	Not reported	Not reported

*Reported as per individual study protocol

Table 3. Assessment of the risk of bias in the included studies according to the Cochrane risk of bias tool

First author and year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessor	Incomplete outcome data	Selective outcome reporting	Other bias
Ainuddin 2015	High	High	Low	Low	Low	Low	Unclear
Chiswick 2015	Low	Unclear	Low	Low	Low	Unclear	Unclear
George 2015	Low	Low	Low	Low	Low	Unclear	Unclear
Ijas 2011	Low	Low	Low	Low	Low	Unclear	Low
Moore 2010	Low	Low	Low	Low	Low	Low	Unclear
Nachum 2017	Low	Low	Low	Low	Low	Low	Unclear
Najafian 2017	Unclear	Unclear	Low	Low	Low	Low	Unclear
Niromanesh 2012	Low	Low	Low	Low	Low	Low	Unclear
Pujara 2017	Unclear	Unclear	Low	Low	High	High	Unclear
Rowan 2008	Low	Unclear	Low	Low	Unclear	Low	Unclear

Saleh 2016	Low	Unclear	Low	Low	Low	High	Low
Silva 2010	Low	Low	Low	Low	Low	Low	Unclear
Spaulonci 2013	Unclear	Unclear	Low	Low	Low	High	Low
Syngelaki 2016	Low	Low	Low	Low	Low	Low	Low
Tertti 2013	Unclear	Unclear	Low	Low	Low	Low	Low

Table 4. Meta-analysis of studies comparing metformin with other compounds in women with gestational diabetes or obesity. Posterior probability of metformin having a beneficial effect is reported by using a Bayesian random-effect meta-analysis.

	No. included studies	Event/Total Metformin	Event/Total Insulin	RR (95% CI)*	I^2	Posterior probability	GRADE
Metformin vs insulin, women with GDM							
- Outcome: Preeclampsia	8	64/856	82/868	0.83 (0.60-1.14)	0%	93.5%[†]	⊕⊖⊖⊖ VERY LOW
- Outcome: PIH	4	31/628	56/632	0.56 (0.37-0.85)	0%	86.7%[†]	⊕⊕⊕⊖ MODERATE
- Outcome: Any HDP	8	95/856	138/868	0.70 (0.54-0.91)	5%	97.7%	⊕⊕⊖⊖ LOW
Metformin vs insulin, obese women	NA	-	-	-	-	-	-
Metformin vs glyburide, women with GDM							
- Outcome: preeclampsia	1	2/75	3/74	0.66 (0.11-3.82)	NA	50.7%[‡]	⊕⊕⊖⊖ LOW
- Outcome: PIH	3	14/148	18/155	0.79 (0.42-1.49)	0%	50.0%[†]	⊕⊖⊖⊖ VERY LOW
- Outcome: Any HDP	5	18/274	26/282	0.71 (0.41-1.25)	0%	74.3%[†]	⊕⊕⊖⊖

							LOW
Metformin vs glyburide, obese women	NA	-	-	-	-	-	-
Metformin vs placebo, women with GDM	NA	-	-	-	-	-	-
Metformin vs placebo, obese women							
- Outcome: preeclampsia	2	13/423	25/417	0.74 (0.09-6.28)	86%	46.0%†	⊕⊖⊖⊖ VERY LOW
- Outcome: PIH	2	34/423	27/417	1.24 (0.76-2.03)	0%	43.4%†	⊕⊕⊕⊖ MODERATE
- Outcome: Any HDP	2	47/423	52/417	0.93 (0.30-2.86)	88%	43.2%†	⊕⊖⊖⊖ VERY LOW
Metformin vs any drug, all women							
- Outcome: preeclampsia	11	79/1354	110/1359	0.75 (0.52-1.09)	33%	92.7% ¶	⊕⊖⊖⊖ VERY LOW
- Outcome: PIH	9	79/1199	101/1201	0.79 (0.59-1.04)	0%	92.8% ¶	⊕⊖⊖⊖ VERY LOW
- Outcome: Any HDP	15	160/1553	216/1567	0.75 (0.59-0.94)	20%	99.2% ¶	⊕⊖⊖⊖ VERY LOW

*Random effects meta-analysis with Mantel-Haenszel method

†Bayesian random-effects meta-analysis with vague priors (Normal or t-distribution)

‡Bayesian fixed-effects meta-analysis with vague priors (Normal or t-distribution)

¶Bayesian random-effects meta-regression using comparator treatment as a covariate

PIH: pregnancy induced hypertension, HDP: hypertensive disorders of pregnancy, NA: not available