Comparative Efficacy and Safety of OADs in Management of GDM: Network Meta-analysis of Randomized Controlled Trials

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Objective: We conducted a network meta-analysis to evaluate the efficacy and safety of oral antidiabetic drugs (OADs) for gestational diabetes.

Data Sources: We searched PubMed, the Cochrane Library, ClinicalTrials.gov, and related reviews from inception to October 2014.

Study Selection: We included randomized clinical trials comparing efficacy and safety between different OADs or OADs vs insulin in patients with gestational diabetes.

Data Synthesis: We included 18 randomized clinical trials. Traditional and network meta-analyses were performed to compare different OADs or OADs vs insulin. Traditional meta-analyses confirmed that there was no significant difference in maternal fasting blood glucose or glycated hemoglobin levels in patients treated with insulin, metformin, and glyburide. Compared to insulin, metformin was associated with lower maternal weight gain (weighted mean difference [WMD], −1.49 kg; 95% confidence interval [CI], −2.26 to −0.31), shorter gestational age (WMD, −0.16 wk; 95% CI, −0.30 to −0.03), and increased incidence of premature birth (odds ratio [OR], 1.63; 95% CI, 1.07 to 2.48). Compared to insulin, glyburide was associated with higher neonatal birth weight (WMD, 130.68 g; 95% CI, 55.98 to 205.38), increased incidence of neonatal hypoglycemia (OR, 2.64; 95% CI, 1.59 to 4.38), and increased incidence of macrosomia (OR, 3.09; 95% CI, 1.59 to 6.04). Network meta-analysis revealed that glyburide was associated with higher maternal weight gain, higher neonatal birth weight, increased incidence of neonatal hypoglycemia, and increased incidence of macrosomia than was metformin.

Conclusion: Both metformin and glyburide are suitable for use in the management of gestational diabetes because of good glycemic control. However, glyburide treatment is associated with increased risk of neonatal hypoglycemia, high maternal weight gain, high neonatal birth weight, and macrosomia. **(*J Clin Endocrinol Metab* 100: 2071–2080, 2015)**

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with its onset or first recognition during pregnancy (1). It has been estimated that up to 6–7% of pregnancies are complicated by diabetes mellitus and that approximately 90% of these cases represent women with GDM. Women with GDM are at higher risk of gestational hypertension, pre-eclampsia, and cesarean delivery and its associated potential morbid-

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Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; NICU, neonatal intensive care unit; NMA, network meta-analysis; OAD, oral antidiabetic drug; OR, odds ratio; RCT, randomized clinical trial; TMA, traditional meta-analysis; WMD, weighted mean difference.

ities. Most importantly, women with GDM have an increased risk of developing diabetes later in life. The offspring of women with GDM are at increased risk of macrosomia, neonatal hypoglycemia, hyperbilirubinemia, idiopathic respiratory distress syndrome, stillbirth, and neonatal death (2, 3).

Subcutaneous insulin therapy has been the mainstay of treatment for women with GDM not controlled by diet modification, but it is expensive and inconvenient (1). Insulin use requires skilled handling and adequate storage and refrigeration facilities, which may be key issues in developing countries. Several authoritative randomized clinical trials (RCTs) and reviews show that oral antidiabetic drugs (OADs) are as effective as insulin in terms of controlling hyperglycemia in patients with GDM, with similar maternal and neonatal outcomes, including studies on glyburide, metformin, and acarbose (4). Regarding their mechanism of action, metformin, glyburide, and acarbose show a series of differences. Metformin inhibits hepatic gluconeogenesis and glucose absorption, stimulates glucose uptake in peripheral tissues, and reduces weight gain (5). Glyburide binds to pancreatic β-cell receptors to increase insulin secretion, with the effect of increasing the insulin sensitivity of peripheral tissues (6). Acarbose is an oligosaccharide that slows down carbohydrate digestion, thus resulting in a lower increase in postprandial glucose levels and blood glucose reduction (7).

Some previous traditional meta-analyses (TMAs) have been performed to compare the effects of OADs with insulin in achieving glycemic control (4, 8, 9). Nevertheless, the effects of any of these OADs compared with another in the management of GDM remains inconclusive due to the lack of evidence from head-to-head RCTs. Network meta-analysis (NMA), also known as mixed treatment comparison, is a potential solution to the above problems. Compared with TMA, NMA is able to offer information on comparisons for which no head-to-head RCTs exist (10). For example, if a trial compares drug A with drug B while another trial compares B with C, then a network consisting of A-B-C-(A) could be established by NMA, as well as an indirect statistically relative effect on A vs C (11). Therefore, we employed both TMA and NMA of OAD clinical trials to assess comparative efficacy and safety between different OADs or OADs vs insulin for the treatment of women with GDM.

Materials and Methods

Search strategy

We searched the databases including PubMed, the Cochrane Library, and ClinicalTrials.gov (last search was updated on October, 2014). We used the search terms "gestational diabetes" in combination with "oral hypoglycemic agents," "oral antidiabetic drugs," "metformin," "glyburide," or "acarbose." We manually searched bibliographies of included trials and related reviews for additional references.

Study selection

Studies were included if they met the following criteria: 1) study design was a RCT; 2) population consisted of patients with GDM; 3) intervention compared different OADs or OADs vs insulin for GDM; and 4) included studies had to report one or more of the following: maternal outcomes— glycemic control, weight gain, cesarean delivery, pre-eclampsia; and neonatal outcomes— hypoglycemia, birth weight, macrosomia, gestational age at delivery, premature birth, and admission to neonatal intensive care unit (NICU).

Data extraction and quality assessment

Data were extracted independently by two reviewers using a standard form including study characteristics (author name, publication year, country, sample size), intervention, control, method (randomization, blinding, and loss to follow-up), and outcomes (maternal and neonatal outcomes). Discrepancies were resolved by discussion.

Two review authors independently evaluated the risk of bias for each study. We assessed the methodological quality of the included RCTs according to standard criteria of The Cochrane Collaboration. In particular, the following key domains were evaluated: 1) random sequence generation; 2) allocation concealment; 3) blinding (both of participants and outcome assessor); 4) incomplete outcome data; and 5) selective reporting. Every question was answered "yes," "no," or "unclear," and two reviewers assessed each trial. In case of a disagreement, judgment was made through open discussion. According to criteria of The Cochrane Collaboration, we divided the studies into three categories: 1) low risk of bias: low risk of bias for all key domains; 2) unclear risk of bias: unclear risk of bias for one or more key domains; and 3) high risk of bias: high risk of bias for one or more key domains (12).

Data synthesis and analysis

For dichotomous outcomes, we calculated pooled odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, we calculated weighted mean differences (WMDs) with 95% CIs. All tests were two-tailed, and a P value $<.05$ was deemed statistically significant.

Traditional meta-analysis

We performed TMA using STATA software, version 12.0 (StataCorp) and RevMan version 5.3 (Nordic Cochrane Center). Interstudy heterogeneity was measured by Q statistics ($P < .01$ was considered heterogeneous) and I^2 statistics ($I^2 > 50\%$ was considered heterogeneous). A fixed-effects model was used when heterogeneity was absent; otherwise, a random-effects model was chosen. Potential publication bias was assessed by Egger linear regression test (13).

Network meta-analysis

We conducted a random-effect Bayesian NMA using WinBUGS software, version 1.4.3 (Medical Research Council [MRC] Biostatistics Unit) and R version 3.0.2 (R Foundation for

Statistical Computing). The codes of random-effect models for multiarm trials were available at http://www.mtm.uoi.gr. Three Markov chains ran simultaneously with different initial values chosen arbitrarily. A total of 40 000 simulations were generated for each of the three sets of initial values, and the first 10 000 simulations were discarded due to the burn-in period (14).

The pooled-effect sizes were reported from the median of the posterior distribution. The corresponding 95% credible intervals with the 2.5th and 97.5th percentiles of the posterior distribution were used in this study, which could be interpreted in a way similar to the conventional 95% CIs. To estimate the network inconsistency between indirect and direct estimates in each closed loop, the absolute difference between the direct and indirect treatment effect estimates was calculated. Loops with the lower CI limit that did not reach the zero line were considered to represent statistically significant inconsistency (14).

Results

Eligible studies and their characteristics

Figure 1 shows the selection process of the included trials in this study. A total of 461 records were identified from the preliminary database and website search, and 121 records were selected after removing non-RCTs. Then 96 records were excluded with reasons, and 25 full-text trials were evaluated for eligibility. Eventually, 18 studies were included in this research. The characteristics of the included studies are listed in Table 1. Quality assessment showed that the lack of blinding of participants was the main cause of potential bias. In the clinical trial designed to compare OADs to insulin, blinding of the treatments was not possible because of the different routes of administration.

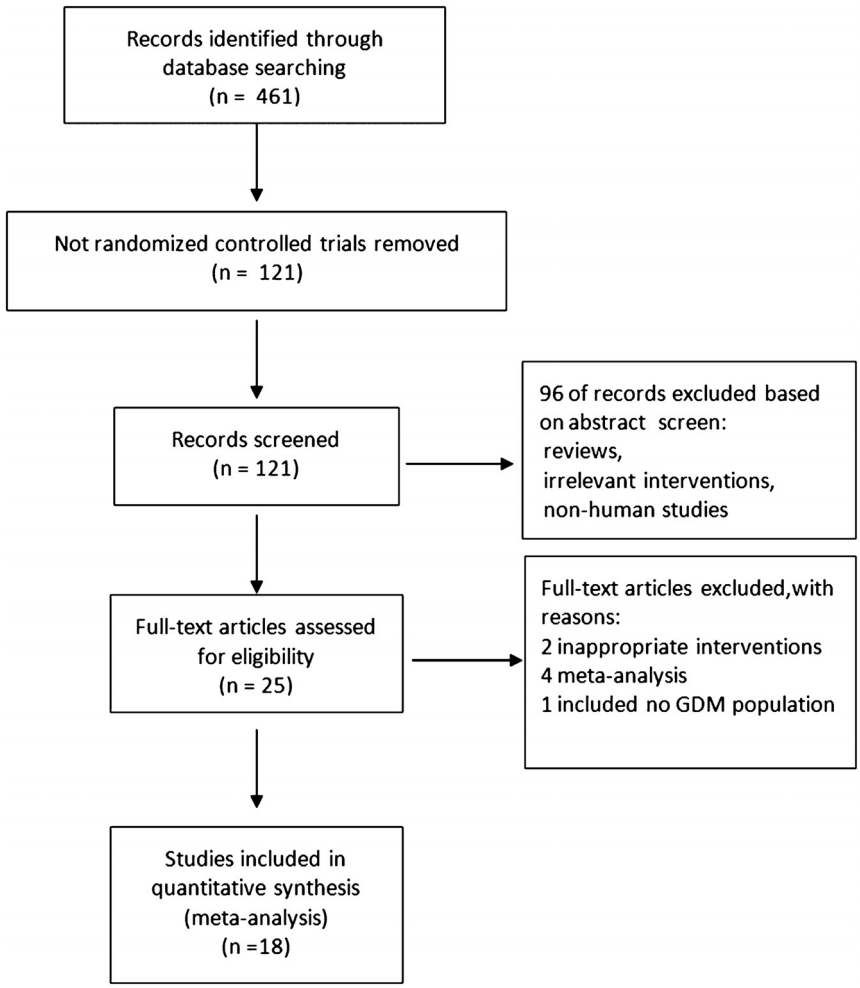

Figure 1. Flowchart of selecting process for meta-analysis.

Main maternal outcomes (Table 2)

Glycemic control (Figure 2)

Data on fasting blood glucose were reported in eight studies. TMA for fasting blood glucose revealed no significant differences between OADs and insulin (WMD, −0.00 mmol/L for metformin vs insulin; 95% CI, −2.56 to 2.55; and WMD, 1.65 mmol/L for glyburide vs insulin; 95% CI, −0.98 to 4.29), and no significant differences were apparent between metformin and glyburide (WMD, −1.12 mmol/L; 95% CI, −8.41 to 6.17; $P = .76$). Similarly, NMA for fasting blood glucose demonstrated no statistically significant differences between groups (WMD, −0.26 mmol/L for metformin vs insulin; 95% CI, −4.16 to 3.51; WMD, 0.85 mmol/L for glyburide vs insulin; 95% CI, −3.87 to 5.31; and WMD, −1.11 mmol/L for glyburide vs metformin; 95% CI, −5.27 to 2.62).

As for glycated hemoglobin (HbA1c), TMA revealed no significant differences between OADs and insulin (WMD, 0.05% for metformin vs insulin; 95% CI, −0.11 to 0.21; and WMD, 0.01% for glyburide vs insulin; 95% CI, −0.26 to 0.28), and no significant differences were apparent between metformin and glyburide (WMD, −0.07%; 95% CI, −0.26 to 0.11). Similarly, the NMA for HbA1c did not show a significant difference between groups (WMD, 0.02% for metformin vs insulin; 95% CI, −0.16 to 0.19; WMD, 0.12% for glyburide vs insulin; 95% CI, −0.10 to 0.27; and WMD, −0.13% for glyburide vs metformin; 95% CI, −0.33 to 0.12).

Table 1. Characteristics of RCTs Identified for the Study

First Author (Ref.)	Year	Country	No. of Patients Enrolled			Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Risk of Bias
			Metformin	Insulin	Acarbose						
Spaulonci (15)	2013	Brazil	46	46		Yes	Unclear	Unclear	Yes	Yes	U
Tertti (16)	2013	Finland	110	107		Yes	Yes	Unclear	Yes	Yes	U
Hassan (17)	2012	Pakistan	75	75		Yes	Unclear	Unclear	Yes	Yes	U
Niromanesh (18)	2012	Iran	80	80		Yes	Yes	Unclear	Yes	Yes	U
Ijas (19)	2011	Finland	50	47		Yes	Yes	No	Yes	Yes	U
Rowan (20)	2008	New Zealand/Australia	363	370		Yes	Yes	Unclear	Yes	Yes	U
Moore (21)	2007	United States	32	31		Yes	Yes	Unclear	Yes	Yes	U
Hague (22)	2003	Australia	16	14		Unclear	Unclear	Unclear	Yes	Yes	U
			Glyburide	**Insulin**		Unclear	Unclear	Unclear	Yes	Yes	U
Tempe (23)	2013	India	32	32		Yes	Yes	Unclear	Yes	Yes	U
Lain (24)	2009	United States	110	107		Yes	Yes	No	Yes	Yes	H
Ogunyemi (25)	2007	Brazil	48	49		Yes	Yes	No	Yes	Yes	H
Silva (26)	2007	Brazil	32	36		Unclear	Unclear	Unclear	Yes	Yes	U
Anjalakshi (27)	2007	India	10	13		Unclear	Unclear	No	Yes	Yes	H
Bertini (7)	2005	Brazil	24	27	19	Yes	Yes	Unclear	Yes	Yes	U
Langer (28)	2000	United States	201	203		Yes	Yes	No	Yes	Yes	H
			Metformin	**Glyburide**		Yes	Yes	No	Yes	Yes	H
Silva (29)	2012	Brazil	104	9		Yes	Yes	No	Yes	Yes	H
Moore (30)	2010	United States	75	74		Unclear	Unclear	Unclear	Yes	Yes	U
Silva (31)	2010	Brazil	40	32		Yes	Yes	Unclear	Yes	Yes	U

Abbreviations: U, unclear risk of bias; H, high risk of bias.

Weight gain (Supplemental Figure 1.1)

In TMA for weight gain, metformin was slightly lower compared with insulin (WMD, −1.49 kg; 95% CI, −2.26 to −0.31; $P = .01$), glyburide showed no statistical significance compared with insulin (WMD, −1.13 kg; 95% CI, −2.47 to 0.21; $P = .10$), metformin was significantly lower compared with glyburide (WMD, −2.22 kg; 95% CI, −3.38 to −0.56; $P = .009$).

NMA for weight gain revealed that metformin was significantly lower compared with insulin (WMD, −1.78 kg; 95% CI, −3.13 to −0.29), whereas there were no significant differences between glyburide and insulin or between metformin and glyburide.

Incidence of cesarean delivery (Supplemental Figure 1.2)

Incidence of cesarean delivery was reported in 16 studies. TMA revealed no significant differences between OADs and insulin (OR, 0.93 for metformin vs insulin; 95% CI, 0.56 to 1.47; and OR, 0.79 for glyburide vs in-

Table 2. Results of NMA and TMA From Maternal Outcomes

Study Group	n	TMA Effect Estimate (95% CI)	*P*	Egger's Test, *P*	NMA (95% CI)
Glycemic control					
HbA1c, %					
Metformin vs insulin	4	WMD, 0.05 (−0.11, 0.21)	.57	.248	0.02 (−0.16, 0.19)
Glyburide vs insulin	2	WMD, 0.01 (−0.26, 0.28)	.93		0.12 (−0.10, 0.27)
Metformin vs glyburide	2	WMD, −0.07 (−0.26, 0.11)	.44		−0.13 (−0.33, 0.12)
Fasting glycemic, mmol/L					
Metformin vs insulin	3	WMD, −0.00 (−2.56, 2.55)	1.00	.053	−0.26 (−4.16, 3.51)
Glyburide vs insulin	2	WMD, 1.65 (−0.98, 4.29)	.22		0.85 (−3.78, 5.31)
Metformin vs glyburide	3	WMD, −1.12 (−8.41, 6.17)	.76	.216	−1.11 (−5.27, 2.62)
Weight gain, kg					
Metformin vs insulin	4	WMD, −1.49 (−2.26, −0.31)	**.01**	.546	**−1.78 (−3.13, −0.29)**
Glyburide vs insulin	3	WMD, −1.13 (−2.47, 0.21)	.10	.327	−0.43 (−2.07, 1.24)
Metformin vs glyburide	2	WMD, −2.22 (−3.88, −0.56)	**.009**		−1.34 (−3.05, 0.38)
Cesarean delivery					
Metformin vs Insulin	7	OR, 0.93 (0.56, 1.47)	.76	.562	0.99 (0.58, 1.60)
Glyburide vs insulin	3	OR, 0.79 (0.55, 1.15)	.22	.207	0.75 (0.35, 1.29)
Glyburide vs metformin	3	OR, 0.72 (0.28, 1.90)	.51	.340	0.78 (0.35, 1.39)
Pre-eclampsia					
Metformin vs insulin	5	OR, 0.74 (0.48, 1.15)	.19	.660	0.78 (0.43, 1.40)
Glyburide vs insulin	2	OR, 1.15 (0.57, 2.32)	.70		1.35 (0.49, 3.05)
Glyburide vs metformin	1	OR, 1.54 (0.25, 9.51)	.64		1.86 (0.61, 4.74)

Abbreviation: n, number of included studies. The bold values mean significant associations.

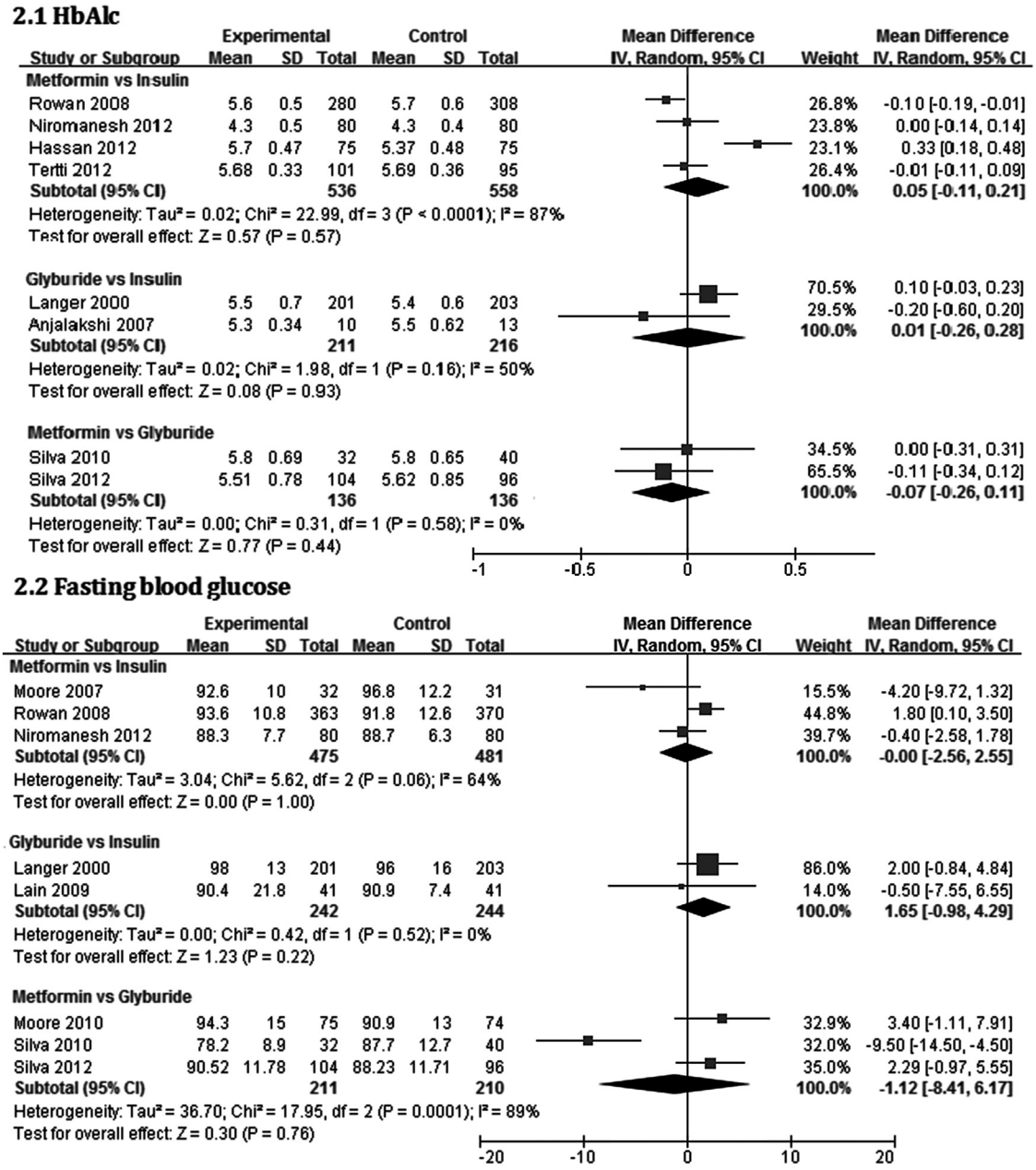

Figure 2. Forest plot for glycemic control from TMA. 2.1, HbA1c; 2.2, fasting blood glucose.

sulin; 95% CI, 0.55 to 1.15), and no significant differences were apparent between metformin and glyburide (OR, 0.72; 95% CI, 0.28 to 1.90).

Similarly, NMA for the incidence of cesarean delivery did not show a significant difference between groups.

Incidence of pre-eclampsia (Supplemental Figure 1.3)

The incidence of pre-eclampsia was reported in eight studies. TMA revealed no significant differences between OADs and insulin (OR, 0.74 for metformin vs insulin; 95% CI, 0.48 to 1.15; and OR, 1.15 for glyburide vs insulin; 95% CI, 0.57 to 2.32), and no significant differences were apparent between metformin and glyburide (OR, 1.54; 95% CI, 0.25 to 9.51).

Similarly, NMA for the incidence of pre-eclampsia did not show significant differences between groups.

Main neonatal outcomes (Table 3)

Birth weight (Supplemental Figure 2.1)

In the TMA for birth weight, metformin was slightly lower compared with insulin, but the difference was not statistically significant (WMD, −48.87 g; 95% CI, −99.13 to 1.39; $P = .06$), glyburide was significantly higher compared with insulin (WMD, 130.68 g; 95% CI, 55.98 to 205.38; $P = .0006$), acarbose showed no statistical significance compared with insulin (WMD, 91.40 g; 95% CI, −145.32 to 328.12; $P = .45$), glyburide was

Table 3. Results of NMA and TMA From Neonatal Outcomes

Study Group	n	TMA		Egger's Test, *P*	NMA (95% CI)
		Effect Estimate (95% CI)	*P*		
Birth weight, g					
Metformin vs insulin	8	WMD, −48.87 (−99.13, 1.39)	.06	.871	−45.1 (−108.3, 30.8)
Glyburide vs insulin	7	WMD, 130.68 (55.98, 205.38)	**.0006**	.093	**142.6 (66.2, 225.4)**
Metformin vs glyburide	3	WMD, −192.14 (−288.81, −95.47)	**<.0001**	.494	**−187.7 (−270.2, −106.5)**
Acarbose vs insulin	1	WMD, 91.4 (−145.32, 328.12)	.45		44.8 (−241.9, 314.1)
Glyburide vs acarbose	1	WMD, 153.00 (−123.52, 429.52)	.28		97.8 (−181.1, 364.5)
Hypoglycemia					
Metformin vs insulin	7	OR, 0.73 (0.55, 0.97)	**.03**	.480	0.91 (0.54, 1.58)
Glyburide vs insulin	6	OR, 2.64 (1.59, 4.38)	**.0002**	.042	**2.24 (1.18, 4.23)**
Glyburide vs metformin	3	OR, 1.09 (0.56, 2.15)	.79	.153	**2.59 (1.25, 5.01)**
Acarbose vs insulin	1	OR, 1.44 (0.08, 24.63)	.80		0.56 (0.01, 2.68)
Glyburide vs acarbose	1	OR, 9.00 (1.01, 80.03)	**.05**		0.25 (0.00, 1.21)
Acarbose vs metformin	0				0.71 (0.01, 3.32)
Gestational age, wk					
Metformin vs insulin	7	WMD, −0.16 (−0.30, −0.03)	**.02**	.939	−0.14 (−0.30, 0.02)
Glyburide vs insulin	5	WMD, 0.03 (−0.20, 0.27)	.79	0.271	0.01 (−0.20, 0.23)
Metformin vs glyburide	3	WMD, −0.09 (−0.37, 0.18)	.50	0.526	−0.13 (−0.35, 0.11)
Acarbose vs insulin	1	WMD, −0.30 (−1.00, 0.40)	.40		−0.11 (−0.82, 0.58)
Glyburide vs acarbose	1	WMD, −0.10 (−0.82, 0.62)	.79		−0.10 (−0.78, 0.53)
Premature birth					
Metformin vs insulin	4	OR, 1.63 (1.07, 2.48)	**.02**	0.337	1.65 (0.82, 2.60)
Glyburide vs insulin	3	OR, 0.86 (0.22, 3.34)	.82	0.729	1.23 (0.48, 2.57)
Glyburide vs metformin	2	OR, 0.84 (0.27, 2.57)	.76		0.79 (0.29, 1.73)
Macrosomia					
Metformin vs insulin	7	OR, 0.76 (0.50, 1.15)	.20	0.082	0.75 (0.33, 1.45)
Glyburide vs insulin	5	OR, 3.09 (1.59, 6.04)	**.0009**	0.185	**4.89 (1.69, 12.86)**
Glyburide vs metformin	2	OR, 3.17 (0.84, 12.00)	.09		**7.46 (2.20, 23.31)**
Glyburide vs acarbose	1	OR, 8.56 (0.43, 169.70)	.16		0.01 (0.00, 0.02)
NICU					
Metformin vs insulin	6	OR, 0.82 (0.63, 1.07)	.14	0.941	0.91 (0.62, 1.38)
Glyburide vs insulin	3	OR, 1.01 (0.53, 1.95)	.97	0.079	0.75 (0.38, 1.37)
Glyburide vs metformin	3	OR, 0.53 (0.24, 1.18)	.12	0.162	0.85 (0.43, 1.54)
Glyburide vs acarbose	1	OR, 2.49 (0.10, 64.62)	.58		0.44 (0.00, 1.56)

Abbreviation: n, number of included studies. The bold values mean significant associations.

significantly higher compared with metformin (WMD, 192.14 g; 95% CI, 95.47 to 288.81; $P < .0001$).

Similarly, the NMA for birth weight revealed that glyburide was significantly higher compared with insulin (WMD, 142.6 g; 95% CI, 66.2 to 205.4) and metformin (WMD, 187.7 g; 95% CI, 106.5 to 270.2), whereas there were no significant differences between metformin and insulin, or between acarbose and insulin, or between glyburide and acarbose.

Incidence of macrosomia (Supplemental Figure 2.2)

In the TMA for the incidence of macrosomia, metformin showed no statistical significance compared with insulin (OR, 0.76; 95% CI, 0.50 to 1.15; $P = .20$); glyburide was significantly higher compared with insulin (OR, 3.09; 95% CI, 1.59 to 6.04; $P = .0009$) and slightly higher compared with metformin (OR, 3.17; 95% CI, 0.84 to 12.00; $P = .09$), but had no statistical significance compared with acarbose (OR, 8.56; 95% CI, 0.43 to 169.70; $P = .16$).

NMA showed that the glyburide group was associated with an increased incidence of macrosomia compared with the insulin group (OR, 4.88; 95% CI, 1.69 to 12.86) and the metformin group (OR, 7.45; 95% CI, 2.20 to 23.31), whereas there were no significant differences between metformin and insulin or between glyburide and acarbose.

Incidence of hypoglycemia (Figure 3)

In the TMA for the incidence of hypoglycemia, metformin showed a slight reduction compared with insulin, and glyburide showed an increase compared with insulin (OR, 2.64; 95% CI, 1.59 to 4.38; $P = .0002$). However, no significant differences in the incidence of hypoglycemia were apparent between the glyburide and metformin groups (OR, 1.09; 95% CI, 0.56 to 2.15; $P = .79$).

NMA showed that glyburide was associated with an increased incidence of hypoglycemia compared with insulin (OR, 2.24; 95% CI, 1.18 to 4.23) and metformin (OR, 2.59; 95% CI, 1.25 to 5.01), whereas there were no

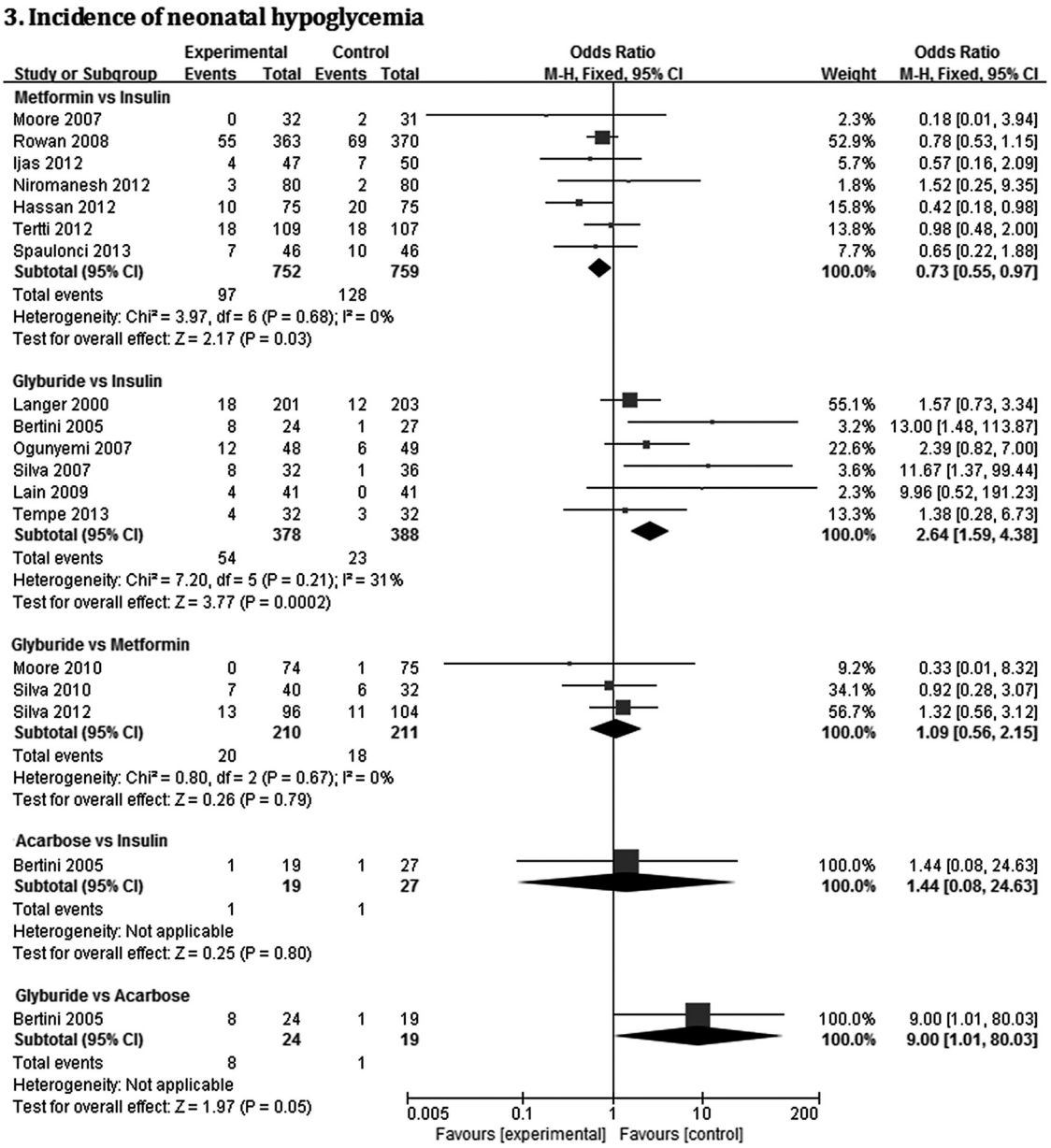

Figure 3. Forest plot for the incidence of neonatal hypoglycemia from TMA.

significant differences between metformin and insulin, or between acarbose and insulin, or between glyburide and acarbose (Supplemental Figure 3).

Gestational age at delivery (Supplemental Figure 2.3)

In the TMA for gestational age, metformin was slightly less than insulin (WMD, −0.16 wk; 95% CI, −0.30 to −0.03; $P = .02$), whereas both glyburide and acarbose showed no statistical significance compared with insulin (WMD, 0.03 wk; 95% CI, −0.20 to 0.27; $P = .79$; and WMD, −0.30 wk; 95% CI, −1.00 to 0.40; $P = .40$, respectively). No significant differences in gestational age were apparent between different OADs (WMD, −0.09 wk for metformin vs glyburide; 95% CI, −0.37 to 0.18; and WMD, −0.10 wk for glyburide vs acarbose; 95% CI, −0.82 to 0.62).

The NMA for gestational age did not show a significant difference between groups.

Incidence of premature birth (<37 wk gestation) (Supplemental Figure 2.4)

In the TMA for the incidence of premature birth, metformin showed an increase compared with insulin (OR, 1.63; 95% CI, 1.07 to 2.48; $P = .02$), glyburide showed no statistical significance compared with insulin, and no significant differences were apparent between metformin and glyburide (OR, 0.84; 95% CI, 0.27 to 2.57; $P = .76$).

The NMA for the incidence of premature birth did not show significant differences between groups.

Incidence of admission to NICU (Supplemental Figure 2.5)

The incidence of admission to the NICU was reported in 12 studies. The TMA for the incidence of admission to the NICU revealed no significant differences between OADs and insulin (OR, 0.82 for metformin vs insulin; 95% CI, 0.63 to 1.07; and OR, 1.01 for glyburide vs insulin; 95% CI, 0.53 to 1.95) and no significant differences between different OADs (OR, 0.53 for glyburide vs metformin; 95% CI, 0.24 to 0.18; and OR, 2.49 for glyburide vs acarbose; 95% CI, 0.10 to 64.62).

Similarly, the NMA for the incidence of admission to the NICU did not show significant differences between groups.

Publication bias

There was no significant publication bias among various studies, as suggested by the Egger linear regression test (Tables 2 and 3).

Comparisons between TMA and NMA

Tables 2 and 3 show the results of TMA and NMA. Although the point estimates showed small differences, the CIs from TMA and the credible intervals from NMA in general overlapped. There was no significant inconsistency within the networks for any of the outcomes (Supplemental Figure 4).

Discussion

This is the first NMA comparing the efficacy and safety of OADs in the management of GDM. Our study confirmed that there was no significant difference in maternal fasting blood glucose or HbA1c levels in patients treated with insulin, metformin, and glyburide. Metformin was associated with lower maternal weight gain and shorter gestational age than insulin. Glyburide was associated with higher neonatal birth weight, increased incidence of neonatal hypoglycemia, and increased incidence of macrosomia than insulin. Moreover, our study revealed that glyburide was associated with higher maternal weight gain, higher neonatal birth weight, increased incidence of neonatal hypoglycemia, and increased incidence of macrosomia than metformin.

The management of GDM is primarily aimed at glycemic targets to reduce the incidence of adverse pregnancy outcomes. We confirmed that there was no significant difference in HbA1c and fasting blood glucose between insulin, metformin, and glyburide. These findings demonstrate that both metformin and glyburide are equally as effective as insulin in the management of GDM. Both TMA and NMA are in accordance with the previous meta-analyses (1, 4, 8, 9). However, previous studies have reported that a high proportion of OAD-treated GDM patients need insulin to maintain adequate glucose control. Moore et al (30) reported that metformin had more than twice the failure rate of glyburide, with 34.7% of patients eventually requiring insulin therapy, compared with a little more than 16% who required insulin therapy in the glyburide group. Langer et al (28) revealed that the failure of glyburide treatment was related to the severity of GDM. Gui et al (8) found that metformin-treated GDM patients requiring supplemental insulin had higher fasting glycemic concentrations in oral glucose tolerance tests. So, clinicians who choose to utilize OADs in their pregnant patients with GDM should counsel them on the risk of failure to achieve optimal glycemic control when used as a single agent.

In a previous meta-analysis, Su and Wang (9) reported that metformin was associated with a slightly lower maternal weight gain than insulin, which is in line with our NMA. In our study, the TMA revealed that metformin was associated with a significant reduction in maternal weight gain compared to glyburide, and the NMA also showed that metformin was slightly lower in maternal weight gain than glyburide.

Macrosomia is likely to be linked with delayed motor development, premenopausal breast cancer, obesity, and diabetes later in life for infants (32). In our NMA, glyburide showed a significant increase in neonatal birth weight and incidence of macrosomia compared to insulin treatment. These results are consistent with the previous meta-analysis (4). Moreover, the NMA showed a significant increase in neonatal birth weight and incidence of macrosomia in glyburide as compared to metformin. Suspected macrosomia is reported to increase the risk of caesarean section. Although the risk of macrosomia was increased significantly in the glyburide group, both TMA and NMA showed no significant differences in the risk of caesarean section as compared glyburide to insulin or compared glyburide to metformin.

Gui et al (8) performed analyses on five RCTs and reported that the average gestational ages at delivery were significantly lower and the incidence of premature birth was significantly greater in the metformin group as compared with the insulin group. From seven RCTs, our TMA confirmed this result. However, both TMA and NMA showed no significant differences in gestational ages or incidence of premature birth as compared glyburide to metformin.

Women with GDM are at higher risk of gestational hypertension and pre-eclampsia. GDM treatment showed a significant reduction in the incidence of gestational hypertension. A decrease in the rate of gestational hypertension is likely to reduce the incidence of pre-eclampsia (32). Gui et al (8) reported that the incidence of gestational hypertension was significantly lower in the metformin group as compared

with the insulin group. The possible explanation might be that metformin has complex properties in endothelial functions and reactive oxygen species production, so as to reduce the endothelial activation and maternal inflammatory response of insulin resistance. There were insufficient data to determine whether glyburide can affect the incidence of gestational hypertension. Although the risk of gestational hypertension was decreased significantly in the metformin group, TMA and NMA showed no significant differences in the incidence of pre-eclampsia in the metformin group as compared to insulin or the glyburide group.

Neonatal hypoglycemia occurs frequently in babies of women with GDM. Su and Wang (9) reported that the incidence of neonatal hypoglycemia in the metformin group was lower than in the insulin group. Zeng et al (4) revealed that the incidence of neonatal hypoglycemia in the glyburide group was higher than in the insulin group. Our analysis confirmed these results. However, TMA showed a nonsignificant increase in the incidence of neonatal hypoglycemia in glyburide as compared to metformin, whereas the NMA showed significant results on this outcome. The absence of association in the TMA was likely due to the insufficient statistical power because only three RCTs were included in this analysis. It is supposed that the infants born to mothers treated with glyburide need additional management for hypoglycemia or NICU admission; however, both the TMA and NMA showed no significant differences in the incidence of NICU admission compared with metformin to insulin or metformin to glyburide.

Only one RCT provided results from patients with GDM who were treated with acarbose (7). This RCT reported that both glyburide and acarbose could be promising alternative therapies for the treatment of GDM, whereas glyburide was more efficient than acarbose. In our study, the NMA for maternal and neonatal outcomes showed no significant differences in the acarbose group as compared to the metformin or glyburide group.

There exists some apprehension regarding the use of OADs during pregnancy. Much of this anxiety stems from reports that these drugs cross the placenta and reach the fetus. Metformin has been shown to be concentrated on the fetal side of the placenta, with cord blood levels approximately twice those of the mothers (33). Glyburide, originally thought not to cross the placenta, has been shown to be present in cord blood samples at levels approximately 70% of maternal levels at the time of delivery (34, 35). Although advocates of glyburide point out that levels were quite low in both maternal and cord bloods (because of the elapsed time since the last dose), this begs the question of what the fetal levels would have been if measured when maternal glyburide was in the therapeutic range. Although no long-term harm to the exposed offspring from either of these drugs has been demonstrated, no long-term studies have been performed with appropriate controls, either in humans or animal models. A 2-year follow-up of the Metformin in Gestational diabetes (MiG) trial did show differences in fat distribution in insulin-exposed vs metformin-exposed offspring, but the significance of these findings is unknown (36). So, patients should be informed of possible unknown effects of in utero exposure to metformin.

Our study had some important strengths. This is the first NMA comparing efficacy and safety of OADs in the management of GDM. The application of the NMA method adds the ability to address comparisons that were not powered in the TMA. All the original studies used a randomized controlled study design, which greatly reduced the likelihood of recall and selection biases. We uniquely carried out meta-analysis to compare efficacy and safety between metformin and glyburide group.

Several limitations involved in this study should be considered. First, to reduce heterogeneity, we included only trials comparing OADs with another OADs or insulin, excluding for example trials comparing different insulin regimens, insulin with diet, OADs with diet, etc. Second, we did not have sufficient data to analyze the effects of acarbose. Third, only 18 RCTs fulfilled the set eligibility criteria for inclusion, and furthermore, not all reported on important outcome measures of interest. This limited the meta-analysis, which may have lacked power to detect important differences in some of the outcomes of interest. Fourth, we planned to perform a sensitivity analysis by excluding studies at high risk of bias or studies with nonstandardized design. However, the sensitivity analysis could not be done because of the small number of studies. Moreover, due to the different routes of administration between OADs and insulin, no trial was adequate in blinding. Finally, potential publication bias might influence the findings, yet little evidence of publication bias was observed.

In conclusion, both metformin and glyburide are suitable for use in the management of GDM because of good glycemic control. However, glyburide treatment is associated with increased risk of neonatal hypoglycemia, high maternal weight gain, high neonatal birth weight, and macrosomia.

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References

1. **Dhulkotia JS, Ola B, Fraser R, Farrell T.** Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2010;203(5):457.e1–e9.
2. **Landon MB, Gabbe SG.** Gestational diabetes mellitus. *Obstet Gynecol*. 2011;118:1379–1393.
3. **Lowe LP, Metzger BE, Dyer AR, et al.** Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations of maternal A1C and glucose with pregnancy outcomes. *Diabetes Care*. 2012;35(3):574–580.
4. **Zeng YC, Li MJ, Chen Y, et al.** The use of glyburide in the management of gestational diabetes mellitus: a meta-analysis. *Adv Med Sci*. 2014;59(1):95–101.
5. **Slagle M.** Diabetes mellitus. Medication update. *South Med J*. 2002;95:50–55.
6. **Rossetti L, Giaccari A, DeFronzo R.** Glucose toxicity. *Diabetes Care*. 1990;13:610–630.
7. **Bertini AM, Silva JC, Taborda W, et al.** Perinatal outcomes and the use of oral hypoglycemic agents. *J Perinat Med*. 2005;33(6):519–523.
8. **Gui J, Liu Q, Feng L.** Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One*. 2013;8(5):e64585.
9. **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):353–357.
10. **Wu HY, Huang JW, Lin HJ, et al.** Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and Bayesian network meta-analysis. *BMJ*. 2013;347:f6008.
11. **Liang WH, Wu X, Fang W, et al.** Network meta-analysis of erlotinib, gefitinib, afatinib and icotinib in patients with advanced non-small-cell lung cancer harboring EGFR mutations. *PLoS One*. 2014;9(2):e85245.
12. **Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L.** β Lactam antibiotic monotherapy versus β lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2014;1:CD003344.
13. **Wang X, Wang X, Liu T, He Q, Wang Y, Zhang X.** Systematic review and meta-analysis of the use of phosphodiesterase type 5 inhibitors for treatment of erectile dysfunction following bilateral nerve-sparing radical prostatectomy. *PLoS One*. 2014;9(3):e91327.
14. **Zeng C, Li H, Yang T, et al.** Effectiveness of continuous and pulsed ultrasound for the management of knee osteoarthritis: a systematic review and network meta-analysis. *Osteoarthritis Cartilage*. 2014;22(8):1090–1099.
15. **Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RP.** Randomized trial of metformin vs insulin in the management of gestational diabetes. *Am J Obstet Gynecol*. 2013;209(1):34.e1–e7.
16. **Tertti K, Ekblad U, Koskinen P, Vahlberg T, Rönnemaa T.** Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. *Diabetes Obes Metab*. 2013;15(3):246–251.
17. **Hassan JA, Karim N, Sheikh Z.** Metformin prevents macrosomia and neonatal morbidity in gestational diabetes. *Pak J Med Sci*. 2012;28:384–389.
18. **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):422–429.
19. **Ijäs H, VääräsmäkiM, Morin-Papunen L, et al.** Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. *BJOG*. 2011;118:880–885.
20. **Rowan JA, Hague WM, Gao W, et al.** Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008;358:2003–2015.
21. **Moore LE, Briery CM, Clokey D, et al.** Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. *J Reprod Med*. 2007;52:1011–1015.
22. **Hague WM, Davoren PM, Oliver J, Rowan J.** Contraindications to use of metformin. Metformin may be useful in gestational diabetes. *BMJ*. 2003;326(7392):762.
23. **Tempe A, Mayanglambam RD.** Glyburide as treatment option for gestational diabetes mellitus. *J Obstet Gynaecol Res*. 2013;39(6):1147–1152.
24. **Lain KY, Garabedian MJ, Daftary A, Jeyabalan A.** Neonatal adiposity following maternal treatment of gestational diabetes with glyburide compared with insulin. *Am J Obstet Gynecol*. 2009;200:501–506.
25. **Ogunyemi D, Jesse M, Davidson M.** Comparison of glyburide versus insulin in management of gestational diabetes mellitus. *Endocr Pract*. 2007;13:427–428.
26. **Silva JC, Bertini AM, Taborda W, et al.** Glibenclamide in the treatment for gestational diabetes mellitus in a compared study to insulin [in Portuguese]. *Arq Bras Endocrinol Metabol*. 2007;51:541–546.
27. **Anjalakshi C, Balaji V, Balaji MS, et al.** A prospective study comparing insulin and glibenclamide in gestational diabetes mellitus in Asian Indian women. *Diabetes Res Clin Pract*. 2007;76(3):474–475.
28. **Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O.** A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med*. 2000;343(16):1134–1138.
29. **Silva JC, Fachin DR, 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):225–228.
30. **Moore LE, Clokey D, Rappaport VJ, Curet LB.** Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. *Obstet Gynecol*. 2010;115(1):55–59.
31. **Silva JC, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM.** Metformin compared with glyburide for the management of gestational diabetes. *Int J Gynaecol Obstet*. 2010;111(1):37–40.
32. **Poolsup N, Suksomboon N, Amin M.** Effect of treatment of gestational diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2014;9(3):e92485.
33. **Vanky E, Zahlsen K, Spigset O, Carlsen SM.** Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril*. 2005;83(5):1575–1578.
34. **Hebert MF, Ma X, Naraharisetti SB, et al.** Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther*. 2009;85(6):607–614.
35. **Schwartz R, Rosenn B, Aleksa K, Koren G.** Transplacental transfer of glyburide: is it clinically significant? *Am J Obstet Gynecol*. 2013;208(suppl 1):S25.
36. **Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM.** Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. *Diabetes Care*. 2011;34:2279–2284.