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The Effectiveness of Glyburide Compared to Insulin in the Management of Gestational Diabetes Mellitus: A Systematic Review

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Abstract

Background: Insulin therapy has been the mainstay in managing women with gestational diabetes mellitus (GDM), but some disadvantages of insulin have led to the use of glyburide, which is inexpensive in some countries, to manage GDM. However, there has been debate over its effectiveness, efficacy and safety when compared to insulin for maternal glycaemic control, and some adverse neonatal outcomes in GDM. Method: A systematic review of eight randomised controlled trial (RCT) studies was undertaken to compare glyburide and insulin. Studies involving 849 participants were included in the quantitative analysis. Results: There was no significant difference between glyburide and insulin in maternal fasting (P = 0.09; SMD: 0.13; 95% CI: −0.02 to 0.28) and postprandial (P = 0.45; SMD: 0.05; 95% CI: −0.09 to 0.19) glycaemic control and glycosylated haemoglobin (P = 0.35; SMD: 0.08; 95% CI: −0.08 to 0.24). When compared with insulin, glyburide had an increase risk ratio (RR) for neonatal hypoglycaemia (P = 0.0002; RR: 2.27; 95% CI: 1.47 to 3.51) and large for gestational age babies (P = 0.03; RR: 1.60; 95% CI: 1.06 to 2.41). Estimation of standard mean difference shows that neonatal birth weight was significantly higher in subjects receiving glyburide than in the insulin group (P = 0.002; SMD: 0.21; 95% CI: 0.08 to 0.35). Conclusions: Glyburide was seen to be clinically effective and a safer alternative to insulin for maternal glycaemic control in GDM women. It is affordable, convenient and requires no comprehensive educative training at the time of initiation of therapy. However, its adverse outcomes—neonatal hypoglycaemia, high neonatal birth weight and large for gestational age babies—call for careful monitoring of GDM patients for any need for supplemental insulin.

Keywords

Gestational Diabetes Mellitus, Glyburide, Insulin

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1. Introduction

Globally, gestational diabetes mellitus (GDM) is associated with about 14% of complicated pregnancy cases per annum. Amongst the common complications are macrosomia, haemorrhage, hypertensive disorder, stillbirth and type 2 diabetes mellitus (T2DM). The World Health Organisation (WHO) prioritised improvement in maternal health, including management of GDM, as one of its Millennium Development Goals (MDG) [1] [2]. However, the rapid rise in the incidence of GDM reduces the likelihood of attaining this goal [3].

There is a wide range of therapeutic measures to control GDM, including dietary changes and physical activities either alone or in combination, but insulin therapy remains the technique of choice after diet and physical exercise [4]-[6]. A majority of women who use diet and physical activities incorporate either insulin or oral hypoglycaemic agents in their treatment plan [4] [5]. However, the disadvantages of insulin use—such as multiple daily injection sites, maternal weight gain, risk of hypoglycaemia, cost of drugs, handling and storage, and the modifications to drug administration based on body mass index, glucose level and lifestyle [6]—have led to the consideration of sulfonylurea (oral hypoglycaemic agents) as a preferred alternative [6].

The formerly traditional use of sulfonylurea drugs in pregnancy has now been discouraged due to the risks of fetal teratogenicity and neonatal hypoglycaemia as a result of its 10% - 16% maternal-to-fetal transfer rate [4] [5]. By contrast, glyburide has been found to have low risk of infant growth and teratogenicity, minimal *in vitro* foetal transfer rate, and safer *in vivo* fetal-to-maternal transfer rate at a dose of up to 20 mg per day [4]. Furthermore, it is an inexpensive oral medication compared to insulin [7] and requires no special storage condition nor special training to administer.

There have been several RCTs that compared glyburide and insulin in the management of GDM. However, most lack statistical power. Therefore, this systematic review aims to provide a pooled estimate of RCTs comparing the relative effectiveness of glyburide and insulin on maternal glycaemic control and neonatal outcomes.

2. Methods

2.1. Search Strategy

We performed a systematic review and meta-analysis in accordance with the standards set by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISM) checklist (**Figure 1**). We carried out an extensive electronic database search of published and unpublished RCTs comparing glyburide and insulin in the management of GDM. We searched Cochrane Library (Issue 6, 2014), PubMed, CINAHL Plus with Full Text, MEDLINE, BioMed Central, Health Technology Assessment (HTA), and Latin American and Caribbean Health Sciences (LILIACS) between the years 2000 and 2014. We use the key words “glyburide” AND “insulin” AND “management of gestational diabetes mellitus”, and also “Glyburide” AND “GDM”. We also hand-searched references of retrieved articles to identify studies not captured by our primary search strategy.

2.2. Study Selection

Figure 1 illustrates how the PRISM checklist was used to document the process of study selection [8]. We included randomised controlled trial studies comparing GDM patients treated with glyburide versus GDM patients treated with insulin. The inclusion criteria were: a) participants were patients with GDM irrespective of their age, gravidity and parity, b) study design was RCT, c) intervention entails studies that compare glyburide and insulin medication, and d) outcome entails studies that measure one or more of these endpoints: 1) maternal fasting plasma glucose (FBS), 2) 2-hour postprandial plasma glucose (OGTT), 3) maternal glycosylated haemoglobin (HbAIC), 4) neonatal hypoglycaemia (NH), and 5) large-for-gestational age baby (LGA) and birth weight at delivery (BW). Case control studies, observational studies, retrospective studies, and women with pre-gestational diabetes and type 2 diabetes were excluded.

2.3. Data Extraction and Quality Assessment

Data were extracted in duplicate by two independent reviewers (J.O. and M.A.M.) [9]. **Table 1** shows the data that were abstracted regarding the baseline characteristics of the included studies [9]. These included: year of publication, study design, country of study, study size, comparison patient characteristics, glyburide group requiring insulin, dose of glyburide, dose of insulin, duration of study, and loss to follow up.

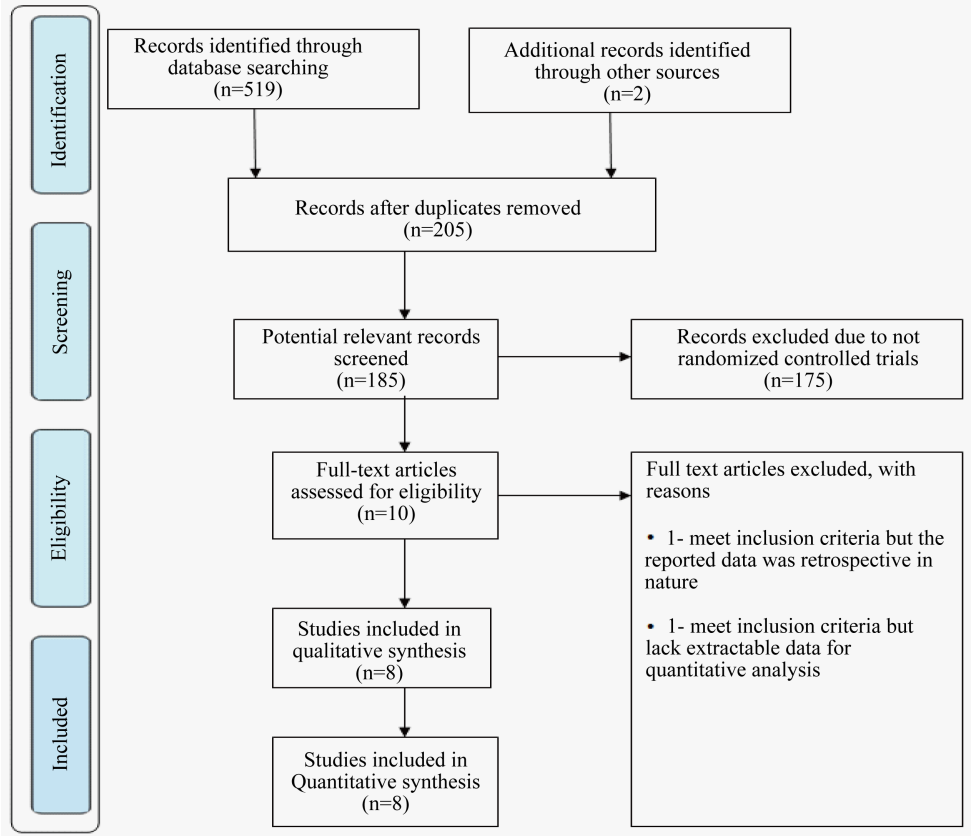


Figure 1. Search strategy for randomised controlled trials included in this study.

Data were extracted and appraised in accordance to the methodological quality, outcomes measures and predetermined criteria relevant to the research questions. **Figure 2** illustrates how the characteristics for quality appraisal such as random sequence generation, blinding treatment for subjects and personnel, outcome assessments, completeness of outcomes data, objective reporting and risks of potential bias were evaluated using Review Manager (Revman) Version 5.1 (CDSR) [10], high risk of selection bias was detected in one of the studies [6] this was taken into consideration in analysis and interpretation of findings. Furthermore, for such a small study it was concluded that including it will not influence the overall outcome of the study.

2.4. Statistical Analysis

All data analyses were performed using Review Manager 5.1 (Nordic Cochrane Centre). The quantitative analyses were performed using the fixed effect model. For continuous outcomes, standardised mean differences (SMD) and 95% confidence intervals (CI) were calculated. For the dichotomous outcomes, risk ratio (RR) and 95% CI were calculated.

The heterogeneity was estimated statistically by the Chi-squared test ($p > 0.1$, which suggested a lack of heterogeneity for continuous variables) and I-squared test value ($I^2 > 75\%$ was regarded as great heterogeneity). In addition, homogeneity of studies was graphically assessed using visual interpretation of forest plots.

3. Results

As represented in **Figure 1**, a total of 185 potential articles were screened. Eight articles fulfilled all the inclusion criteria and were included in the systematic review. The characteristics and quality assessments of the studies are presented in **Table 1** and **Table 2**. Overall quality and each study assessment are represented in **Figure 2**. Both glyburide and insulin subjects were matched for age, body mass index, gestational weeks, fasting and 2-hour postprandial blood glucose, and glycosylated haemoglobin level at the time of entry to the study.

Table 1. Characteristics and quality assessment of included studies.

First author (year of publication)	Study design	Country of study	Study size/comparison		Patient characteristics	Glyburide group requiring insulin (n)	Dose of glyburide	Dose of insulin	Duration of study	Loss to follow up
			Glyburide (n)	Insulin (n)						
Langer *et al*. 2000 [1]	Randomised controlled trials	Texas, United States	201	203	404 GDM women between 18 and 40 years old	8	9 ± 6 mg/day	85 ± 48 units/day	Not stated	undeclared
Bertini *et al*. 2005 [2]	Randomised controlled trials	Joinville SC, Brazil	24	27	70 GDM women	5	5 - 20 mg/day	0.7 - 0.9 units/kg	9 months	undeclared
Anjalakshi *et al*. 2006 [3]	Randomised controlled trials	Chennai, India	10	13	26 GDM women	0	0.625 mg and dose titrated once a week	0.1 units/kg and increased weekly	Not stated	Greater than 10%
Silva *et al*. 2007 [4]	Randomised controlled trials	Joinville SC, Brazil	32	36	68 GDM women, minimum 18 years old	6	5 - 20 mg/day	0.7 - 0.9 units/kg	1 year and 5 months	Not significant
Ogunyemi *et al*. 2007 [5]	Randomised controlled trials	Los Angeles, United States	48	49	97 GDM women	3	5 mg	60 units	3 years	Less than 10%
Lain *et al*. 2009 [6]	Randomised controlled trials	Pittsburgh, United States	41	41	99 GDM women	1	8 ± 6.7 mg/day	51.3 ± 33.4 units/day	3 years	Greater than 10%
Mukhopadhyay *et al*. 2012 [7]	Randomised controlled trials	Kolkata, India	30	30	60 GDM women	0	2.5 mg and increased weekly to a maximum dose of 20 mg/day	0.7 units/kg three times a day and increased when necessary	1 year	undeclared
Anjali *et al*. 2013 [8]	Randomised controlled trials	New Delhi, India	32	32	64 GDM women	2	5 ± 1.9 mg/day to a maximum dose of 20 mg/day	33.8 ± 22.9 units/day to a maximum dose of 84 units/day	1 year	Less than 10%

A total of 849 subjects were included in these eight studies (418 on glyburide and 431 on insulin).

3.1. Maternal Glycaemic Control

The data on fasting blood glucose were reported in five studies (**Figure 3(a)**). The average blood glucose was slightly lower in the insulin group than the glyburide group, but the difference was not statistically significant (P = 0.09; SMD: 0.13; 95% CI: −0.02 to 0.28) and the 95% confidence interval crosses the line of no effect.

The mean postprandial blood glucose was reported in seven studies (**Figure 3(b)**). There was no significant difference in postprandial glycaemic control between glyburide and insulin (P = 0.45; SMD: 0.05; 95% CI: −0.09 to 0.19), although the overall estimated effects slightly favours insulin groups compared to glyburide with the 95% confidence interval crossing the line of no effect.

Glycosylated haemoglobin control was reported in four studies (**Figure 3(c)**) and no statistical difference was observed between the two treatment groups (P = 0.35; SMD: 0.08; 95% CI: −0.08 to 0.24), although again the overall estimated effects slightly favours insulin and the 95% confidence interval crosses the line of no effect.

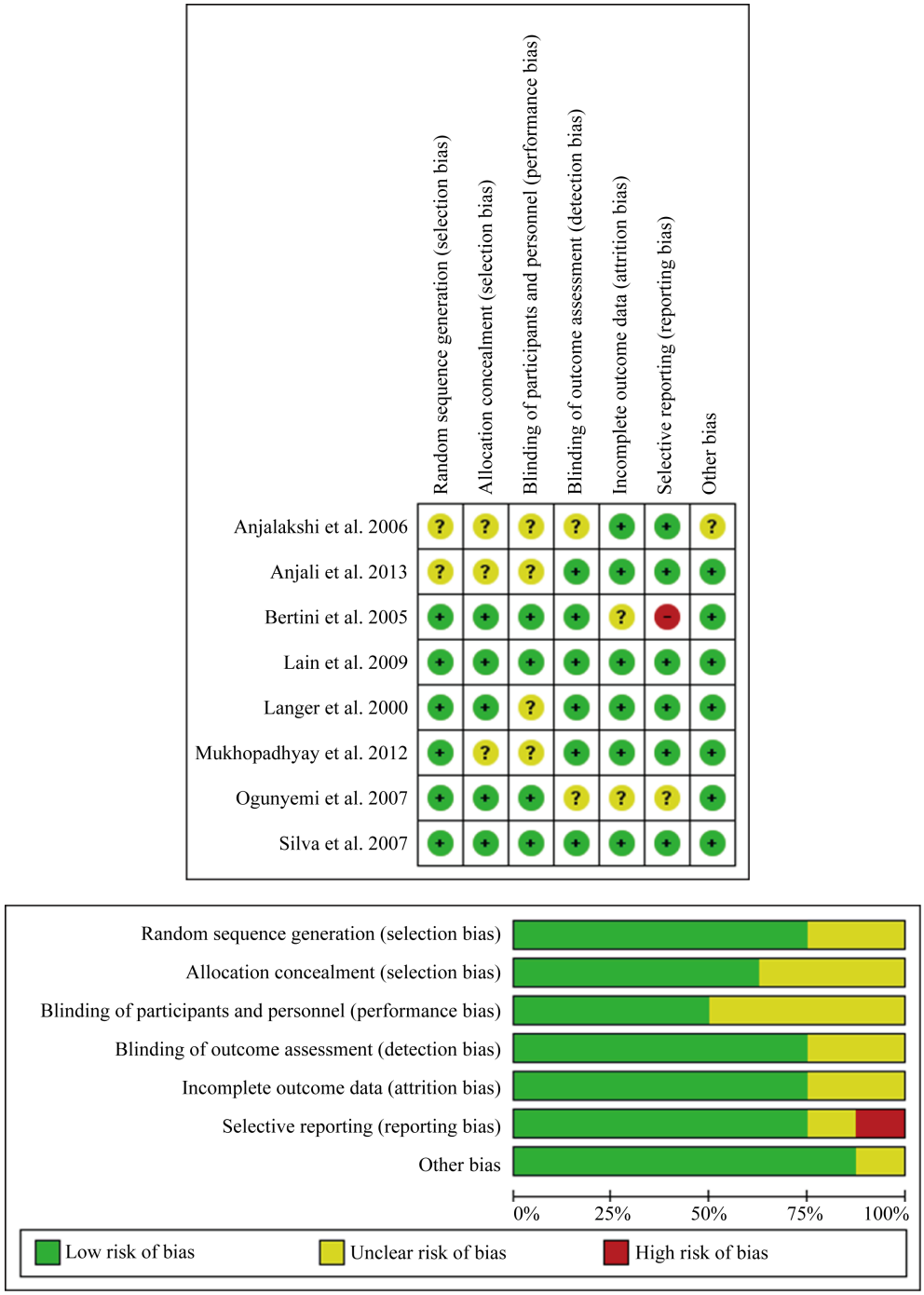


Figure 2. Summary of systematic review authors' judgement on methodological quality of included studies.

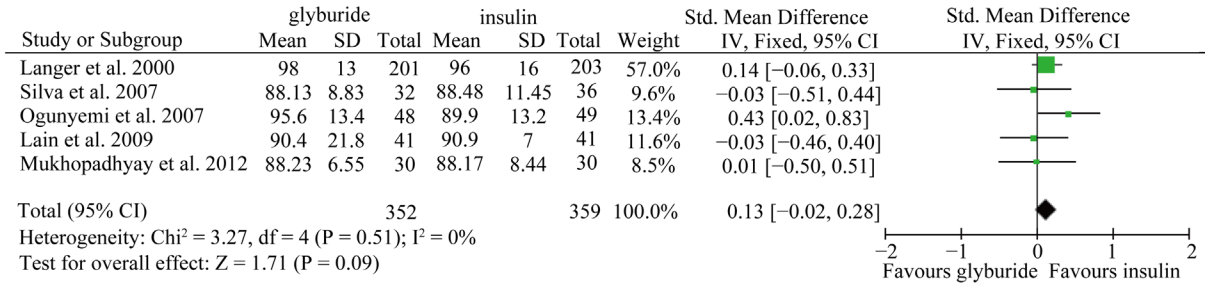
3.2. Neonatal Outcomes

Neonatal birth weight was reported in eight studies (**Figure 4(a)**). There was a significant difference in the neonatal birth weight between glyburide and insulin groups (P = 0.002; SMD: 0.21; 95% CI: 0.08 to 0.35). The overall estimated effects favours insulin, indicating neonatal birth weight was significantly higher in patients receiving glyburide than those receiving insulin. The 95% confidence interval does not cross the line of no effect.

Neonatal hypoglycaemia was observed in seven studies, defined as when the mean neonatal blood glucose

Table 2. Summary of systematic review analysis results.

Outcome	Included studies	Included participants	Heterogeneity Chi-squared (p)	I-Squared (%)	95% CI	P
Maternal fasting plasma glucose control	5	711	3.27 (p = 0.51)	0.0	SMD 0.13 (−0.02 to 0.28)	0.09
Maternal postprandial plasma glucose control	7	798	14.41 (p = 0.03)	58	SMD 0.05 (−0.09 to 0.19)	0.45
Glycosylated haemoglobin control	4	584	5.51 (p = 0.14)	46	SMD 0.08 (−0.08 to 0.24)	0.35
Neonatal birth weight	8	849	6.84 (p = 0.45)	0.0	SMD 0.21 (0.08 to 0.35)	0.002
Neonatal hypoglycaemia	7	829	6.88 (p = 0.33)	13	RR 2.27 (1.47 to 3.51)	0.0002
Large for gestational age	5	661	9.99 (p = 0.04)	60	RR 1.60 (1.06 to 2.41)	0.03



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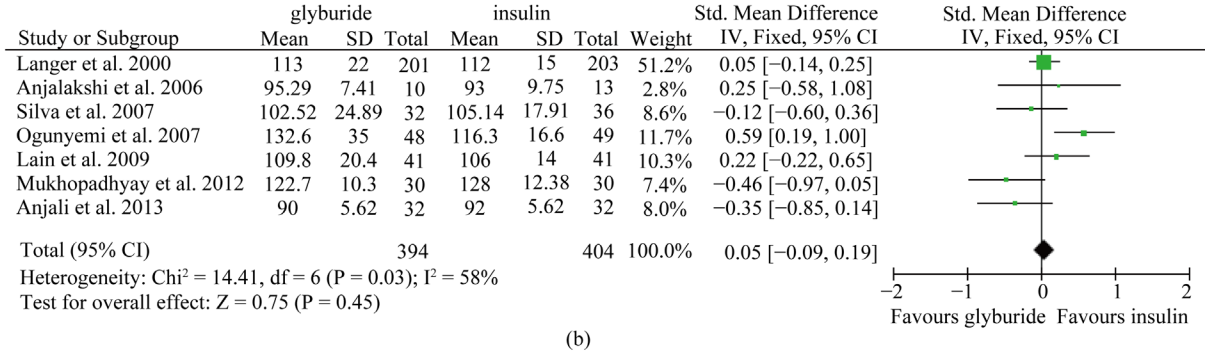

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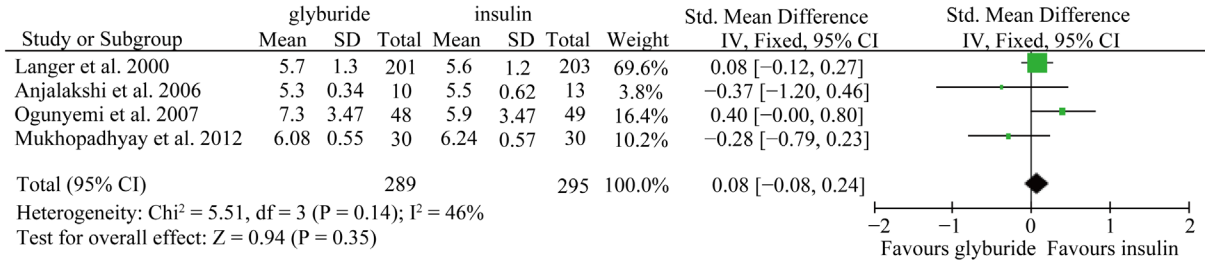
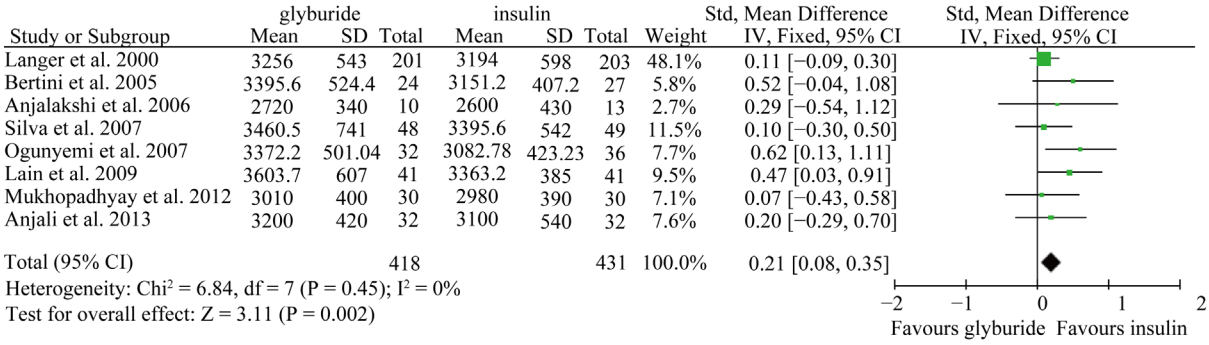


(c)

Figure 3. (a): Data on fasting blood glucose in insulin group compared with the glyburide group; (b): Mean postprandial blood glucose between glyburide and insulin; (c): Glycosylated haemoglobin control.

value was less than 40 mg/dl (**Figure 4(b)**). Incidence of cases of neonatal hypoglycaemia was significantly greater among neonates born from GDM women treated with glyburide than those treated with insulin. There was a statistically significant difference between the two treatments groups (P = 0.0002; RR: 2.27; 95% CI: 1.47 to 3.51), and the 95% confidence interval does not cross the line of no effect.



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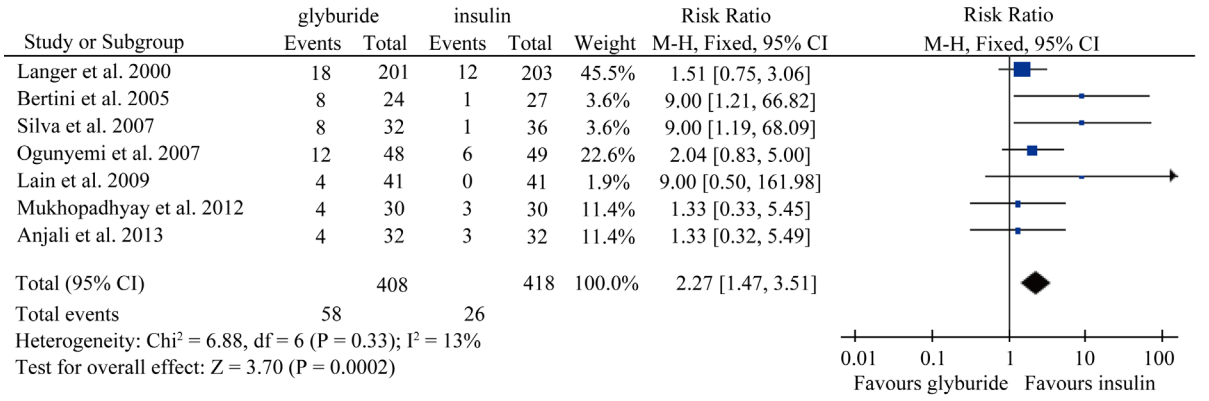

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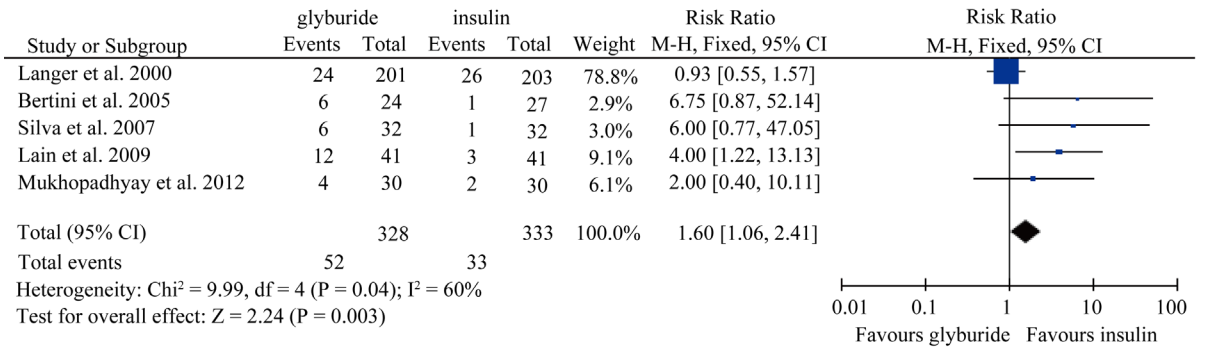

(c)

Figure 4. (a): Neonatal birth weight between glyburide and insulin groups; (b): Neonatal hypoglycaemia among neonates born from GDM women treated with glyburide compared to insulin groups; (c): Incidence of large for gestational age babies in glyburide groups compared to insulin groups.

Neonatal birth weight at or above the 90th percentile was considered large for gestational age and was reported in five studies (**Figure 4(c)**). There was a significant difference between the two groups treated with glyburide and insulin (P = 0.03; RR: 1.60; 95% CI: 1.06 to 2.41), with incidence of large for gestational age babies significantly higher in glyburide groups. The 95% confidence interval does not cross the line of no effect.

Chi-squared test value $p > 0.1$ suggested a lack of heterogeneity for continuous variables.

I-squared test value $I^2 > 75\%$ was regarded as great heterogeneity.

4. Discussion

Eight RCT studies were included in the systematic review, aiming at comparing glyburide and insulin for the management of GDM (**Figures 3(a)-(c)**). The results showed a P value of (P = 0.09; SMD: 0.13; 95% CI: −0.02 to

0.28 in maternal fasting blood glucose, 2-hours postprandial glucose level and glycosylated haemoglobin level, which could be interpreted as no strong evidence that the intervention has an effect. However, it has be noted that this study presented two P values one represented summary effect is from Z test and the other from χ^2 related to the degree of heterogeneity. In both cases P values in this study, they have been greater than arbitrary $P \geq 0.05$. This could be attributed to the fact that most of the studies included in this review were small. It has been established that in small meta-analysis greater P values are common, however, this should not be taken to imply that an intervention has no important benefits.

Figure 3(a) indicates SMD = 0.13 in favour of glyburideoverinsulin in the control of blood glucose. These findings compare favourably with previous studies thatcompared glyburide and insulin therapy in management of GDM [4] [5]. Langer, Conway, Berkus *et al*. [5] went further, explaining that glyburide reduces hyperglycaemia by increasing peripheral glucose utilisation, decreasing hepatic gluconeogenesis and increasing insulin sensitivity through an increase in intracellular calcium in the beta cell and concurrently stimulating insulin productivity [5].

The analysis revealed that there was a direct relationship between postprandial glycaemic level and pregnancy outcomes (**Figures 4(a)-(c)**) [11]-[16]. Consistent with previous studies which showed that glyburide was effective on postprandial glycaemic control [17] [18]; seven studies [11]-[16] showed no significant difference between patients treated with insulin and those treated with glyburide (**Figures 4(a)-(c)**).

With regard to neonatal birth weight, this study showed significant difference between the two groups treated with glyburide and insulin (P = 0.03; RR: 1.60; 95% CI: 1.06 to 2.41), with incidence of large for gestational age babies significantly higher in glyburide groups (**Figure 4(c)**). These findings were inconsistent with the previous observational study conducted by Chmait, Dinise and Moore [19] which showed no statistical differences between these two treatment groups [19].

Furthermore, this study showed a positive RR = 1.6 (**Figure 4(c)**) of large for gestation age babies among GDM women treated with glyburide compared to those treated with insulin. These findings can be compared with a retrospective cohort study conducted by Cheng *et al*. [20] which also indicated a greater likelihood of higher birth weight of infants above 4000 g for GDM mothers treated with glyburide compared to insulin treatments.

While glyburide appears to be a promising alternative to insulin in treating GDM, there have been several prominent side effects associated with it. Several studies [4] [20] found that there is a 2.27 times greater likelihood of neonatal hypoglycaemia in mothers treated with glyburide compare to insulin treatments. In addition there are other reported side effects such as respiratory distress, jaundice, skin allergy, anaphylactic reactions, elevated liver enzymes, haematological disorder and low visual acuity due to imbalanced glycaemic level [20]. The retrospective cohort study conducted by Cheng *et al*. [20] revealed that neonates born to mothers treated with glyburide have a greater propensity to be admitted to NICU compared to those managed using insulin.

5. Conclusion

In summary, glyburide is clinically as effective as insulin when used alone in the management of GDM, and provides a best efficacy and safety option when supplemented with insulin for those patients unresponsive to glyburide.

Competing Interests

The authors declare that they have no competing interest.

Authors' Contributions

J.O. originated the research idea, performed the analysis and drafted the manuscript, while M.A.M. provided methodological expertise, assisted with analysis, and shaped and prepared the manuscript for publication. Both authors read and approved the final manuscript.

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