International Journal of Science and Healthcare Research
Vol.7; Issue: 3; July-Sept. 2022
Website: ijshr.com
Systematic Review *ISSN: 2455-7587*

Metformin Versus Glyburide in the Management of Gestational Diabetes; A Systematic Review and Meta-Analysis

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DOI: https://doi.org/10.52403/ijshr.20220746

ABSTRACT

Background: Globally gestational diabetes remains one most common medical problem facing a significant proportion of women in pregnancy. Understanding safe therapeutic and management measures is imperative to inform effective and sound decision and judgment for clinicians and concerned groups.
Aim: This review aimed to compare the effectiveness and safety of Metformin versus Glyburide in managing gestational diabetes mellitus (GDM).
Methods: Cochrane Library, PUBMED, MEDLINE and LILACs were subjected to literature search for randomized controlled trials addressing the primary aim of this study. The Key used for the search strategy was: "Metformin", "Glyburide", 'Gestational Diabetes" and other varying terms from Medical subject Headings. The review systematized a PRISMA Checklist and demonstrated Meta analyzed studies mathematically on weight gain after using glyburide and metformin during and after pregnancy, fasting blood glucose, birthweight and postprandial blood glucose.
Results: Neonatal hypoglycaemia, mode of delivery, birth weight, Apgar score, weight during and after pregnancy, postprandial blood glucose and requirement for intensive care were all assessed in the study. In 60% of the studies safety and efficacy of glyburide and metformin diabetes management showed no significant difference. From postprandial blood glucose (P=0.217), birth weight (p=0.194), and fasting blood glucose (p=0.821) revealed no statistical differences between the medications in the meta analysis conducted. However, on the other hand, weight growth during pregnancy among patients revealed significant variations (p=0.036).
Conclusion: Both metformin and glyburide showed no differences in safety and efficacy considering birth weight, fasting blood glucose and postprandial blood glucose. However, in babies of women treated with metformin, problems associated with neonates such as respiratory issues and hypoglycemia and also increase in weight during pregnancy or gestation are more less common and lower.

Keywords: Diabetes, Therapy, Metformin, Glyburide, Gestational Diabetes Mellitus

INTRODUCTION

Pregnancy-related production of placental enzymes (which help break down insulin) and hyperglycemic hormones has already been identified as a diabetes risk factor [1,2]. This increases tissue production and resistance, which might result in pancreatic cell dysfunction [2]. Gestational diabetes mellitus (GDM), various degrees of glucose intolerance, and other outcomes are some of

them. [3], highlighted that this condition, which manifests during pregnancy and has no recognised cause, poses risks to the mother, foetus, and baby. The second or third trimester of pregnancy is when the condition is often first detected.

Depending on who is examined and the diagnostic standards used, [4] estimated that gestational diabetes mellitus (GDM) affects anywhere between 1% and 35% of pregnant women worldwide. According to [5], early detection and appropriate treatment can considerably reduce the damage and repercussions on both the mother and the foetus. In order to moderate glycemic levels, lifestyle changes are employed to start the treatment process. However, when they are insufficient, prescription therapy is required [2,6]. [17] advises starting therapy for GDM with insulin (ADA). Additionally, despite the fact that insulin is administered initially, [18] thinks oral hypoglycemic medications are just as effective as insulin because no research has been done on the long-term effects of these medications during pregnancy [7, 5].

It has been shown to be effective to treat type 2 diabetes in non-pregnant women with glyburide and metformin [4]. Such an association may be a realistic alternative for pregnant women with gestational diabetes who have glucose levels that continue to be over the upper limit beyond what is allowed by oral monotherapy [1]. This treatment can eliminate the discomfort of subcutaneous injections, the high cost of insulin therapy, as well as any potential drawbacks like uncertainty about the proper method of use, disregarding the strategy, or even difficulty tolerating insulin as an aggressive form of treatment for the body [8, 9]. This supports the necessity for this study to compare the safety and effectiveness of metformin with glyburide in the treatment of gestational diabetes.

Aims and Objectives

The review aimed to compare metformin versus glyburide in the management of gestational diabetes mellitus.

METHODS

The methodology of this study adopted a PRISMA Checklist for reporting the systematic review and Meta analysis of the study.

Only studies published in the English language were taken into consideration for inclusion.

The search terms for this study is stated in table 1 below

Table 1: Search Strategy

Terms	Joining Type	Database	Search fields
Metformin	N/A	MEDLINE, PUBMED	All fields
Glyburide	N/A	MEDLINE, PUBMED	All fields
Gestational Diabetes	N/A	MEDLINE, PUBMED	All fields
Efficacy	N/A	MEDLINE, PUBMED	All fields
Safety	N/A	MEDLINE, PUBMED	All fields
#1, #2, #3, #4, #5	AND	MEDLINE, PUBMED	N/A
Placebo	N/A	MEDLINE, PUBMED	All Fields
#6, #7	AND	MEDLINE, PUBMED	All fields
Randomized Control Trials	N/A	MEDLINE, PUBMED	All fields
#8, #9	AND	MEDLINE, PUBMED	N/A

Search was conducted at the following databases,

i. MEDLINE,
ii. PUBMED,
iii. Latin America Health Science Literature (LILACS)
iv. Cochrane Library

In other to obtain studies of high scientific evidence and clinical relevance, only studies of randomized controlled trial (RCT) design were added in the study.

The PICO framework of the study consisted of the following;

Population: Women aged 18 years and above and between 11-36 weeks gestational age having gestational diabetes having

unable to adopt lifestyle changes in controlling blood glucose.

Intervention: Metformin (Monotherapy)

Control: Glyburide (Monotherapy)

Outcomes: Maternal Outcomes include Fasting blood glucose, Pregnancy weight gain, postprandial blood, mode of delivery. Neonatal outcomes include; Apgar Score, Macrosomia, Neonatal hypoglycemia and intensive care.

Analysis and Synthesis

With the heterogeneity of studies taken into account, a random and fixed effect analysis was performed using Revman software on a meta-analysis of fasting blood glucose, gestational weight, blood glucose, postprandial blood glucose, and birth weight. The 95% confidence interval for each research was determined, and a composite of chosen studies was then calculated. Additionally, the study's mean and standard deviation were evaluated, and p values (p0.05) were utilised to determine significance.

RESULTS

A total of 342 papers were found after searches were conducted on numerous databases (MEDLINE, PUBMED, LILACS, and Cochrane Library) to find suitable research. These studies included the phrases metformin, glyburide, and gestational diabetes in their search criteria. A total of 5 papers were included in the meta-analysis of this study after being eligible for inclusion had been determined by screening and reviewing abstracts and full texts [10, 11, 12, 13, 14]. The PICO framework of the study is illustrated below in figure 1.

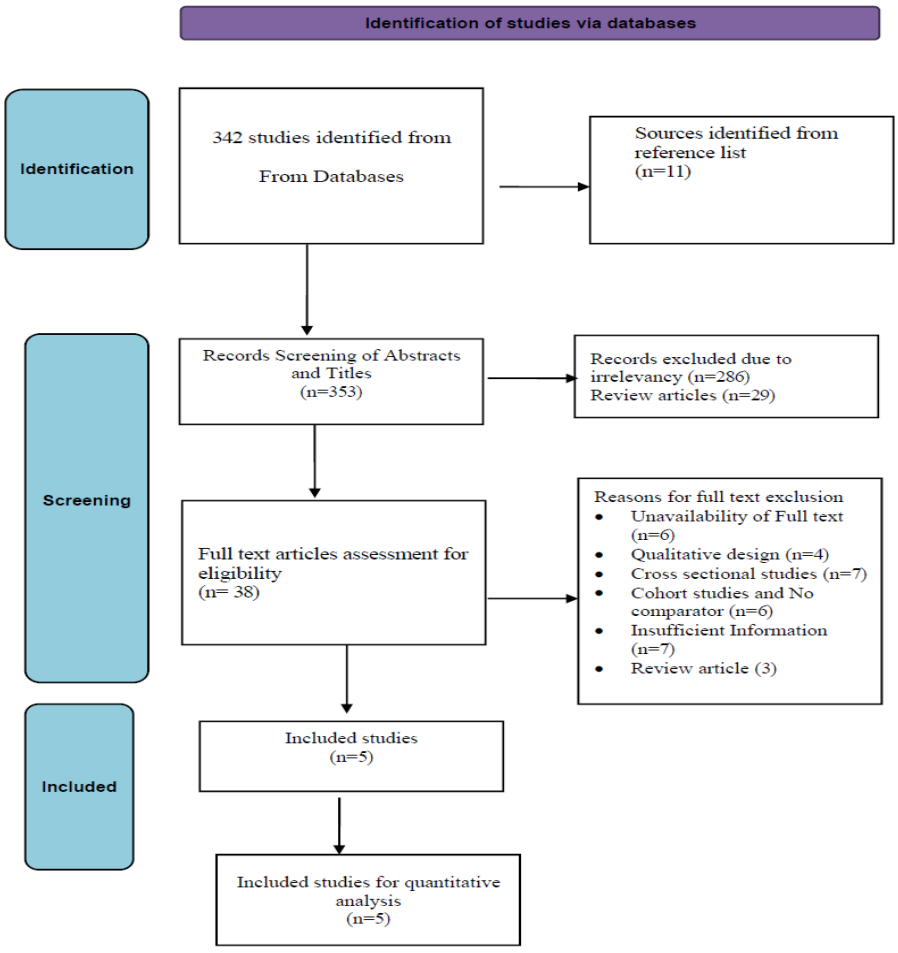


Figure 1: Flow Chart for PRISMA

In all, 684 women between the ages of 11 and 36 weeks of pregnancy participated in the study. However, there was no discernible difference between glyburide and metformin in terms of safety and effectiveness across three investigations [10, 11, 13]. As seen in Table 2 from four of the five trials, neonatal problems were much less prevalent in babies of mothers who received metformin medication [10, 11, 13, 14].

Table 2: Characteristics of included studies in metformin and glyburide use in gestational diabetes management

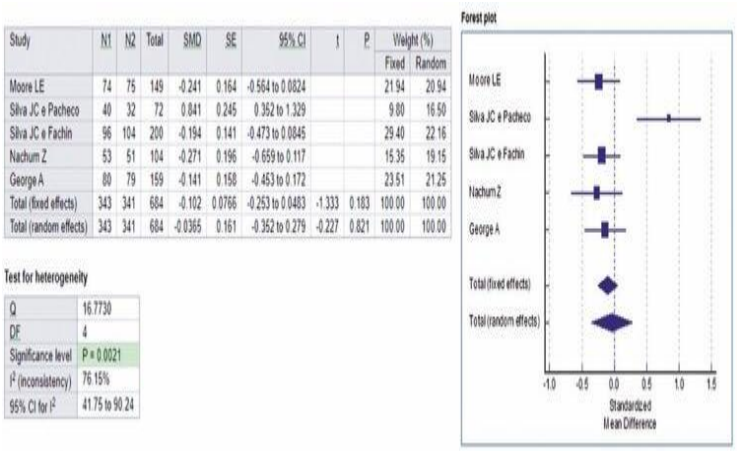
Included Studies	Interventions	Patients	Post-prandial blood glucose	Macrosomia	Neonatal hypoglycemia	Weight gain in pregnancy	Fasting blood glucose	Need for intensive care	Birth weight	Apgar score	Need for Cesarean section
[13]	GG: 5-20mg/day MG:500-2500mg/day	72 women (MG-32) (GG-40)	p=0.10 M=G*	>4kg p=0.24 M=G*	p=0.89 M=G*	p=0.02 M>G+	p=0.15 M=G*	p=0.23 M=G*	p=0.36 M=G*	In 1': p=0.57 In 5': p=0.24 M=G*	p=0.91 M=G*
[14]	GG: 2.5-15mg/day MG:500-2500mg/day	159 women (MG-79) (GG-80)	p=0.28 M=G*	>3.7kg p=0.73 M=G*	p=0.09 M>G+	N/R	p=0.37 M=G*	N/R	N/R	N/R	N/R
[11]	GG: 2.5-20mg/day MG:850-2550mg/day after meals	104 women (MG-51) (GG-53)	p=0.3 M=G*	>4,000g p=0.6 M=G*	p=0.09 M>G+	p=0.8 M=G*	p=0.2 M=G*	N/R	p=0.6 M=G*	Apgar score>7 p= 1 M=G*	p=0.7 M=G*
[12]	GG: 5-20mg/day MG:500mg-2g/day	149 women (MG-75) (GG-74)	p=0.24 M=G*	N/R	p=0.32 M=G*	N/R	p=0.23 M=G*	p=0.02 M=G*	p=0.02 M>G+	N/R	p=0.02 G>M++
[10]	GG: 5-20mg/day MG:1000-2500mg/day	200 women (MG-104) (GG-96)	p=0.98 M=G*	N/R	p=0.81 M=G*	p=0.04 M>G+	p=0.18 M=G*	p=0.94 M=G*	p=0.01 M>G+	In 1': p=0.56 up to 5': p=0.50 M=G*	p=0.88 M=G*

MG= Metformin Group
GG= Glyburide Group
** MG and GB use does not have a significant Difference between them at outcome*
+Metformin MG was superior at outcome compared to Glyburide GB'
++ Glyburide GB was superior at outcome compared to Metformin MG

Meta-analysis of Studies

For the purposes of evaluating newborn weight, postprandial glucose, and fasting glucose in both groups for intervention, all the studies included in these analyses provided information that was adequate [10, 11, 12, 13, 14]. Three studies offered information on maternal weight growth that could be compared [10, 11, 13].

Based on Meta analysis performed on the 684 pregnant patients that participated in the study regarding fasting blood glucose, a standardized mean difference of -0.1.2 and -0.0365 was obtained for reported and random effects respectively. The forest plot in figure 2 below explained the glyburide and metformin comparative effect analysis on fasting blood glucose among pregnant ladies having gestational diabetes and it also indicated the statistical differences between these drugs exerted on fasting blood glucose. Analysing the studies on the basis of heterogeneity showed that it was significant (p=0.0021). Also possible effects of glyburide was investigated in the meta-analysis of all the studies in managing gestational diabetes with doses per day of 2.5-20mg compared to 500-2550mg per day in metformin.



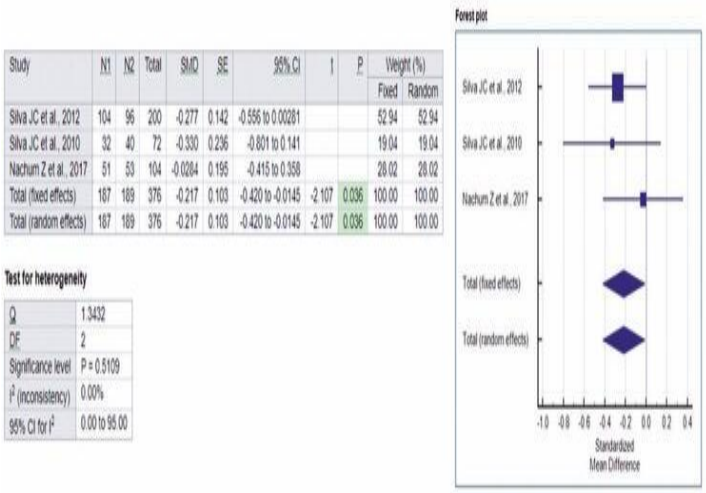
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Moore LE	74	75	149	-0.241	0.164	-0.564 to 0.0824			21.94	20.94
Silva JC e Pacheco	40	32	72	0.841	0.245	0.362 to 1.329			9.80	16.50
Silva JC e Fachin	96	104	200	-0.194	0.141	-0.473 to 0.0845			29.40	22.16
Nachum Z	53	51	104	-0.271	0.196	-0.659 to 0.117			15.35	19.15
George A	80	79	159	-0.141	0.158	-0.453 to 0.172			23.51	21.25
Total (fixed effects)	343	341	684	-0.102	0.0766	-0.253 to 0.0483	-1.333	0.183	100.00	100.00
Total (random effects)	343	341	684	-0.0365	0.161	-0.362 to 0.279	-0.227	0.821	100.00	100.00

Test for heterogeneity

Q	16.7730
DF	4
Significance level	P = 0.0021
I^2 (inconsistency)	76.15%
95% CI for I^2	41.75 to 90.24

Figure 2: Standardized Mean difference forest plot for fasting blood glucose (Fixed and random Effect; 95% CI).

Meta analysis was performed in four articles to ascertain the postprandial glycemia and based on random and fixed effects, -0.00365 and -0.102 was the standardized mean differences respectively [10, 11, 13, 14]. Also, effect of glyburide and metformin on postprandial glycemia of the pregnant women was illustrated in the forest plot in figure 3 below. It revealed that between these drugs on postprandial glycemia, there was no statistical difference seen (p=0.2014). however, from doses of 500-2550mg per day of metformin compared to 2.5-20mg of glyburide in managing gestational diabetes, there was possibility of effects in the included meta-analysis



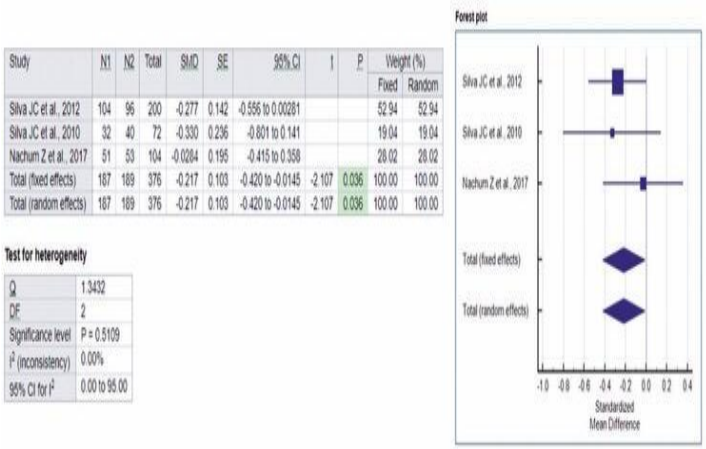
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Silva JC et al., 2012	104	96	200	-0.277	0.142	-0.556 to 0.00281			52.94	52.94
Silva JC et al., 2010	32	40	72	-0.330	0.236	-0.801 to 0.141			19.04	19.04
Nachum Z et al., 2017	51	53	104	-0.0284	0.195	-0.415 to 0.358			28.02	28.02
Total (fixed effects)	187	189	376	-0.217	0.103	-0.420 to -0.0145	-2.107	0.036	100.00	100.00
Total (random effects)	187	189	376	-0.217	0.103	-0.420 to -0.0145	-2.107	0.036	100.00	100.00

Test for heterogeneity

Q	1.3432
DF	2
Significance level	P = 0.5109
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 95.00

Figure 3; Standardized Mean difference forest plot for weight gain (Fixed and random Effect; 95% CI).

Three studies from this review provided sufficient data for the comparison of gestational weight in metformin versus glyburide [10, 11,13]. A total of 367 pregnant patients were in the sample and a meta-analysis showed that for fixed and random effects, -0.217 and -0.217 respectively was the standardized mean differences. In addition, the analysis for glyburide and metformin weight gain effect among pregnant patients with gestational diabetes revealed that metformin was superior to glyburide. Statistical analysis on the homogeneity test of this studies showed that in terms of statistics, there was no notable effect (p=0.5109). However, metformin in doses of 500-2550mg per day in the management of gestational diabetes compared to 2.5-20mg in glyburide was analyzed for the possibility of effects in figure 4.



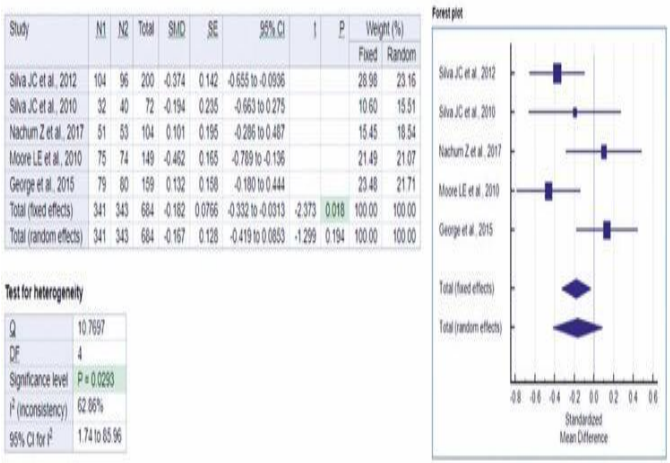
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Silva JC et al., 2012	104	96	200	-0.277	0.142	-0.556 to 0.00281			52.94	52.94
Silva JC et al., 2010	32	40	72	-0.330	0.236	-0.801 to 0.141			19.04	19.04
Nachum Z et al., 2017	51	53	104	-0.0284	0.195	-0.415 to 0.358			28.02	28.02
Total (fixed effects)	187	189	376	-0.217	0.103	-0.420 to -0.0145	-2.107	0.036	100.00	100.00
Total (random effects)	187	189	376	-0.217	0.103	-0.420 to -0.0145	-2.107	0.036	100.00	100.00

Test for heterogeneity

Q	1.3432
DF	2
Significance level	P = 0.5109
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 95.00

Figure 4; Standardized Mean difference forest plot for gestational weight (Fixed and random Effect; 95% CI).

Again, the five studies showed sufficient data in the analysis of birthweight between the Metformin and glyburide group [10,11,12, 13, 14]. However, for the standardized mean difference for the study, -0.167 and -0.812 was obtained respectively for random and fixed effects (Figure 5). Also, considering the forest plot in figure 5, there was no statistical difference between the drugs on weight gain in the analysis of the effect of glyburide and metformin. Based on the test for heterogeneity, an effective value of p=0.0293 was seen thus demonstrating heterogeneity among the studies. Nevertheless, metformin in doses of 500-2550mg per day in the management of gestational diabetes compared to 2.5-20mg in glyburide was analyzed for the possibility of effects (figure 5).



Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Silva JC et al., 2012	104	96	200	-0.374	0.142	-0.655 to -0.0936			28.98	23.16
Silva JC et al., 2010	32	40	72	-0.194	0.235	-0.663 to 0.275			10.60	15.51
Nachum Z et al., 2017	51	53	104	0.101	0.195	-0.286 to 0.487			15.45	18.54
Moore LE et al., 2010	75	74	149	-0.462	0.165	-0.789 to -0.136			21.49	21.07
George et al., 2015	79	80	159	0.132	0.158	-0.180 to 0.444			23.48	21.71
Total (fixed effects)	341	343	684	-0.182	0.0766	-0.332 to -0.0313	-2.373	0.018	100.00	100.00
Total (random effects)	341	343	684	-0.167	0.128	-0.419 to 0.0853	-1.299	0.194	100.00	100.00

Test for heterogeneity

Q	10.7697
DF	4
Significance level	P = 0.0293
I^2 (inconsistency)	62.86%
95% CI for I^2	1.74 to 85.96

Figure 4; Standardized Mean difference forest plot for Birth weight (Fixed and random Effect; 95% CI).

DISCUSSION

To assess the effectiveness of metformin and glyburide in managing gestational diabetes mellitus, this study's goal was created. According to the study's findings, there were no differences between metformin and glyburide when it came to safety and effectiveness when taking into account birth weight, postprandial blood sugar, and fasting blood sugar [10, 13, 14]. However, prior studies only compared glyburide or metformin and insulin, whereas this study compared metformin and glyburide. Previous studies have evaluated a number of outcomes, including pregnancy-induced hypertension, hypertensive diseases, and preeclampsia [15, 16, 3]. According to this study, the metformin groups gained less weight during pregnancy than the Glyburide groups because of the

drug's action [11, 13]. The failure to regulate glycemic level was found to be 2.1 times larger in the Metformin Group than in the Glyburide Group in the study by [12], with 34.7 percent of patients in the former group needing insulin treatment compared to around 16 percent in the former. [10, 11] discovered that metformin-glyburide association and insulin-metformin association were superior than glyburide in monotherapy, with the latter being the most therapeutically effective.[13] noted that pregnancy has no effect on the pharmacokinetics of metformin but increases the oral clearance rates of glyburide. In comparison to metformin, glyburide also crosses the placental barrier, advancing 50% to 70% of total plasma concentration, which may help to explain why there is a higher risk of newborn hypoglycemia and neonatal illness (such as respiratory distress and injury at birth) when using this medication [11,1, 15]. Additionally, [1] noted that there is insufficient evidence to support the notion that the combination of metformin and insulin provides superior glycemic control, with a lower incidence of glucose excursions to levels below 63.063mg/dL. This makes it appear that the combination of glyburide and metformin is inferior to the combination of insulin and metformin. Numerous systematic studies including meta-analysis found that metformin was superior to insulin because it caused less maternal weight gain, fewer cases of gestational hypertension, and less neonatal hypoglycemia, macrosomia, and postprandial glycemia [3, 16, 15]

Compared to insulin, glyburide was more likely to cause macrosomia, respiratory distress, neonatal hypoglycemia, birth damage, and higher birth weight. When compared to metformin, glyburide was linked to higher maternal weight gain, birth weight, macrosomia, and neonatal hypoglycemia. When metformin and insulin are available for the treatment of gestational diabetes mellitus, these findings led to the conclusion that glyburide should be avoided. Both oral therapies have potential adverse effects, including treatment failure, the requirement for insulin, a variation in the medication's pharmacokinetics, the emergence of general abnormalities in babies, and maternal morbidity [12, 11]. Intense insulin treatment is frequently utilised to maintain strict control of gestational diabetes mellitus [7]. Contrarily, pregnant women find it challenging to adhere to this type of medication, which may call for up to four injections per day, impeding treatment and efficacy while also being costly. It is important to consider this issue from the standpoint of developing nations like Brazil. When using a lot of insulin, [10] said that hypoglycemia can potentially be a concern. Because of this, oral treatment medications are better tolerated and may be given more regularly throughout pregnancy, according to [17]. Because of this, several studies have discovered that combining glyburide with metformin is an effective alternative method for managing gestational diabetes mellitus [15, 3,4]. This review has limitations, especially because there aren't many trials that explicitly address glyburide or metformin monotherapy, which reduces the sample size for analysis. The fact that there is little to no information on these topics that the research is studying and might potentially use to guide decision-making is a potential strength, though.

CONCLUSION

Based on this study both metformin and glyburide showed no differences in safety and efficacy considering birth weight, postprandial blood glucose and fasting blood glucose. However, in babies of women treated with metformin, problems associated with neonates such as respiratory issues and hypoglycemia and also increase in weight during pregnancy or gestation are less common. Nevertheless, it is imperative for randomized controlled trials of large-scale options and strategies (metformin, insulin, glyburide) to be executed and also examining long term effects or

complications with comparators is necessary for future research.

Ethical Approval & Consent to Participate: Not applicable

Consent to Publish
Not applicable

Availability of Data and Materials
The Data set from the study are available to the corresponding author upon request.

Acknowledgement: None

Conflict of Interest: Authors have declared that they have no competing interests

Source of Funding: No funds were received for this study

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How to cite this article: David Chinaecherem Innocent; Advait Vasavada; Angelica Chinecherem Uwaezuoke et.al. Metformin versus glyburide in the management of gestational diabetes; a systematic review and meta-analysis. *International Journal of Science & Healthcare Research.* 2022; 7(3): 336-344. DOI: *https://doi.org/10.52403/ ijshr.20220746*

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