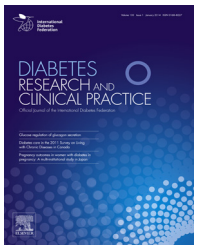
Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Metformin for the treatment of gestational diabetes: An updated meta-analysis

Pimprapa Kitwitee [a], *Supon Limwattananon* [a], *Chulaporn Limwattananon* [a], *Ornanong Waleekachonlert* [b], *Tananan Ratanachotpanich* [b], *Mattabhorn Phimphilai* [c], *Tuan V. Nguyen* [d], *Chatlert Pongchaiyakul* [e,*]

[a] *Social and Administrative Pharmacy Program, Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand*
[b] *Clinical Pharmacy Research Unit, Faculty of Pharmacy, Mahasarakham Univeristy, Thailand*
[c] *Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Chiang Mai University, Thailand*
[d] *Bone and Mineral Research Program, Garvan Institute of Medical Research, Sydney, Australia*
[e] *Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand*

ARTICLE INFO

Article history:
Received 21 July 2014
Received in revised form
2 March 2015
Accepted 3 May 2015
Available online 14 May 2015

Keywords:
Gestational diabetes mellitus
Insulin
Metformin
Oral hypoglycemic agent

ABSTRACT

Objective: To assess the efficacy of metformin and insulin in the treatment of pregnant women with gestational diabetes mellitus (GDM).
Methods: A meta-analysis was conducted by including randomized controlled trials comparing metformin and insulin in GDM. An electronic search was conducted to identify relevant studies. Data were synthesized by a random effects meta-analysis model. A Bayesian analysis was also performed to account for uncertainties in the treatment efficacy.
Results: Eight clinical trials involving 1712 individuals were included in the final analysis. The pooled estimates of metformin–insulin differences were very small and statistically non-significant in fasting plasma glucose, postprandial plasma glucose and HbA1c, measured at 36–37 weeks of gestation. Notably, 14–46% of those receiving metformin required additional insulin. Compared with the insulin group, metformin treatment was associated with a lower incidence of neonatal hypoglycemia (relative risk, RR 0.74; 95% CI 0.58–0.93; $P = 0.01$) and of neonatal intensive care admission (RR 0.76; 95% CI 0.59–0.97; $P = 0.03$). Bayesian analysis revealed that the efficacy of metformin was consistently higher than insulin with a probability of over 98% on these two neonatal complications. Other outcomes were not significantly different between the two treatment groups.
Conclusion: In women with gestational diabetes, metformin use and insulin therapy have comparable glycemic control profile, but metformin use was associated with lower risk of neonatal hypoglycemia.

* *Corresponding author at*: Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine, Khon Kaen University, 40002, Thailand. Tel.: +66 43 363664; fax: +66 43 202491.
E-mail address: pchatl@kku.ac.th (C. Pongchaiyakul).
http://dx.doi.org/10.1016/j.diabres.2015.05.017
0168-8227/

1. Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance of variable severity with onset of first recognition during pregnancy. GDM can cause significant problems, including maternal and perinatal complications [1]. GDM also increases the risk of progression to type 2 diabetes (T2D) and metabolic syndrome in the mother as well as increased risk of glucose intolerance, obesity, and possibly adult cardiovascular disease in the infant [2–4]. Although the prevalence of GDM has not been not well documented, recent estimate based on birth certificate in the United States suggested that is approximately 9% [5]. During the past 20 years, the prevalence of GDM has increased between 10 and 100%, depending on ethnicity group [6]. In Thailand, data from the National Diabetes Data Group for GDM Diagnosis [7,8] suggest that the prevalence of GDM was 5.3 and 4.9% in women with gestation of <20 weeks and 28–32 weeks, respectively [9].

In clinical practice, medical nutrition therapies (MNT), including dietary changes, meal planning, increased physical activity and life-style modification, are recognized as the cornerstone of treatment for GDM [10]. However, in mother with persistent hyperglycemia with MNT, treatment with additional insulin is traditionally considered to be the first-line medical treatment [11–13]. Although, insulin therapy has been accepted as a standard treatment for GDM, there are several disadvantages including hypoglycemia, excessive weight gain, multiple injections requirement, training process requirement and additional costs [13,14]. Therefore, the use of effective and safe oral hypoglycemic agents (OHAs) for decreasing medical service burden may offer advantages over insulin.

Metformin is a biguanide OHA which inhibits hepatic glucose production and improve peripheral insulin resistance. Metformin is increasingly recognized as an alternative to insulin therapy for GDM [14–16]. In the metformin in gestational Diabetes (MiG) trial [17], patients appeared to prefer metformin over insulin as a therapy for GDM, because metformin was not associated with increased risks of maternal and neonatal complications. However, a higher rate of preterm birth (<37 weeks of gestation) was found in patients on metformin, among whom 46% was also on insulin supplement. Recently, some benefits and risks of metformin as compared to insulin were reported in two separate meta-analyses of randomized clinical trials [16,18]. The average gestational age at delivery and weight gain after treatment, neonatal hypoglycemia and risk of pregnancy-induced hypertension (PIH) were significantly lower in the metformin group compared with the insulin group [17,19]. Since the publication of the meta-analyses, at least two additional trials [20,21] comparing metformin with insulin have been published. It is relevant to update the meta-analysis with the latest results.

Traditionally, meta-analysis is done within the frequentist framework, in which results are presented in terms of *P*-values. However, *P*-values can be misunderstood and does not reflect the certainty of an effect. In the Bayesian approach, there is no *P*-value, and as a result, no arbitrary classification of significance or not significance. Instead, Bayesian analysis can "measure" the *certainty* (or uncertainty) of an effect size. Once a clinically relevant effect size is determined or agreed upon, it is possible to use the Bayesian analysis to make a direct inferential statement on the uncertainty of the effect size. For instance, if a risk reduction of 10% or more is considered clinically significant, Bayesian analysis allows us to make a statement such as "there is a 90% chance that the relative risk reduction is more than 10%". This statement, also referred to as "posterior probability", is considered more informative than a *P*-value [22], because it directly addresses the clinically relevant question. Moreover, the Bayesian method approach to scientific evidence is a learning and updating process, which allows the incorporation of prior data into the present data to arrive at a better conclusion. An effect or an association is continuously updated when new data become available [23], which can be considered equivalent to a meta-analysis. Bayesian methods have gained prominence among clinical researchers, not only because it offers a logical and direct inference on an effect [24], it is also useful in cases where data collection is difficult or too expensive.

The present study sought to ascertain the efficacy of metformin in comparison with insulin in GDM patients by using a Bayesian approach to meta-analysis. We also provide an updated estimate of the effect of metformin on maternal glycemic control and risks of maternal and neonatal complications.

2. Methods

The protocol of this systematic review has been approved by the Khon Kaen University Ethics Committee for Human Research. For any discrepancies throughout all processes, discussion for consensus of the research team was made. In case of unclear information, we contacted authors of the original studies for clarification. The process of review and writing report were conducted in accordance to the PRISMA guideline [25].

2.1. *Identification of studies*

We searched for articles published in English in MEDLINE, EMBASE, Cochrane Reviews, Cochrane Pregnancy and Childbirth Group's Trials Register, Cochrane Central Register of Controlled Trials and DARE database from inception to March 2014. The search strategy included the terms 'metformin', 'oral hypoglycemic', 'gestational diabetes' and 'gestational diabetes mellitus'. In addition, we also conducted hand search on the reference lists of included trials, meta-analyses, reviews, and guidelines.

The inclusion criteria were (a) English language; (b) human studies; and (c) randomized controlled trial. We excluded one abstract that had been latterly published in the journal with exactly same data and study design. We included trials that used oral glucose tolerance test for the diagnosis of gestational diabetes. However, we did not apply any restriction on level of glycemic control. We excluded studies on people with preexisting diabetes mellitus.

2.2. *Data extraction and assessment of risk of bias*

Study outcomes included in the analysis were: (1) three maternal glycemic control measures during the last 1–2 weeks

before delivery: fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and hemoglobin A1c (HbA1c); (2) maternal complications: PIH, pre-eclampsia, gestational age at delivery, shoulder dystocia, cesarean section and weight gain after treatment; and (3) neonatal outcomes: preterm birth, neonatal hypoglycemia, hyperbilirubinemia, phototherapy, respiratory distress syndrome, admission to neonatal intensive care unit (NICU), large for gestational age (LGA, 90th percentile), macrosomia (birth weight >4000 or 4500 g) and small for gestational age (SGA, 10th percentile).

We used a designed form to extract the outcome data. From the full-text literature review, two authors independently abstracted relevant information. Any relevant but missing or unclear information on the trial characteristics and results was sought from authors of the original articles, if required.

Two investigators independently assessed the risk of bias using the criteria outlined in Cochrane Handbook for Systematic Reviews of Interventions [26]. The risk of bias criteria included the following: random sequence generation, allocation concealment, blinding personnel and outcome assessment and incomplete data. For each study, we assessed the completeness of data, including attrition and exclusion at each stage by comparing with the total randomized participants and reasons for missing data. For other potential biases, the risk of bias was classified as low, high, or unclear. Baseline characteristics of the included trials were assessed for a balance between the metformin and insulin groups.

2.3. Statistical analysis

Meta-analyses were performed for pooling estimates of the treatment effects from individual study results using Review Manager 5.2. A presence of publication bias of the reviewed studies was detected using the funnel plot and Egger test [27]. The treatment effects were reported in relative risk (RR) for a binary outcome and in standardized mean difference (SMD), which expresses the treatment effect in terms of standard deviation (SD) units rather than the original measurement units used in each study. The pooled estimate of treatment effects was calculated based on a random-effects model. This is a conservative approach, which accounts for both individual variation within a study and heterogeneity across studies due to the study designs and population.

To examine heterogeneity of treatment effects across the obtained studies, forest plots were visually inspected and I^2 statistic was determined. The I^2 is the percentage of between-study variability that is due to true differences rather than sampling error. An I^2 of greater than 75% is an indication of heterogeneity among trials [28,29]. To examine whether the accumulation of recent studies [20,21] make any impact on the pooled estimate, we conducted a cumulative meta-analysis, in which studies were arranged chronologically based on publication year and meta-analyses were sequentially done [30].

A Bayesian meta-analysis was also performed to ascertain the clinical significance of treatment effect. In the Bayesian approach, a posterior probability which quantified likelihood of various magnitudes of the treatment effect was estimated based on two information: the prior distribution of the effect size, and the current estimate of effect size. The effect size is log relative risk for categorical outcomes, and weighted mean difference for continuous outcomes [31]. Three prior distributions were considered: equivocal, skeptical, and optimistic priors. In the equivocal prior, it is assumed that the effect of metformin relative to insulin could be negative as well as positive equally. In the skeptical analysis, it was hypothesized that there is little chance (i.e., 5%) that metformin can reduce the risk of an outcome by more than 50% (RR $\leq$ 0.5). In log(RR) scale, this is equivalent to the statement $P[\log(\text{RR}) \leq -0.693] = 0.05$, and by symmetry, $P[\log(\text{RR}) \geq 0.693] = 0.05$. 0.05. With this skeptical assumption and a normal distribution, it can be shown that the prior variance of log (RR) is $(0.693/1.645)^2 = 0.177$, in which 1.645 is a Z-score that matches a probability of 0.05. Therefore the skeptical prior distribution was specified as mean = 0 and variance = 0.177. In the optimistic scenario, it was assumed that metformin could reduce the risk of an outcome by 50% (i.e., RR = 0.5), with the same variance as in the skeptical scenario. Under this assumption, it can be shown that the prior distribution is characterized by mean = −0.693 and variance = 0.177. After assuming the prior distribution, the posterior distribution of RRs and other posterior parameters were derived by Bayes theorem. Probability that RR is less than 1.0, 0.8, and 0.6 was estimated. All statistical analyses were performed using Stata 11.

3. Results

3.1. Description of individual studies

The literature search initially identified 399 relevant publications; among which, 53 studies were excluded because of duplication. After further excluding studies that did not meet the inclusion criteria, 8 studies were used in the final analysis (Fig. 1). The 8 RCTs comparing metformin with insulin which involved 1712 pregnant women with GDM but without pre-existing DM. The studies were conducted in the US [32], Finland [33,34], Pakistan [35], Iran [20,36], Brazil [21], New Zealand and Australia [17].

Baseline characteristics of studies are summarized in Table 1. Most studies reported sample size and power calculation. Three trials had sample sizes less than 100 individuals [21,32,33]. Half of the studies did not report the method of allocation concealment [17,20,21,35]. Double blind was not possible because of the different routes of administration. Most studies did not use blinding outcome assessment. Loss to follow up was modest. Intention-to-treat analysis was performed in most studies. Treatment groups were comparable at baseline in most characteristics.

Three trials [20,21,36] had the diagnosis of GDM based on Carpenter–Coustan criteria [37] and started the treatment based on a lower fasting plasma glucose (FPG) of 95 mg/dl (Table 2). For the remaining trials, the diagnostic criteria varied and the FPG criteria for starting the treatment were relatively higher. The initial daily dose of metformin ranged from 500 to 1000 mg, except for Spaulonci et al. of 1700 mg [21]. The maximum daily dose of metformin ranged from 2000 to 2550 mg, except for Hassan et al. who used the 3000 mg dosage [35]. Half of the trials did not report the dose of insulin [17,33–35], whereas the remaining trials indicated the dose of 0.4–0.7 IU/kg/day.

Table 1 – Risk of bias of included trials.

Entry	Moore et al. (N = 63) [32]	Rowan et al. (N = 733) [17]	Ijas et al. (N = 97) [33]	Hassan et al. (N = 150) [35]	Niromanesh et al. (N = 160) [36]	Mesdaghinia et al. (N = 200) [20]	Spaulonci et al. (N = 92) [21]	Tertti et al. (N = 221) [34]
Risk of bias assessment								
Random sequence generation	Low	Low	Low	High	Low	Low	Low	Low
Allocation concealment	Low	Unclear	Low	Unclear	Low	High	Unclear	Low
Blinding of participants and personnel	High	High	High	High	High	High	High	High
Blinding of outcome assessment	High	High	High	High	High	High	High	High
Incomplete outcome data addressed	Low	High	High	Low	High	High	Low	High
Selective reporting	Low	Low	Low	Low	Low	High	Low	Low
Loss to follow up (%)	0	2.4	3.0	0	7.0	0	2.1	2.3
Intention to treat analysis	Yes	No	No	Yes	No	No	No	No
Baseline comparable	No (weight[a])	Yes	Yes	No (Weight gain[b])	Yes	Yes	No (number of pregnancies[b])	Yes

[a] Higher in metformin group.
[b] Higher in insulin group.

Table 2 – Study description and baseline characteristics.

	Moore et al. [32]	Rowan et al. [17]	Ijas et al. [33]	Niromanesh et al. [36]	Hassan et al. [35]	Mesdaghinia et al. [20]	Spaulonci et al. [21]	Tertti et al. [34]
Sample size (metformin, insulin)	(31, 32)	(363, 370)	(47, 50)	(80, 80)	(150, 150)	(100, 100)	(46, 46)	(110, 107)
Criteria for diagnosis	NDDG	ADPIS	Study site's guideline	Carpenter–Coustan	WHO 2006	Carpenter–Coustan	Carpenter–Coustan	Finish national
Criteria for starting treatment								
FPG (mg/dl)	105	97.2	100	95	100	95	95	99
2-h PPPG (mg/dl)	120	120.6	120 (1.5 h)	120	126	120	120	140 (1 h)
Dose of metformin								
Initial dose (mg/day)	1000	500–1000	750	1000	500	500	1700	500
Maximum dose (mg/day)	2000	2500	2250	2500	3000	2500	2550	2000
Dose of insulin (IU/kg/day)	0.7	n/a	n/a	0.7	n/a	0.5	0.4	n/a
Age (years, mean ± SD)	27.4 ± 5.8	33.2 ± 5.3	32.0 ± 5.8	31.3 ± 5.3	30.6 ± 3.3	29.9 ± 5.6	32.3 ± 5.4	32.0 ± 5.2
Body mass index at entry (kg/m^2, mean ± SD)	n/a	34.8 ± 7.8	31.2 ± 6.0	27.6 ± 3.2	29.0 ± 2.3	n/a	31.7 ± 5.3	29.2 ± 5.3
Gestational age at entry (weeks, mean ± SD)	28.3 ± 5.8	30.1 ± 3.2	30.0 ± 4.5	28.7 ± 3.7	29.4 ± 1.4	28.4 ± 3.5	32.1 ± 3.5	30.3 ± 1.9
FPG–OGTT (mg/dl, mean ± SD)	n/a	102.6 ± 20.7	98.9 ± 13.7	105.9 ± 8.9	n/a	n/a	n/a	99.9 ± 8.2
2-h PPPG-OGTT (mg/dl, mean ± SD)	n/a	171.9 ± 37.8	146.7 ± 33.3	168.6 ± 29.3	n/a	n/a	n/a	145.8 ± 31.5
HbA1c at entry (%, mean ± SD)	n/a	5.8 ± 0.7	5.9 ± 0.4	5.7 ± 0.7	5.3 ± 0.5	6.3 ± 1.4	5.9 ± 0.8	5.5 ± 0.3
Insulin supplement (%)	0	46.3	31.9	14.0	24.0	22.0	26.1	20.9
Adverse events of metformin								
Gastrointestinal effect (%)	n/a	10.7	8.3	7.5	n/a	n/a	45.7	1.8

FPG = fasting plasma glucose, 2-h PPPG = 2-h postprandial plasma glucose, OGTT = oral glucose tolerance test, HbA1c = hemoglobin A1c. Carpenter–Coustan criteria: positive if ≥2 values ≥95 mg/dl fasting blood glucose, ≥180 mg/dl blood glucose at 1 h, ≥155 mg/dl at 2 h, ≥140 mg/dl at 3 h. NDDG criteria: positive if ≥2 values ≥105 mg/dl fasting blood glucose, ≥195 mg/dl blood glucose at 1 h, ≥165 mg/dl at 2 h, ≥145 mg/dl at 3 h. ADPIS criteria: positive if ≥1 values ≥99 mg/dl fasting blood glucose, ≥144 mg/dl at 2 h. Finish national criteria: positive if ≥2 values are ≥86 mg/dl fasting blood glucose, ≥180 mg/dl blood glucose at 1 h, ≥156 mg/dl at 2 h (June 2006 to December 2008). Positive if ≥2 values are ≥95 mg/dl fasting blood glucose, ≥180 mg/dl blood glucose at 1 h, ≥155 mg/dl at 2 h (January 2009 to December 2010). Study site's guideline: positive if ≥1 values are ≥95 mg/dl fasting blood glucose, ≥198 mg/dl blood glucose at 1 h, ≥172 mg/dl at 2 h. WHO 2006 criteria: positive if ≥2 values are ≥95 mg/dl fasting blood glucose, ≥180 mg/dl blood glucose at 1 h, ≥155 mg/dl at 2 h.

Most trials enrolled pregnant women aged greater than 30 years and mean body mass index greater than 28 kg/m^2. All studies had the mean gestational age at diagnosis above 28 weeks. Half of the trials did not report the results of FPG-oral glucose tolerance test (OGTT) or 2-h PPPG-OGTT parameters [20,21,32,35]. The mean hemoglobin A1c (HbA1c) was less than 6.0%, (42 mmol/mol) except for one trial (6.3% or 45 mmol/mol) [20]. For seven trials, insulin supplement was given to 14.0–46.3% of women in the metformin group [17,20,21,33–36]. Reported metformin-associated gastrointestinal adverse events varied widely across trials.

4. Classical meta-analysis

Maternal glycemic control. Four trials reported maternal glycemic control outcomes at 36–37 weeks [17,21,32,36]. The pooled estimates of metformin–insulin differences was statistically insignificant in all three measures. There was a significant heterogeneity in the study results, especially for HbA1c (I^2 = 82%) (Table 3).

Maternal complications. The pooled risk of having PIH in the metformin group was lower than in the insulin group (4 trials; RR 0.62; 95% CI 0.38 to 1.02; P = 0.06; I^2 = 0%) [17,21,34,36]. Three trials reported a non-significantly lower risk with metformin [17,34,36], while one trial reported a non-significantly higher risk with a wide 95% CI in metformin group [21] (Fig. 2).

The average gestational age at delivery in the metformin group was statistically lower than in the insulin group (7 trials; SMD −0.13; 95% CI −0.23 to −0.03; P = 0.01; I^2 = 0%) [17,21,32–36]. Six out of seven trials favored metformin but the individual results did not reach a statistical significance level [17,32–36].

Mothers receiving metformin had a significantly *less weight gain* than those receiving insulin, on average (4 trials; SMD −0.52; 95% CI −0.78 to −0.26; $P < 0.01$) [17,21,34,36]. However, there was a high degree of heterogeneity across studies (P = 0.01; I^2 = 73%).

The risks of pre-eclampsia, shoulder dystocia and Cesarean section were not significantly different between metformin and insulin groups. The effect on pre-eclampsia was reported in four trials and the pooled estimate did not show a statistically significant difference (RR 0.82; 95% CI 0.55–1.22; I^2 = 0%) [17,21,34,36]. Data on shoulder dystocia were available in three trials which showed an overall RR of 1.16 (95% CI 0.27–5.00; I^2 = 11%) [17,20,36]. For these two outcomes, heterogeneity of the results was low. For the Cesarean section outcome, with a moderate heterogeneity across seven trials reporting, metformin had a comparable effect to insulin (RR 0.92; 95% CI 0.75–1.14; I^2 = 50%) [17,21,32–36].

Neonatal complications. All trials reported data on neonatal hypoglycemia. The metformin group had a significantly lower risk of neonatal hypoglycemia than the insulin group (8 trials; RR 0.74; 95% CI 0.58–0.93; P = 0.01). The result was consistent

Table 3 – Pooled estimates of the effects of metformin as compared with insulin on maternal and neonatal outcomes – classical meta-analysis.

Outcomes	No of studies	Sample size	SMD	(95% Cl)	RR	(95% Cl)	P-value for heterogeneity	I^2 (%)
Maternal glycemic control at 36–37 wks								
Fasting plasma glucose	4	1048	0.03	(−0.16, 0.23)			0.18	39
Postprandial plasma glucose	4	1048	−0.10	(−0.32, 0.12)			0.11	50
HbA1c	5	1460	0.00	(−0.27, 0.27)			<0.001	82
Maternal complications								
Pregnancy-induced hypertension	4	1202			0.62	(0.38, 1.02)	0.39	0
Pre-eclampsia	4	1202			0.82	(0.55, 1.22)	0.46	0
Shoulder dystocia	3	1093			1.16	(0.27, 5.00)	0.33	11
Cesarean section	7	1512			0.92	(0.75, 1.14)	0.06	50
Gestational age at delivery	7	1512	−0.13	(−0.23, −0.03)			0.95	0
Weight gain after entry	4	1202	−0.52	(−0.78, −0.26)			0.01	73
Neonatal complications								
Preterm birth	5	1402			1.34	(0.73, 2.46)	0.17	38
Neonatal hypoglycemia	8	1712			0.74	(0.58, 0.93)	0.53	0
Hyperbilirubinemia	8	1712			0.82	(0.60, 1.12)	0.25	22
Phototherapy	3	990			0.93	(0.65, 1.33)	0.44	0
Respiratory distress syndrome	6	1398			0.84	(0.53, 1.35)	0.35	11
Neonatal intensive care admission	7	1620			0.76	(0.59, 0.97)	0.24	25
Congenital anomaly	4	1310			0.80	(0.42, 1.51)	0.36	7
Neonatal death	2	796			1.01	(0.11, 9.53)	0.35	0
Small for gestational age	4	1072			0.70	(0.33, 1.49)	0.06	60
Large for gestational age	7	1649			0.79	(0.63, 1.01)	0.35	11
Macrosomia	7	979			0.73	(0.50, 1.07)	0.28	19
Birthweight	8	1712	−0.09	(−0.22, 0.04)			0.15	35

SMD – standardized mean difference, RR – relative risk, CI – confidence interval.

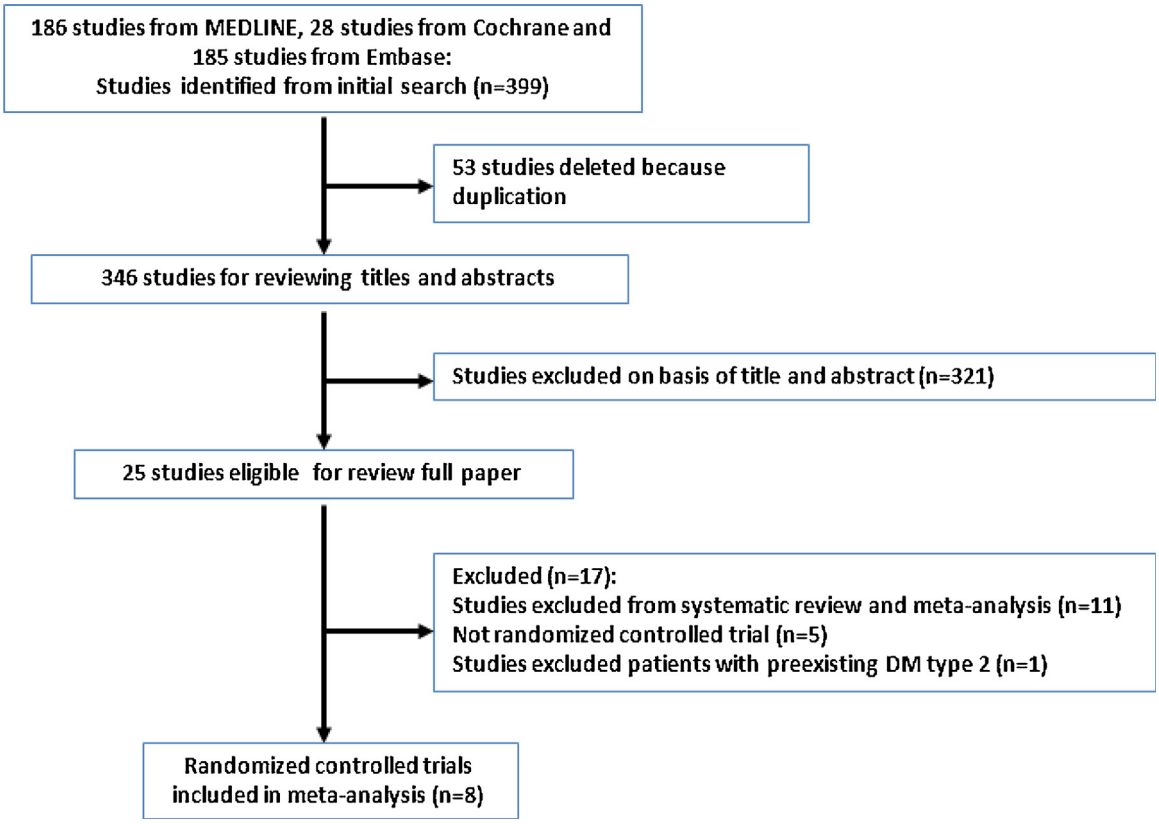


Fig. 1 – Search strategy.

(I^2 = 0%), whereby 7 out of 8 trials favored metformin despite statistically non-significance [17,20,21,32–35] (Fig. 3).

Seven out of eight trials provided data on the NICU admission [17,20,32–36]. The pooled estimate reveals that metformin use was associated with a significant reduction in the NICU admission (RR 0.76; 95% CI 0.59–0.97; P = 0.03; I^2 = 25%). Six trials reported a non-significantly lower risk of the admission for metformin [17,32–36].

The pooled effect on LGA was based on seven trials [17,20,21,33]. The incidence of the LGA babies in the metformin group was lower than that in the insulin group (RR 0.79; 95% CI 0.63–1.01; P = 0.06; I^2 = 11%).

Two trials reported neonatal deaths [17,32] and four reported congenital anomalies [17,20,34,36]. For these two outcomes, heterogeneity across studies was relatively low. There was only one death in each of the two treatment groups (metformin, N = 395; insulin, N = 401). There was no statistically significant difference between the two groups (RR 1.01; 95% CI 0.11–9.53; I^2 = 0%). There were 20 and 27 babies with congenital anomaly in the metformin (N = 653) and insulin (N = 657) groups, respectively, but the difference did not reach a statistical significance (RR 0.80; 95% CI 0.42–1.51; I^2 = 7%).

Five trials reported the incidence of the preterm birth [17,20,21,34,36]. The pooled result based on a moderate degree of heterogeneity (I^2 = 38%) showed that metformin had a higher but statistically insignificant risk of the preterm birth (RR 1.34; 95% CI 0.73–2.46) which is inconsistent with the two previous meta-analyses [16,18].

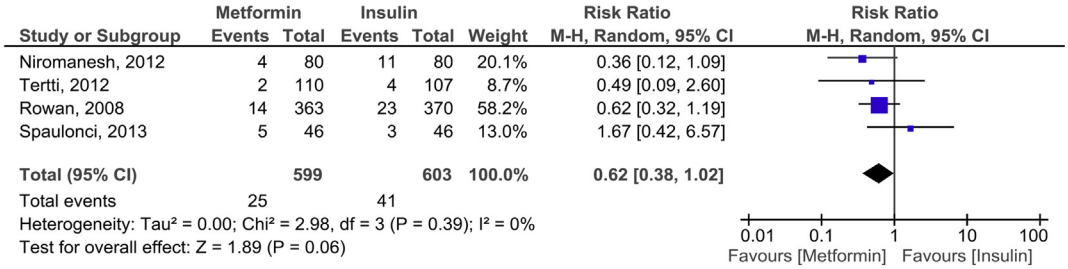
Risks of neonatal hyperbilirubinemia, phototherapy and respiratory distress syndrome were lower in the metformin group but did not reach a statistically significance level. Effect on hyperbilirubinemia was obtained from eight trials and the pooled estimate was statistically non-significant (RR 0.82; 95% CI 0.60–1.12; I^2 = 22%). The pooled effect on the risk of having phototherapy was arrived from only three trials reported and showed a non-significant effect (RR 0.93; 95% CI 0.65–1.33; I^2 = 0%) [17,33,36]. The incidence of respiratory distress was available in six trials [17,20,21,32,35,36]. Similarly, the two-arm difference was statistically non-significant (RR 0.93; 95% CI 0.65–1.33; I^2 = 11%).

While metformin had a marginally significant lower risk of LGA babies, the effects on macrosomia (7 trials, RR 0.73; 95% CI 0.50–1.07; I^2 = 19%) and average birth weight (8 trials, SMD −0.09; 95% CI −0.22 to 0.04; I^2 = 35%) did not differ significantly from insulin. SGA data were available from only 4 trials [17,21,35,36], and there was a non-significant difference in SGA between groups (RR 0.70; 95% CI 0.33–1.49; I^2 = 60%.

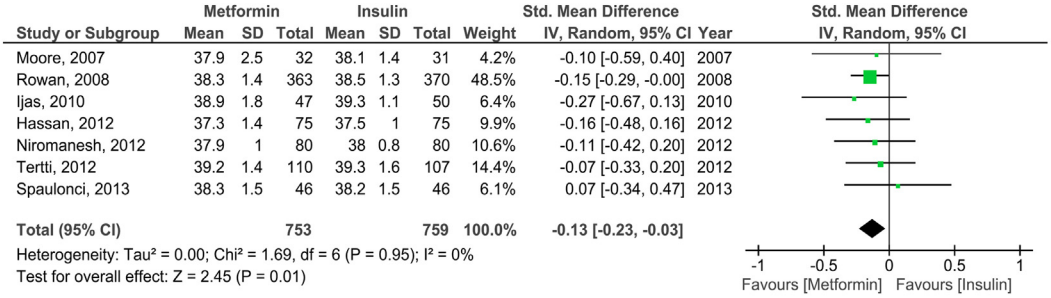
5. Cumulative meta-analysis

Adding the most recent data from Iran and Brazil [20,21] to the previously published studies increased the statistical significance level of the relative efficacy of metformin on neonatal hypoglycemia and NICU admission (Fig. 4A and B). On the

A: Pregnancy-induced hypertension



B: Gestational age at delivery



C: Weight gain after entry

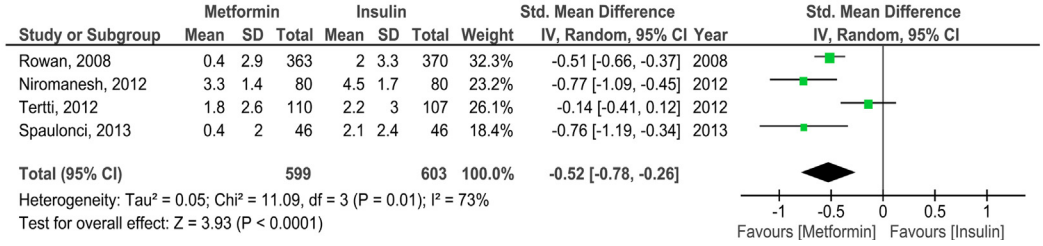


Fig. 2 – Effects of metformin relative to insulin on maternal complications – classical meta-analysis.

contrary, adding the Iranian study [20] reduced the magnitude of risk of preterm birth found in the previous studies of metformin and increased the uncertainty of the pooled results.

6. Bayesian meta-analysis

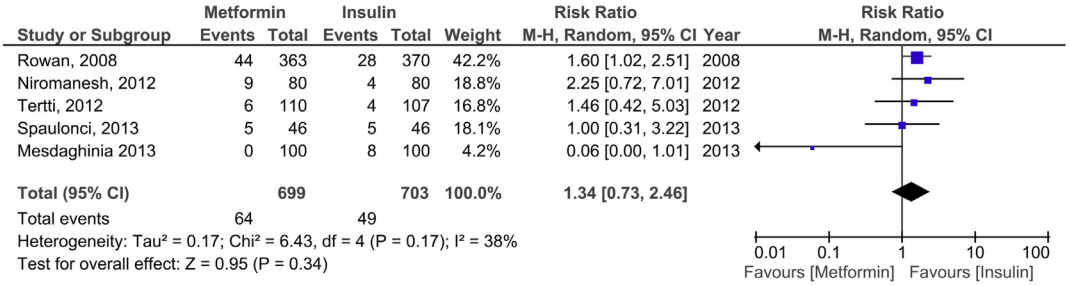
The overall RR for metformin and probability of being effective in various degrees on neonatal hypoglycemia and NICU admission under three assumptions of prior distribution of the treatment effects are presented in Table 4. There was a probability of more than 98–99% that metformin reduces the risks of neonatal hypoglycemia and NICU admission greater than insulin. The probability that metformin reduces the hypoglycemic risk by 20% greater than insulin was between 68% and 82% under the skeptical and optimistic views, respectively. The probability that metformine reduces the risk of NICU of 20% compared with was 59–76%. It was very unlikely that metformin could reduce the risks of these two neonatal complications by more than 40% compared with insulin.

7. Discussion

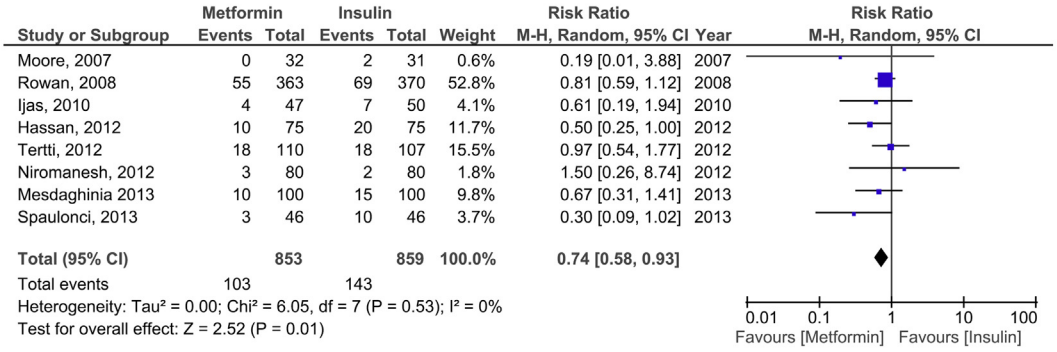
The effect of metformin on GDM has been discussed for quite some time, and it appears that a consensus has not been reached. In this meta-analysis we have shown that metformin has a favorable effects on neonatal hypoglycemia and NICU admission. The probability of such effect was consistently over 98%. However, metformin may be more suitable to mild GDM, because between 14 and 46% of the women receiving metformin in the reviewed trials required additional insulin. We consider that the finding is clinically relevant and deserved a further elaboration.

GDM is associated with worse clinical outcomes in both mothers and neonates than those with normal pregnancy. The risk of all adverse outcomes in both mothers and neonates continuously increases with the severity of hyperglycemia

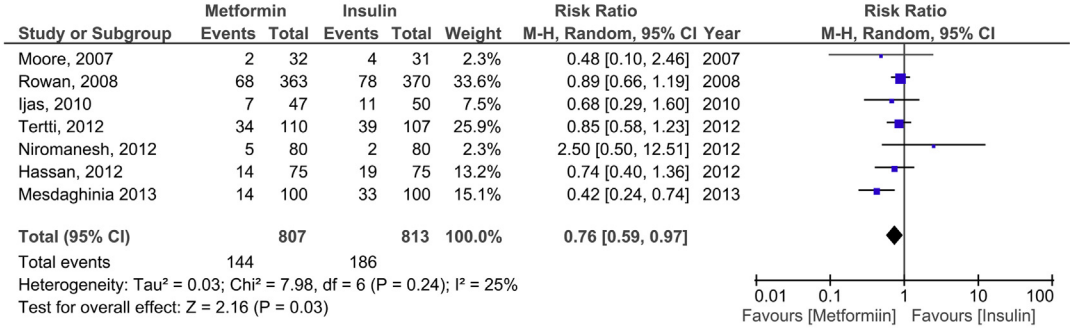
A: Preterm birth



B: Neonatal hypoglycemia



C: Neonatal intensive care admission



D: Large for gestational age

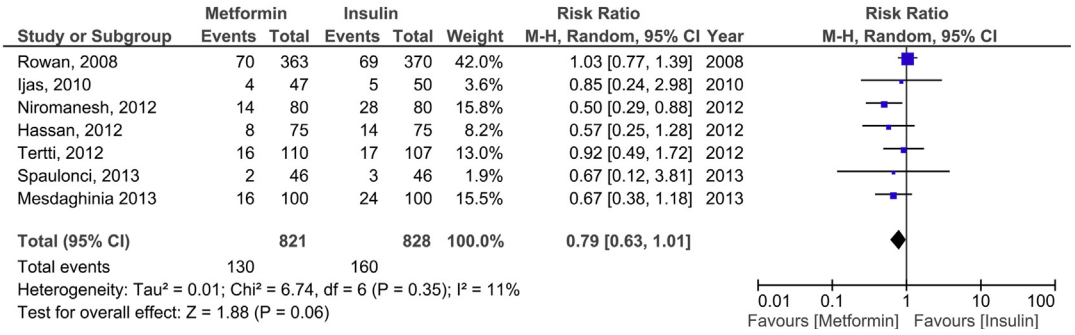


Fig. 3 – Effects of metformin relative to insulin on neonatal complications – classical meta-analysis.

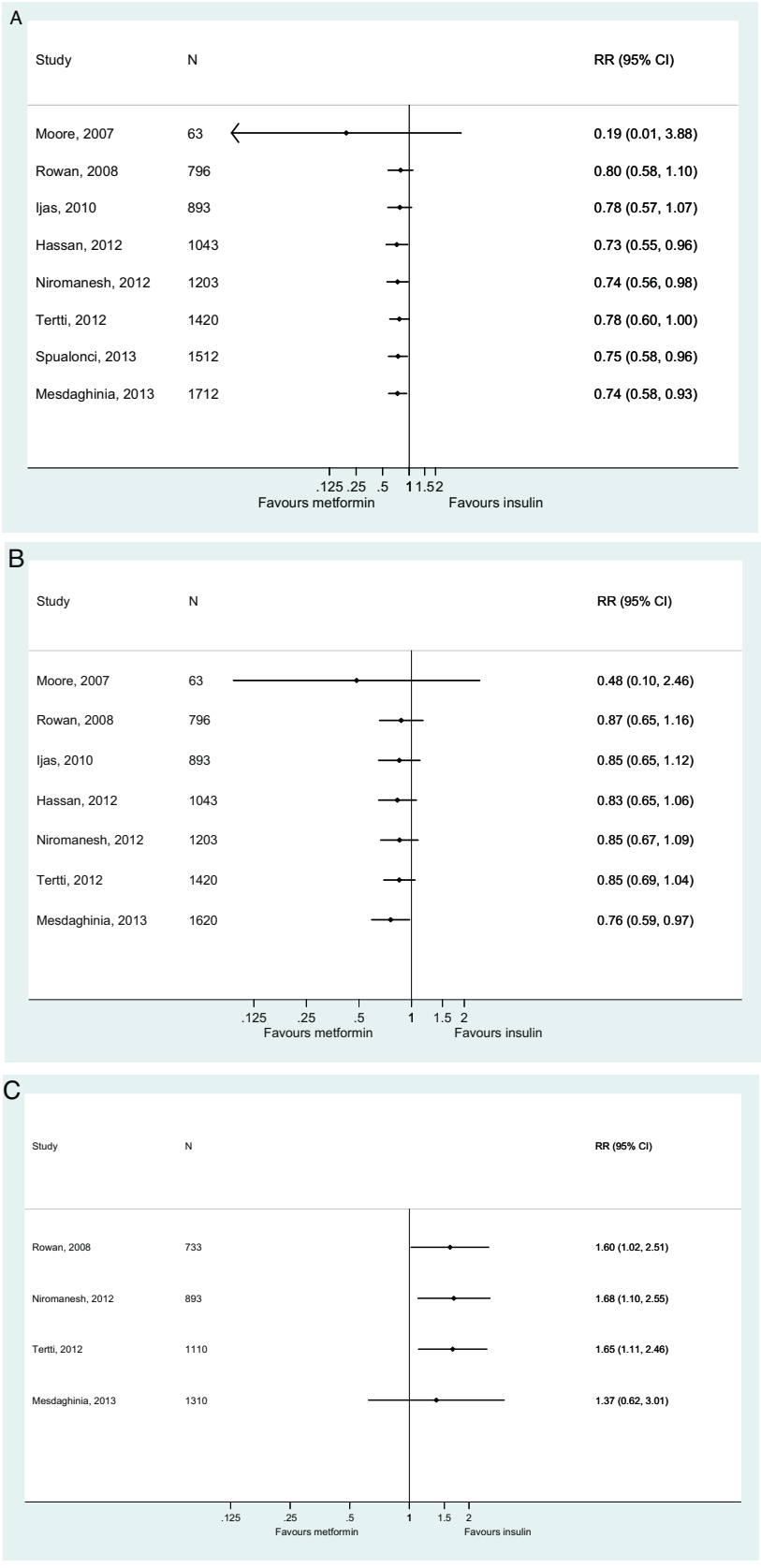


Fig. 4 – (A) Relative risk of neonatal hypoglycemia for metformin, compared with insulin – cumulative meta-analysis. (B) Relative risk of neonatal intensive care admission for metformin, compared with insulin – cumulative meta-analysis. (C) Relative risk of preterm birth for metformin, compared with insulin – cumulative meta-analysis.

Table 4 – Relative risk for metformin and probability of being effective, compared with insulin under three prior assumptions – Bayesian analysis.

	Overall RR (95% CrI)	Probability (%) that RR		
		≤1.0	≤0.8	≤0.6
1. Equivocal view				
Neonatal hypoglycemia	0.74 (0.58–0.94)	99.4	74.1	4.1
Neonatal intensive care admission	0.76 (0.59–0.97)	98.5	65.7	3.1
2. Skeptical view				
Neonatal hypoglycemia	0.76 (0.60–0.95)	99.2	68.3	2.2
Neonatal intensive care admission	0.78 (0.61–0.99)	98.1	59.3	1.6
3. Optimistic view				
Neonatal hypoglycemia	0.72 (0.57–0.90)	99.8	82.4	6.0
Neonatal intensive care admission	0.73 (0.58–0.93)	99.5	76.1	4.8

RR – relative risk; CrI – credible interval.

whereas a tight glycemic control could reduce adverse pregnancy outcomes. Apart from control hyperglycemia, the goal of GDM treatment is to reduce the incidence of maternal and fetal complications. Insulin has been considered a gold standard of hyperglycemic treatment in individuals with GDM who fail to respond to lifestyle modification. Even though it is very effective and safe, the main barrier of insulin is the use of injection. To date, metformin and glyburide are only two oral hypoglycemic agents that have proven efficacy and safety in GDM. Therefore, these two agents are attractive alternatives to insulin in the treatment of GDM, especially in those who could not tolerate the injection.

In this meta-analysis, we have demonstrated that metformin has comparable efficacy to insulin in controlling blood glucose. Our results confirmed the findings from previous meta-analyses [16,18] which reported a similar efficacy on the glycemic control between OHAs (metformin and glyburide) and insulin [15]. However, we did not perform the meta-analysis for the glycemic control measures at one week after treatment in two trials that have been reported in a previous meta-analysis [16]. Because between 14 and 46% of GDM individuals on metformin required additional insulin for glycemic control, we could not delineate the independent effect of metformin in glycemic control for all individuals. However, in cases with mild GDM it seems clear that metformin has a comparable efficacy to insulin in the control of blood glucose.

In term of maternal outcomes, compared with insulin, metformin use was associated with a lower gestation age and lower risk of PIH. The finding in this study on PIH ($N = 1202$; RR 0.62; 95% CI 0.38–1.02) was opposite to a previous meta-analysis of three RCTs ($N = 1110$; RR 0.52; 95% CI 0.30–0.90) by Gui et al. [16]. A recent trial of 92 subjects [21] was included in our study found a non-significantly increased risk of PIH in the metformin group (RR 1.67; 95% CI 0.42–6.57), which was contrary to the findings of three other trials [17,34,36]. Moreover, metformin was previously shown to increase risk of preterm delivery [16], however this result was inconclusive in our present meta-analysis. The overall effect on weight gain after entry was found in favor of metformin. Our finding may be explained by the fact that obesity and PIH are highly correlated, and that the risk of PIH and weight gain was lower with metformin in our study. Thus, lower maternal weight gain with metformin may lead to the lower risk of PIH found in our study. Because metformin had a more favorable weight change without adverse effect on maternal outcomes, metformin may also be considered in obese mothers.

In term of neonatal outcomes, as compared with the insulin group, metformin had a lower risk of neonatal hypoglycemia and NICU admission by 26% and 24%, respectively. A Bayesian analysis revealed that the efficacy of metformin was consistently higher than insulin with a probability of over 98% on neonatal hypoglycemia and NICU admission. These two neonatal complications are relevant to developing countries where health services are mostly not promptly accessible. For selected neonatal complications deemed close to the ultimate endpoints, such as hyperbilirubinemia, phototherapy, respiratory distress syndromes, all results except for preterm birth were in favor of metformin despite statistical non-significance.

The risk of LGA in the metformin group was marginally lower than in the insulin group. Because mothers receiving metformin had an average gestational age at delivery significantly lower than those receiving insulin, the earlier delivery in the metformin group may contribute to a lower risk of LGA. Although metformin treatment showed a lower average gestational age at delivery, this treatment did not lead to a higher risk of the preterm birth in our study. Metformin was shown to increase the risk of preterm delivery in two previous reports [16,18], which included fewer studies than in ours. However, with additional study [21] included in our analysis, metformin had a comparable effect to insulin for this outcome. Therefore, our study provided an additional safety data for using metformin for mild GDM. In addition, metformin was not associated with an increased risk of fetal anomaly.

Although our study showed some favorable results of using metformin in GDM, the lower number of individuals being included in each individual trial and single-country studies is a main limitation of this study. Heterogeneity with respect to ethnicity and health services across studies could be a potential bias which we could not control for in the meta-analysis. One additional limitation of this analysis is that it was not possible to estimate the effect of metformin alone, because the majority of studies (7/8) used metformin and insulin supplement. The only one study that used metformin alone vs insulin [32] found no significant differences in glycemic control, maternal and neonatal outcomes between

metformin and insulin group. The larger RCTs to elucidate both maternal and neonatal complications are further required. A large-scale, cross-country trial is warrant. To our knowledge, the RCTs comparing metformin with glyburide are limited despite increasing interest at the presence [38,39]. The benefit of metformin and glyburide combination remains to be explored.

In conclusion, metformin use and insulin therapy have comparable glycemic control profile in women with gestational diabetes, but metformin use was associated with lower risk of neonatal hypoglycemia and NICU admission than insulin therapy. The finding suggests that metformin is a reasonable alternative treatment, particularly in patients who could not tolerate insulin injection.

Conflict of interest

All authors declare that they have no conflict of interest in relation to this work.

REFERENCES

[1] Metzger BE. Summary and recommendations of the Third International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes 1991;40(Suppl. 2):197–201.
[2] Reece EA, Wiznitzer LGA. Gestational diabetes: the need for a common ground. Lancet 2009;373(9677):1789–97.
[3] Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. Diabet Med 2004;21:103–13.
[4] Landon MBGS. Gestational diabetes mellitus. Obstet Gynecol 2011;118(6):1379–93.
[5] DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States. Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. Prev Chronic Dis 2014;19(11):E104.
[6] Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. Diabetes Care 2007;30(Suppl. 2):S141–6 [Erratum in: Diabetes Care 2007;30(12):3154].
[7] Kongubol A, Phupong V. Prepregnancy obesity and the risk of gestational diabetes mellitus. BMC Pregnancy Childbirth 2011;11:59.
[8] Hansarikit J, Manotaya S. Sensitivity and specificity of modified 100-g oral glucose tolerance tests for diagnosis of gestational diabetes mellitus. J Med Assoc Thai 2011;94(5):540–4.
[9] Boriboonhirunsarn D, Sunsaneevithayakul P, Nuchangrid M. Incidence of gestational diabetes mellitus diagnosed before 20 weeks of gestation. J Med Assoc Thai 2004;87(9):1017–21.
[10] Serlin DCLR. Diagnosis and management of gestational diabetes mellitus. Am Fam Physician 2009;80(1):57–62.
[11] Horvath K, Koch K, Jeitler K, Matyas E, Bender R, Bastian H, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ 2010;340:c1395.
[12] Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. Am J Obstet Gynecol 2005;192:989–97.
[13] Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane Database Syst Rev 2009;(3):CD003395.
[14] Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstet Gynecol 2009;113(1):193–205.
[15] Dhulkotia JS, Ola B, Fraser R, Farrell T. Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol 2010;203(5):457e1–9.
[16] Gui J, Feng LQL. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. PLoS ONE 2013;8(5):e64585.
[17] Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. MiG. Trial investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358(19):2003–15.
[18] Su DF, Wang XY. Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2014;104(3):353–7.
[19] Rowan JA, Gao W, Hague WM, McIntyre HD. Glycemia and its relationship to outcomes in the metformin in gestational diabetes trial. Diabetes Care 2010;33(1):9–16.
[20] Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi SG, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: a randomised blinded trial. Int J Prev Med 2013;4(3):327–33.
[21] Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Vieira Francisco RP. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obstet Gynecol 2013;209(1):34.e1–7.
[22] Matthews AJR. Why should clinicians care about Bayesian methods? J Stat Plan Inference 2001;94:43–58.
[23] Ades T. Bayesian approaches to clinical trials and health-care evaluation. In: Spiegelhalter DJ, Abrams KR, Miles JP, editors. Biometrics. Blackwell Publishing; 2006. p. 306–7.
[24] Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. Ann Intern Med 1999;130:1005–13.
[25] Liberati A, Tetzlaff AD, Mulrow J, Gøtzsche C, Ioannidis PC, Clarke JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700. doi:10.1136/bmj.b2700.
[26] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011.
[27] Egger M, Schneider DSG, Minder MC. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[28] Higgins JPT, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[29] Higgins JPT, Deeks TS, Altman JJDG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
[30] Lau J, Chalmers SCTC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. J Clin Epidemiol 1995;48(1):45–57. discussion 9–60.
[31] Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Methods in health service research. An introduction to Bayesian methods in health technology assessment. BMJ 1999;319(7208):508–12.
[32] Moore LE, Briery CM, Clokey D, Martin RW, Williford NJ, Bofill JA, et al. Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. J Reprod Med 2007;52(11):1011–5.
[33] Ijas H, Vaarasmaki M, Morin-Papunen L, Keravuo R, Ebeling T, Saarela T, et al. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. BJOG 2011;118(7):880–5.
[34] Tertti K, Ekblad U, Koskinen P, Vahlberg T, Ronnemaa T. Metformin vs. insulin in gestational diabetes. A

randomized study characterizing metformin patients needing additional insulin. Diabetes Obes Metab 2013;15(3):246–51.
[35] Hassan J, Karim N, Sheikh Z. Metformin prevents macrosomia and neonatal morbidity in gestational diabetes. Pak J Med Sci 2012;28(3):384–9.
[36] Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res Clin Pract 2012;98(3):422–9.
[37] Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982;144(7):768–73.
[38] Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol 2010;115(1):55–9.
[39] Silva JC, Fachin DRRN, Coral ML, Bertini AM. Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus. J Perinat Med 2012;40(3):225–8.