Glyburide versus metformin in management of gestational diabetes mellitus: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of glyburide and metformin for the management of patients with gestational diabetes mellitus (GDM)

METHODS

We systematically searched through electronic databases including Pubmed, Scopus and The Cochrane Library as well as hand searching of both published and unpublished randomized controlled trials (RCT) and observational studies of acceptable quality to assess the effectiveness of glyburide compared with metformin the in management of gestational diabetes mellitus. The primary outcome was maternal fasting glucose (FBG) level.

RESULTS

We included three RCTs with a total of 421 pregnant women with gestational diabetes mellitus. Most of included trials had a low risk of bias. The meta-analysis showed no difference between glyburide and metformin for controlling maternal FBG (standard mean difference [SMD] 0.10; 95% confidence interval [CI] [-0.46 to 0.66]; I^2=87%). Comparing between glyburide group and metformin group, the former had a significant increase in neonatal birth weight (SMD 0.37; 95% CI [0.18 to 0.57]; I^2=0%), higher rate of infant with large for gestational age (relative risk [RR] 2.32; 95% CI [1.23 to 4.37]; I^2=0%), higher maternal weight gain (SMD 0.32; 95% CI [0.08 to 0.56]; I^2=0%) and lower capillary glycemia (mg/dL) at 1 and 3 hour (SMD -0.34; 95% CI [-0.58 to -0.10]; I^2=0%; SMD -0.46; 95% CI [-0.70 to -0.22]; I^2=0%, respectively).

CONCLUSION

Glyburide comparing with metformin in the management of GDM had no statistical difference in controlling maternal FBG.

INTRODUCTION

Definition of gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with first identified during pregnancy.[1] GDM is associated with an increased risk of maternal and neonatal complications during pregnancy and birth.[2] Treatment for GDM aims to keep maternal FBG levels equal to those of pregnant women who do not have GDM.[3] Insulin is the first recommended for treating women with GDM whose FBG cannot be controlled by diet and exercise.[3-8] There is increasing evidence that metformin and glyburide are safe in women with GDM.[4,6] Randomized controlled trials (RCTs) and a systematic review have reported that glyburide and metformin are as effective as insulin and no significant differences of maternal or neonatal outcome were found with the use of glyburide or metformin compared with the use of insulin.[9-13] One RCT comparing between metformin and glyburide for the treatment of GDM found their equivalent efficacy regarding maternal FBG level or neonatal and maternal complications.[14] However, an RCTs in 2012 evaluating the impact during the perinatal period of the use of metformin and glyburide, suggested that neonatal birth weight was lower while glucose levels at 1 and 3 hours after birth were higher in the newborns of the metformin group.[15] Regarding adverse events from the drugs, maternal hypoglycemia symptoms were more common in the glyburide group.[15] Therefore, we conducted systematic review and meta-analysis to compare the effectiveness and maternal and neonatal outcomes between metformin and glyburide in treating women with GDM with hope to clarify the controversies that mentioned above.

METHODS

SEARCH STRATEGIES

We searched for studies through Pubmed, Scopus and The Cochrane database of systematic review since the commencement of the databases till 2014 without any language restriction. We used a combination of Medical Subject Headings (MeSH) for Pubmed and Cochrane Library searching ("diabetes, gestational" AND "glyburide" AND "metformin") and used keyword "gestational diabetes AND glyburide AND metformin", "gestational diabetes AND glibenclamide AND metformin", "gestational diabetes AND neogluconin AND metformin", "gestational diabetes AND euglucon AND metformin", "gestational diabetes AND diabeta AND metformin","gestational diabetes AND micronase AND metformin","gestational diabetes AND daonil AND metformin","gestational diabetes AND maninil AND metformin", "gestational diabetes AND oral hypoglycemic agents", "pregnancy induced diabetes AND glyburide AND metformin", "pregnancy induced diabetes AND glibenclamide, "pregnancy induced diabetes AND neogluconin AND metformin", "pregnancy induced diabetes AND euglucon AND metformin", "pregnancy induced diabetes AND maninil AND metformin", "pregnancy induced diabetes AND micronase AND metformin", "pregnancy induced diabetes AND daonil AND metformin" in Scopus. We checked the references of included studies and handy searched for

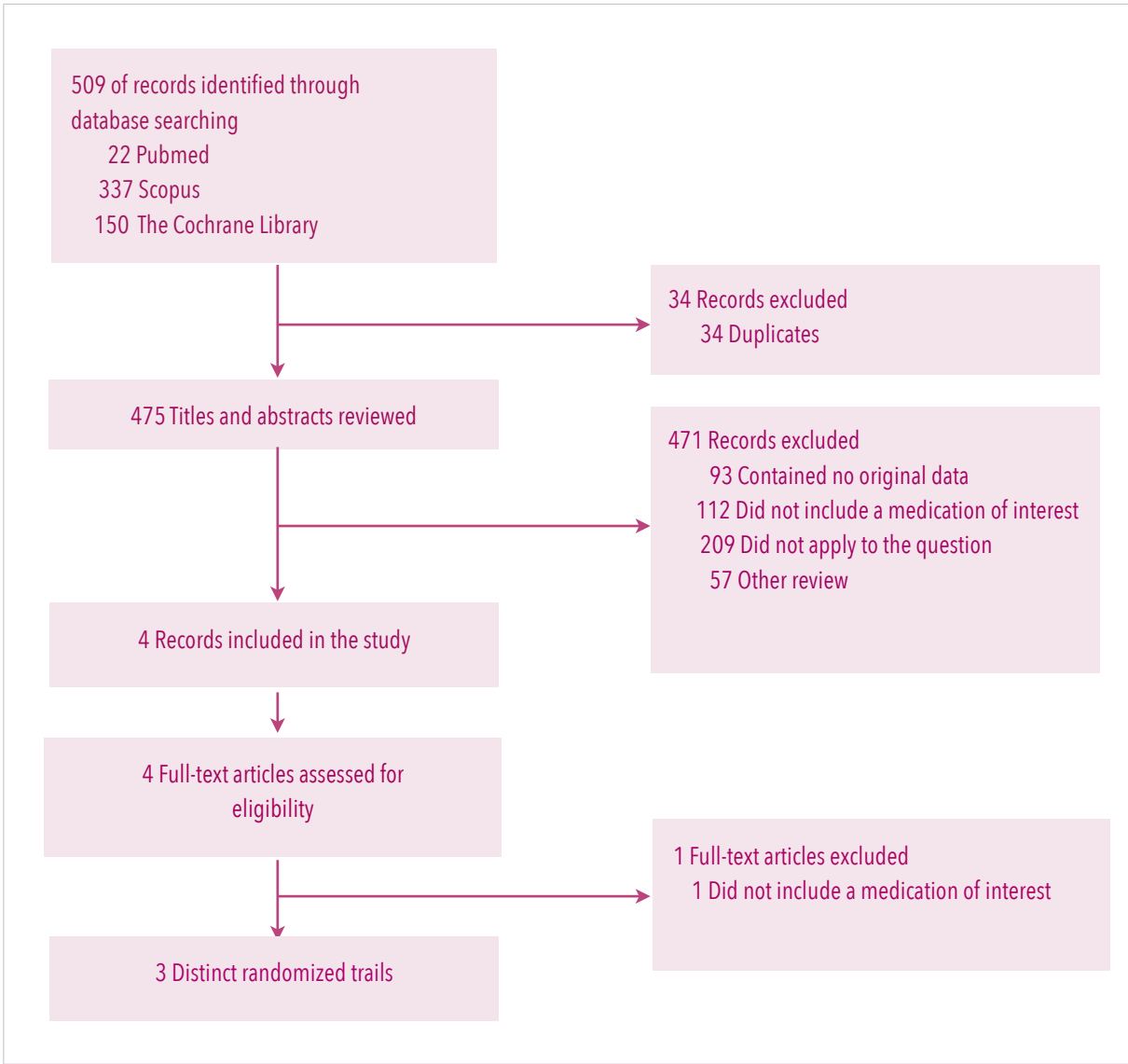

Figure 1. Flow of the study

additional studies which were relevant. Overall, 77 abstracts were reviewed.

INCLUSION AND EXCLUSION

The systematic review is performed by collecting both published and unpublished randomized controlled trials and observational studies of acceptable quality to evaluate the effectiveness of glyburide compared with metformin in achieving maternal fasting blood glucose (FBG) level and to assess the maternal and neonatal outcomes in GDM. The primary outcome was maternal FBG level. Secondary outcomes were maternal outcomes including maternal weight gain,

neonatal birth weight, large for gestational age, capillary glycemia at 1 hour, 3 hour, 2-hour postprandial glucose, rate of cesarean delivery, hypertensive syndrome, participants who change to insulin treatment and neonatal outcomes including incidence of neonatal hypoglycemia, gestational age of delivery, macrosomia, Apgar score at 1 minutes, 5 minutes, capillary glycemia at 6 hour, needed intensive care. We included observational studies and RCTs in which the units of randomization are individuals. We excluded quasi-RCTs, cross-over trials and the studies that include pregnant women with preexisting type 2 diabetes.

STUDY SELECTION AND DATA EXTRACTION

This review was conducted following the recommendations of The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.29 Four review authors independently assessed for all titles and abstracts to include and exclude the studies. Then we read full-text of all potentially relevant studies. Disagreements were resolved by discussion. Four review authors individually extracted data are as follows: the language of publication, inclusion and exclusion criteria, interventions, number of participant and baseline data, date and duration of the study and outcomes. We extracted data into simple standard forms.

QUALITY OF REPORTING AND RISK OF BIAS

The four authors evaluated the quality and risk of bias of the included studies with Jadad score to appraise the quality of selected articles. A score of 3 or more is considered as high-quality study. Moreover, we used the domain base-evaluation following The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.29 The Domain base-evaluation evaluated in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting and others bias. They specified the criteria and classified the study into three groups; low risk, high risk and, unclear risk. Potential publication bias was assessed by using a funnel plot.

DAT ANALYSES

To standardize the reporting of our results, we calculated the standard mean difference (SMD) and relative risk (RR) with 95% confidence interval (CI) from continuous or dichotomous data in each group for every trial. All analyses were performed with Revman 5.3 statistical software using fixed-effect model meta-analysis to assess the effectiveness of glyburide compared with metformin in achieving glycemic control and maternal and neonatal outcomes in GDM. The statistical heterogeneity was evaluated by chi-square and I2. The statistical test of heterogeneity was significant if $P<0.05$ and heterogeneity was considered high if the I^2 statistic was more than 50%. We used a random effect model for the meta-analysis when heterogeneity was statistical significance.

RESULTS

Overall 509 records were identified through database searching. Of these, 475 records after duplicates removed were identified. After screened

Table 1. Characteristics of the included study

	Moore, 2010	Silva, 2010	Silva, 2012
Study design	RCT, not blind	RCT, double blind	RCT, double blind
Language of publication	English	English	English
Date and duration	July 2003 to May 2008 4 years 10 months	July 1,2008 to October 30,2009 1 year 4 months	July 1,2008 to September 30, 2010 2 years 3 months
Inclusion criteria	(i) Pregnant women with GDM, and (ii) not maintain fasting blood glucose less than 105 mg/dL or 2-hour postprandial blood glucose less than 120 mg/dL	(i) Pregnant women with GDM, (ii) age≥18 years old, (iii) singleton pregnancy, (iv) GA 11 to 33 weeks, (v) fetal abdominal circumference was within normal percentiles, and (vi) no maternal or fetal conditions likely to affect treatment or neonatal outcome	(i) pregnant women with GDM, (ii) age≥18 years old, (iii) singleton pregnancy, (iv) GA 11 to 33 weeks, (v) fetal abdominal circumference within normal percentile, and (vi) absence of other pathologies that might interfere with perinatal results or hypoglycemic therapy
Exclusion criteria	(i) History of significant renal or hepatic disease, (ii) chronic hypertension necessitating medication, and (iii) substance misuse.	(i) Intolerance of the drugs, (ii) unwillingness to participate; fetal risk , (iii) lack of follow up during pregnancy, and (iv) malformation diagnosed on delivery.	(i) intolerance of the drugs, (ii) unwillingness to participate, fetal risk, (iii) lack of follow-up, and (iv) fetal malformation diagnosed upon delivery.
No of pregnancy in each group	G=74 M=75	G=40 M=32	G=96 M=104
Age-years	G=29.6±7.8 M=31.0±7.1	G=31.5±5.4 M=33.6±5.8	G=31.3±5.4 M=32.6±5.6
Gestational age at inclusion -weeks	G=29.1±5.0 M=27.3±6.8 (Below 24 wk at entry G=8 (11%) M=13 (17%))	G=26.8±6.0 M=25.6±6.4	G=25.4±7.1 M=27.0±6.4
No. of previous pregnancies	Not available	G=2.8±1.5 M=2.9±1.2	G=2.5±1.3 M=2.8±1.3
Pre-pregnancy BMI-kg/m^2	G=32.7±7.0 M=32.8±5.8	G=28.8±5.8 M=30.3±5.7	G=28.6±5.9 M=28.7±5.4
Diagnosis	50g OGTT/ Carpenter and Coustan guidelines	75g OGTT/ WHO criteria	75g OGTT/ WHO criteria
Dose of oral hypoglycemic drugs	G=2.5 mg twice daily Max.=20 mg/d M=500 mg/d Max.=2000 mg/d	G=2.5-5 mg/d Max.=20 mg/d M=500-1000 mg/d Max.=2500 mg/d	G=2.5-5 mg/d Max.=20 mg/d M= 500-1000 mg/d Max.=2500 mg/d

Table 1. (Continued)

FBS-mg/dL	G=90.9±13.0 M=94.3±15.0	G=87.7±12.7 M=78.2±8.9	G=88.23±11.71 M=90.52±11.78
2-hour PPG-mg/dL	G=111.67±19.44 M=109.67±16.43	G=129.1±20.8 M=136.0±23.7	Not available
weight gain-kg	Not available	G=10.3±5.8 M=7.6±8.1	G=9.84±6.42 M=7.78 ± 7.42
Hypertensive syndrome-no. (%)	G=3 (4) M=2 (2.7)	G=1 (2.5) M=0	Not available
Changing to insulin treatment-no.(%)	G=12 (16.22) M=26 (34.67)	G=10 (23.8) M=8 (25)	G=28 (29.17) M=22 (21.15)
Neonatal birth weight-g	G=3,329.6±334 M=3,103±600	G=3.463±535.6 M=3.360±509.5	G=3387.98±512.16 M=3193.87±521.22
Rate of infant with large for gestational age-no.(%)	Not available	G=9 (22.5) M=3 (9.4)	G=19 (19.79) M=9 (8.65)
Capillary glycemia at 1 hour-mg/dL	Not available	G=54.7±15.4 M=57.9±20.3	G=54.08±12.97 M=59.78±15.21
Capillary glycemia at 3 hour-mg/dL	Not available	G=54±12.2 M=65.8±25.5	G=55.89±11.65 M=61.53±15.53
Capillary glycemia at 6 hour-mg/dL	Not available	G=55.4±11.2 M=58.3±12.6	G=57.12±10.77 M=59.14±10.66
Neonatal hypoglycemia-no. (%)	G=0 M=1 (1.3)	G=7 (17.5) M=6 (18.7)	G=13 (13.54) M=11 (10.58)
Gestational age of delivery-weeks	G=38±1 M=38±2	G=38.6±1.1 M=38.6±1.3	G=38.41±1.17 M=38.25±1.41
Macrosomia-no. (%)	G=4 (5.4) M=1 (1.3)	G=6 (15) M=2 (6.2)	Not available
APGAR score at 1 minute	Not available	G=8±1 M=8.1±0.9	G=8.08±1.07 M=8.17±1.18
APGAR score at 5 minutes	Not available	G=9.3±0.6 M=9.1±0.7	G=9.23±0.59 M=9.17±0.69
Needed intensive care-no. (%)	G=1 (1.3) M=4 (5.33)	G=2 (5) M=5 (15)	G=7 (7.29) M=9 (8.65)
Jadad score	3	5	5

G=glyburide, M=metformin,
RCT=randomized controlled trial, GA=gestational age, FBG=fasting blood glucose, 2-h PPG=2 hour postprandial glucose, Max.=maximum, WHO=World Health Organization; Normal percentiles of fetal abdominal circumference=percentile >10% and <75%; Fetal risk=abdominal circumference at percentile >97% or <5%, BMI=body mass index

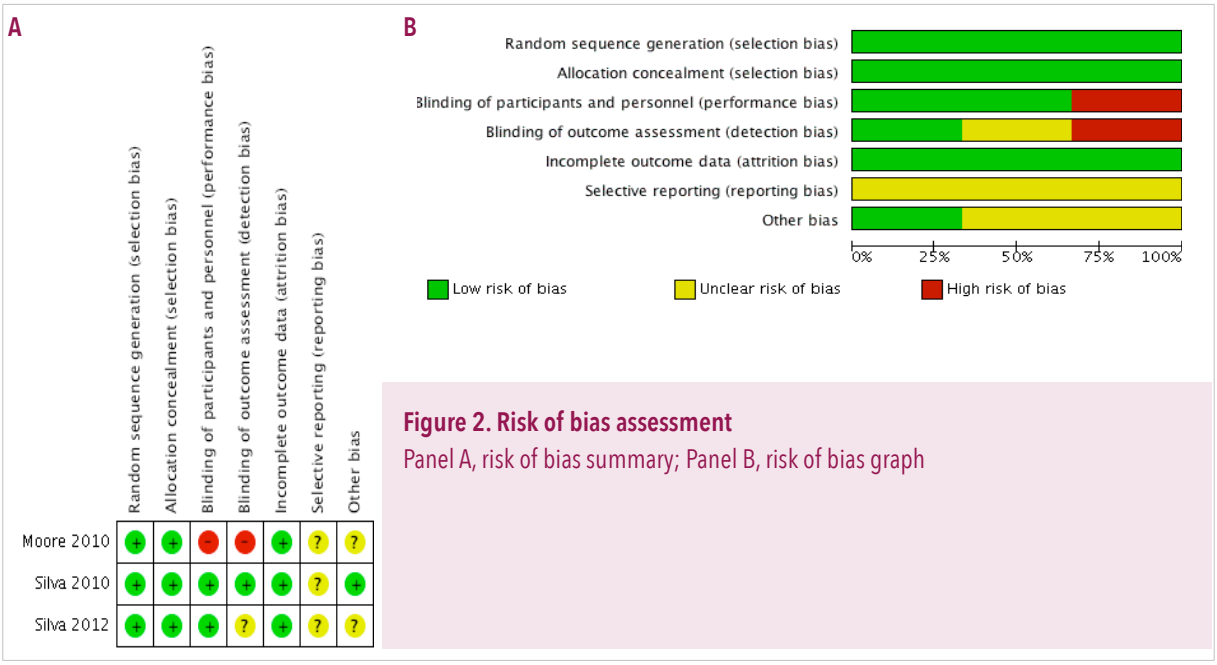

Figure 2. Risk of bias assessment
Panel A, risk of bias summary; Panel B, risk of bias graph

titles, 398 records were excluded and then 73 records after screening the abstract were excluded following the exclusion criteria (Figure 1). Four full-text articles were assessed as eligible. One study was not included the medication of interest. We collected 3 distinct randomized controlled trials and no observational studies. The included studies assigned 421 patients to receive either glyburide (n=202) or metformin (n=219).

STUDY CHARACTERISTICS

All included studies were conducted in Brazil and the United States. Two studies were double-blind and one was open-label trial. Four hundred and twenty-one participants were enrolled in the studies; their means of age were 29.6 to 33.6 years and means of gestational age were 25.4 to 29.1 weeks. The oral hypoglycemic agents; glyburide doses used in eligible studies was 2.5 to 20.0 mg/d and metformin was 500 to 2,500 mg/d. The duration of eligible studies was vary from 1 year 3 months to 4 years 10 months (Table 1).

BIAS RISK ASSESSMENT

Three included trials were assessed using Jadad score (Table 1) and domain base-evaluation (Figure 2). All studies reported low risk of bias in the domain of sequence generation, allocation concealment, and incomplete outcome data. All studies were unclear risk of bias in the domain of selective reporting. Only one study had high risk in the domain of blinding of participant and blinding of outcome assessment.16 We evaluated the potential publication bias by using a funnel plot of intervention effect versus the standard error for the studies. Visually our funnel plot which constructed from the three trials included in the analysis appeared to be symmetrical (Figure 21).

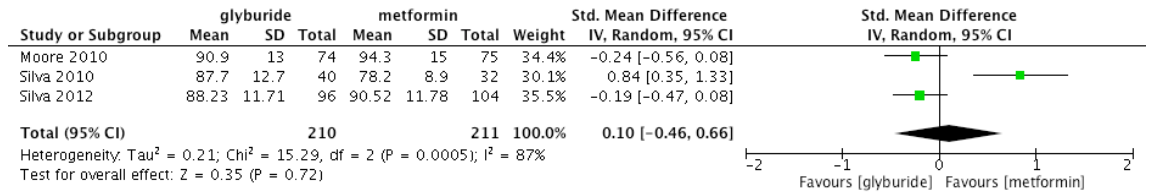

Figure 3. The forest plot showing meta-analysis of maternal FBG level in glyburide comparing with metformin for managing GDM

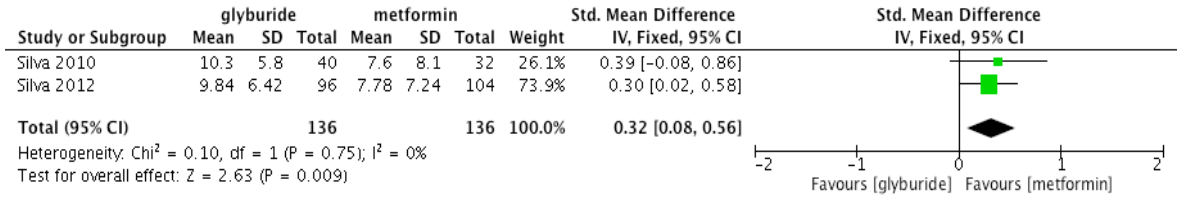

Figure 4. The forest plot showing meta-analysis of maternal weight gain in glyburide comparing with metformin for managing GDM

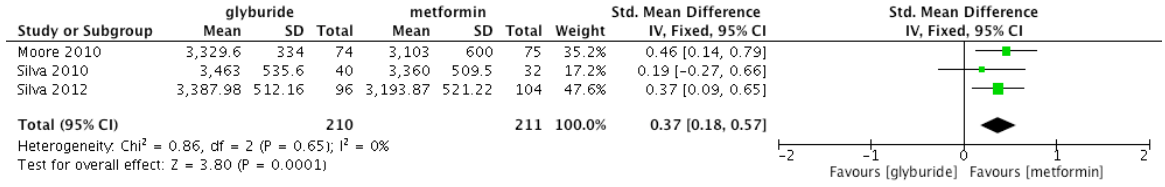

Figure 5. The forest plot showing meta-analysis of neonatal weight gain in glyburide comparing

CLINICAL OUTCOMES

PRIMARY OUTCOME

The primary outcome was maternal FBG. The meta-analysis of three studies showed no statistically significant difference between glyburide and metformin for controlling maternal FBG level (SMD 0.10; 95% CI [-0.46 to 0.66]; chi-square=15.29; I^2=87%) (Figure 4).

SECONDARY OUTCOMES

Comparing between glyburide group and metformin group, the former had a significant

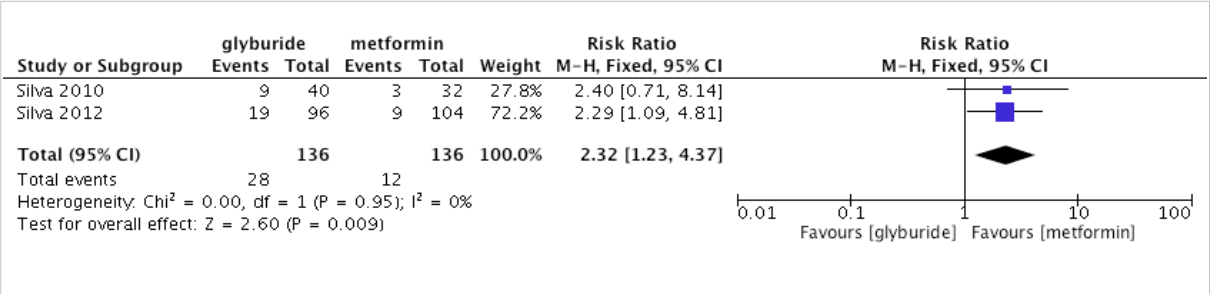

Figure 6. The forest plot showing meta-analysis of gestational age in glyburide comparing with metformin for managing GDM

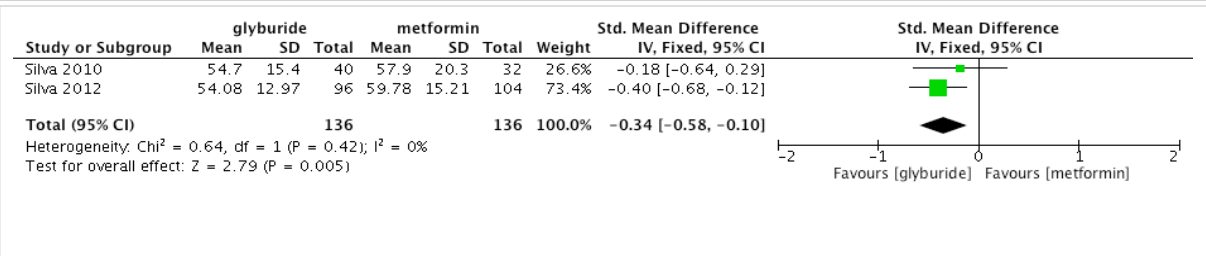

Figure 7. The forest plot showing meta-analysis of capillary glycemia at 1 hr (mg/dL) in glyburide comparing with metformin for managing GDM

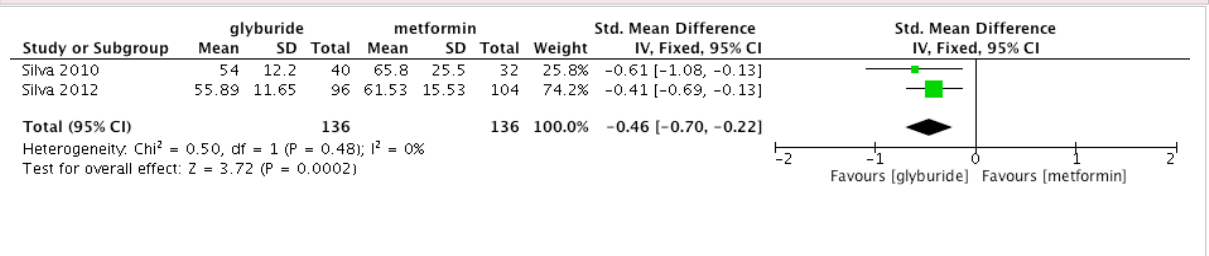

Figure 6. The forest plot showing meta-analysis of gestational age in glyburide comparing with metformin for managing GDM

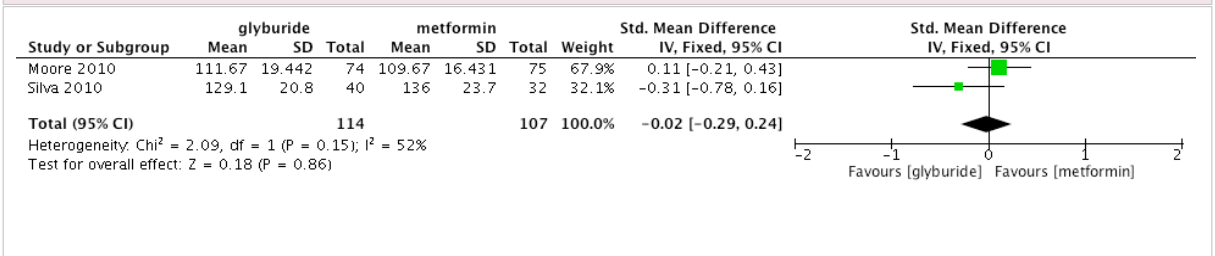

Figure 9. The forest plot showing meta-analysis of 2-hour postprandial glucose in glyburide comparing with metformin for managing GDM

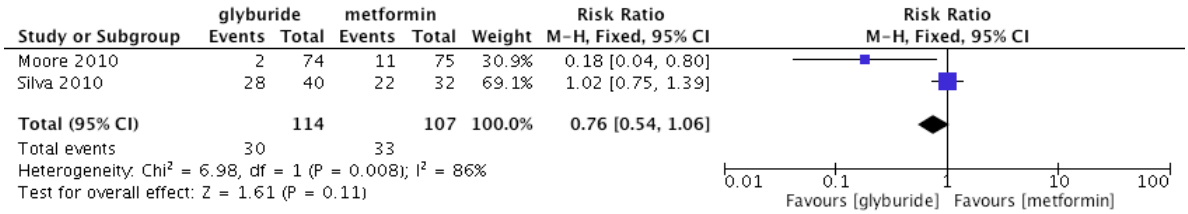

Figure 10. The forest plot showing meta-analysis of rate of cesarean delivery in glyburide comparing with metformin for managing GDM

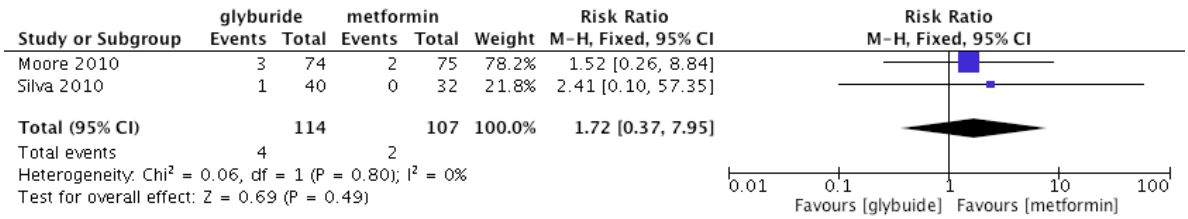

Figure 11. The forest plot showing meta-analysis of hypertensive syndrome in glyburide comparing with metformin for managing GDM

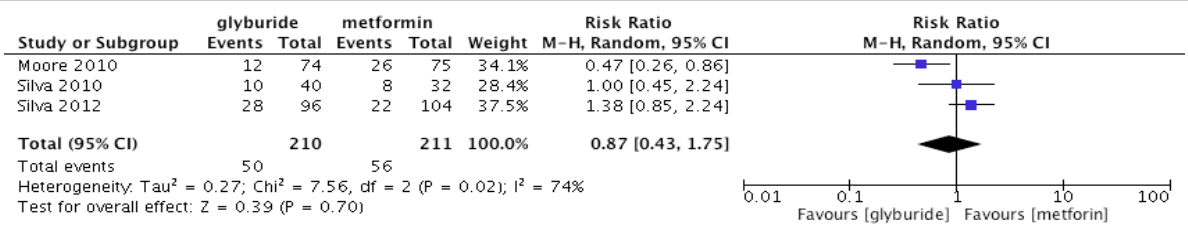

Figure 12. The forest plot showing meta-analysis of participant changed to insulin treatment in glyburide comparing with metformin for managing GDM

increase in maternal weight gain (SMD 0.32; 95% CI [0.08 to 0.56]; chi-square=0.10; I^2=0%), higher in neonatal birth weight (SMD 0.37; 95% CI [0.18 to 0.57]; chi-square=0.86; I^2=0%), higher rate of infant with large for gestational age (relative risk [RR] 2.32; 95% CI [1.23 to 4.37]; chi-square=0.00; I^2=0%) and lower capillary glycemia (mg/dL) at 1 and 3 hour (SMD -0.34; 95% CI [-0.58 to -0.10]; chi-square=0.64; I^2=0%; SMD -0.46; 95% CI [-0.70 to -0.22]; chi-square=0.50; I^2=0%, respectively). However, the other outcomes including 2-hour postprandial glucose, rate of cesarean delivery, hypertensive syndrome, changing to insulin treatment, incidence of neonatal hypoglycemia, gestational age of delivery, macrosomia, apgar score at 1 and 5 minutes, capillary glycemia at 6 hour and needed intensive care were not significantly different between the those with glyburide and metformin (Figure 4-19).

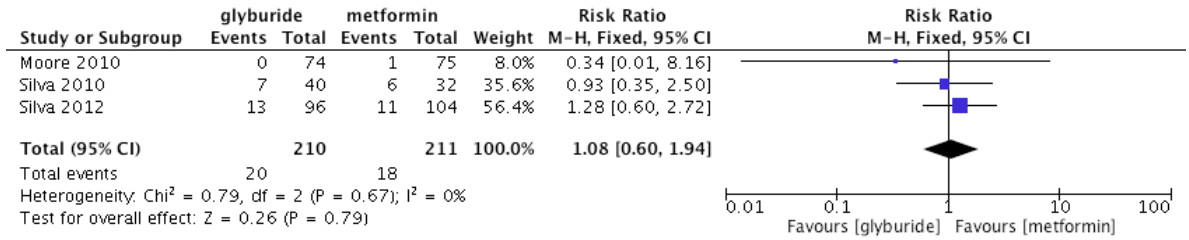

Figure 13. The forest plot showing meta-analysis of neonatal hypoglycemia in glyburide comparing with metformin for managing GDM

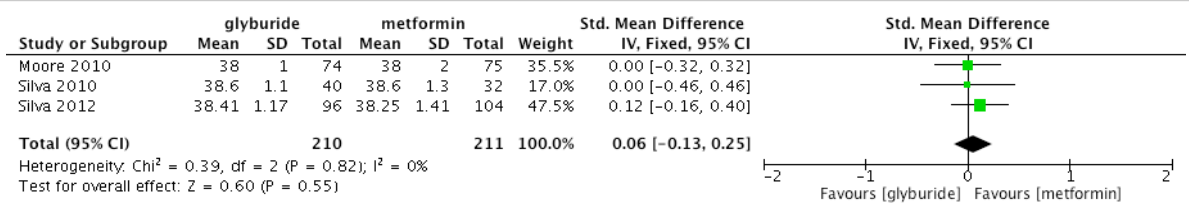

Figure 14. The forest plot showing meta-analysis of gestational age of delivery, weeks in glyburide comparing with metformin for managing GDM

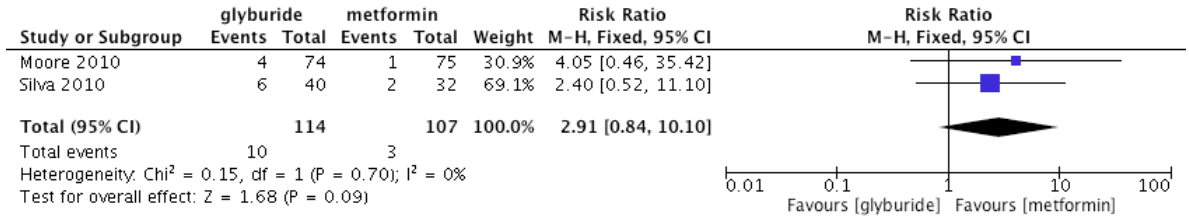

Figure 15. The forest plot showing meta-analysis of macrosomia in glyburide comparing with metformin for managing GDM

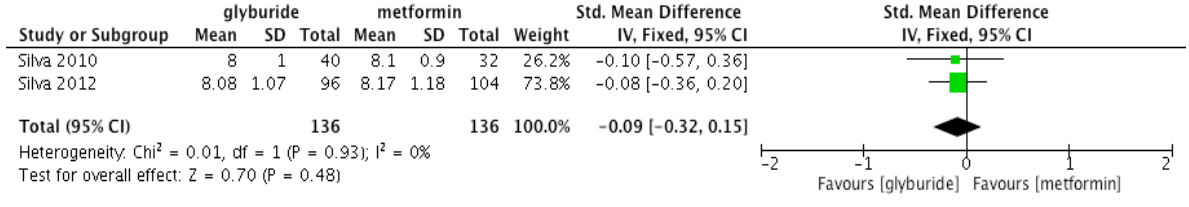

Figure 16. The forest plot showing meta-analysis of apgar score at 1 minute in glyburide comparing with metformin for managing GDM

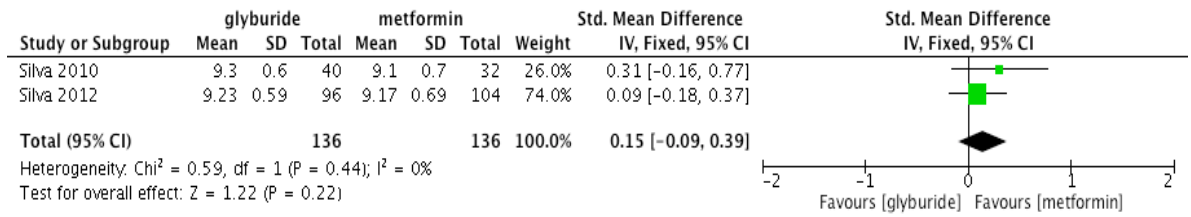

Figure 17. The forest plot showing meta-analysis of apgar score at 5 minute in glyburide comparing with metformin for managing GDM

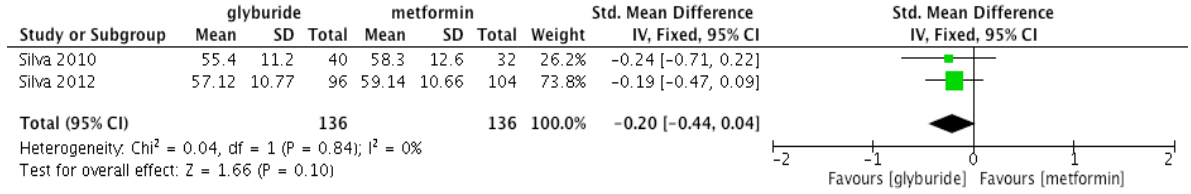

Figure 18. The forest plot showing meta-analysis of capillary glycemia at 6 hr (mg/dL) in glyburide comparing with metformin for managing GDM

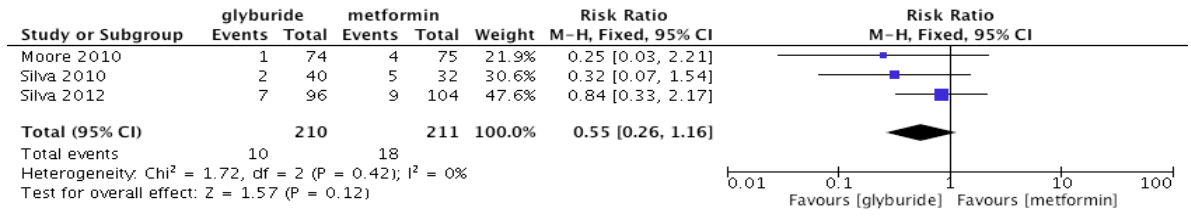

Figure 19. The forest plot showing meta-analysis of needed intensive care in glyburide comparing with metformin for managing GDM

Moreover, we produced the funnel plot to assess the potential of publication bias, however, the included studies were to few to assess the bias.

DISCUSSION

in this meta-analysis, three randomized controlled trials in women with GDM were included. Our study showed that there was no statistically significant difference in maternal FBG. There were the significant increase in maternal weight gain, neonatal birth weight, the rate of infant with large for gestational age and lower capillary glycemia (mg/dL) at 1 and 3 hours in glyburide group. According to secondary outcomes, the result showed that metformin was preferable to

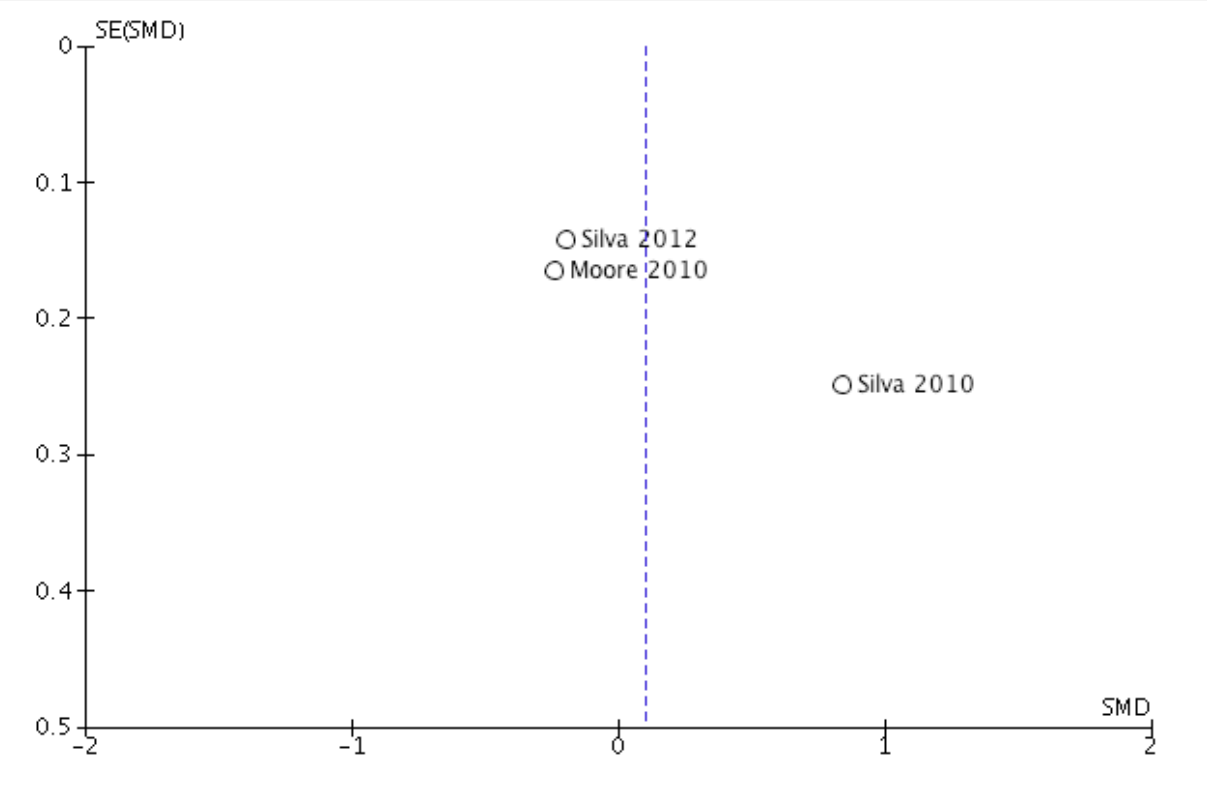

Figure 20. Funnel plot of included studies in meta-analysis

glyburide. In our study, maternal weight gain in women with GDM treated by glyburide was higher than those in the metformin group. This difference between two groups may due to the particular mechanism of drug action. Mechanisms of metformin were hepatic glucose output deduction and gluconeogenesis inhibitor. Moreover, it also seemed to induce weight reduction, principally involving adipose tissue.[23,26]

SSTRENGTH AND LIMITATION OF THE REVIEW

Our systematic review and meta-analysis followed the Guide for developing a Cochrane protocol.[31] Four authors screened all titles and abstracts, extracted data independently. Our study examined the risk of bias of each study carefully using Jadad score and domain base-evaluation. Our included studies were considered as high-quality studies. Moreover, our meta-analysis had high homogeneity that confirmed the potential benefit of the treatment. However, many countries still not used glyburide and metformin as alternative drugs in the treatment of GDM. Thus, the limitations of our review were a few included studies which compared the effectiveness of glyburide and metformin and small sample size (n=421).

Furthermore, one study with potential to be included in our review had to be excluded due to the inability to find full-text article. Therefore, publication bias was unavoidable.

COMPARISON WITH OTHER STUDIES

To our knowledge, this was the first published systematic reviews on the use of glyburide compared to metformin in GDM. We found guidelines of GDM in some countries showed that pregnant women with GDM whose FBG were not controlled by diet and exercise should be treated with insulin injection.[3,5-8] In some guidelines reported that oral hypoglycemic agents (e.g. metformin, glyburide) can be used as a second line of therapy instead of insulin.[24-28] Moreover, we found one narrative review about oral hypoglycemic agents for GDM treatment.[20] The review reported that glyburide and metformin can be used in GDM as same as insulin. Maternal weight gain had the same result as our study but failure rate in control maternal FBG levels occurred twice as often among users of metformin compared to those taking glyburide.[20] Unlike our study, there was not significantly different between the two groups.

CONCLUSION AND IMPLICATION

In summary, this meta-analysis showed that using glyburide and metformin as oral hypoglycemic agents to treat women with GDM was not significantly different in control maternal FBG level. Therefore the limited number of patients included in this meta-analysis, further RCT including more participants with adequate power to assess the effects of glyburide and metformin for pregnant women with GDM are needed not only to confirm the result of our study but also to support the oral hypoglycemic agents to be used as the alternative drug in management of GDM instead of insulin. Complications from using these oral hypoglycemic agents and health service costs should be evaluated in the further study aside from the their efficacies.

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