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Comparison between metformin and glibenclamide as antidiabetic oral in gestational diabetes mellitus: a review

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ABSTRACT

Gestational diabetes mellitus (GDM) is one of the most frequent clinical complications during pregnancy that affects up to 6% of women with pregnancies around the world. Gestational diabetes mellitus treatment used insulin as first-line therapy. In addition, several professional associations are also considering treatment using antidiabetic oral which has equivalent efficacy compared with insulin. However, many oral antidiabetic recommendations have been administered to treat GDM, including metformin and glyburide or glibenclamide. This article's review aims to compare the usage between metformin and glyburide or glibenclamide in GDM patients. This review compared research results from PubMed as literature resources and the PRISMA flow chart as the protocol for the article selection process. Based on inclusion and exclusion criteria there are six research articles that are appropriate to the article's topic and aim. Metformin is superior compared with glyburide or glibenclamide administration as antidiabetic oral in GDM. Metformin showed a significant effect in lowering preprandial and postprandial glucose level, elevating insulin sensitivity, while glibenclamide administration decreased dynamic pancreatic β-cell responsivity significantly and had a higher risk compared with insulin and metformin.

ABSTRAK

Diabetes melitus gestasional (GDM) merupakan salah satu komplikasi klinis paling sering terjadi selama kehamilan yang mencapai pada 6% wanita hamil di dunia. Terapi GDM menggunakan insulin sebagai terapi lini pertama. Beberapa asosiasi profesional juga mempertimbangkan penggunaan terapi antidiabetes oral yang memiliki efikasi ekuivalen dibandingkan dengan pemberian insulin. Namun, banyak antidiabetik oral yang direkomendasikan sebagai terapi GDM, termasuk metformin dan gliburid atau glibenklamid. Ulasan artikel ini bertujuan untuk membandingkan penggunaan metformin dengan gliburid atau glibenklamid pada pasien GDM. Ulasan artikel bertujuan membandingkan hasil penelitian yang diperoleh dari PubMed sebagai sumber literatur dan diagram PRISMA sebagai protokol pada proses seleksi artikel. Dari hasil ulasan artikel berdasarkan pada kriteria inklusi dan eksklusi diperoleh 6 artikel penelitian yang sesuai dengan topik dan tujuan. Dapat disimpulkan bahwa metformin adalah antidiabetik oral yang lebih unggul dibandingkan dengan gliburid atau glibenklamid sebagai antidiabetik oral pada GDM. Metformin menunjukkan efek nyata dalam menurunkan kadar gula darah preprandial dan postprandial serta meningkatkan sensitivitas insulin. Sedangkan pemberian glibenklamid dapat menurunkan respon dinamik sel β pankreas secara nya dan memiliki risiko yang tinggi dibanding insulin dan metformin.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition of blood glucose elevation beyond normal limits, usually occurring in the second trimester of pregnancy and during pregnancy. Around the world, up to 6% of pregnant women have GDM. Its prevalence increases continuously along with the increased risk of obesity.[1] Insulin is the first line in treating GDM. However, Langer *et al.*,[2] have revealed that glibenclamide is an alternative therapy that can be used other than insulin. Antidiabetic oral is currently one of the therapies being considered today.[2] It is because oral treatment is easier to use, more affordable, and more preferred by patients rather than insulin.[3] Several observational studies and randomized controlled trials (RCT) have been discussed the use of oral antidiabetics in GDM, particularly glibenclamide and metformin.[4-7]

Although the use of glibenclamide and metformin in pregnancy is not licensed, their use as adjunctive therapy has been considered by some guidelines for the treatment of GDM. Glibenclamide has been recognized for use in a Fifth International Workshop-Conference in Gestational Diabetes Mellitus.[9] In a retrospective cohort study of 10,778 women who received treatment for GDM in the United States. The use of glibenclamide increased from 7.4% in 2000 to 64.5% in 2011.[10] In addition, the National Institute for Health and Care Excellence (NICE) guidance and the American College of Obstetricians and Gynecologists (ACOG) practice bulletin, the use of metformin and glibenclamide has been considered.[11,12] The review aimed to compare the efficacy and safety between metformin and glibenclamide for GDM.

MATERIALS AND METHODS

Article criteria and sources

A literature review of comparison between metformin and glyburide as antidiabetic oral in GDM was carried out using the source of the primary literature website, namely PubMed. Specific terms including “metformin”, “glibenclamide or glyburide”, and “gestational diabetes mellitus” was chosen as search keywords based on the main article topic. All articles were assessed with inclusion and exclusion criteria. Inclusion criteria such as appropriate with keywords, published at the last of 10 years, full paper accessed, and RCT study design. In addition, the exclusion criteria consist of article review types.

Article extraction

The PRISMA flowchart was used as a guideline for the article selection process (FIGURE 1).

RESULT

All the main articles used to discuss the efficacy and safety of metformin compared with glibenclamide in GDM have different results. The outcome of each stud is presented in TABLE 1.

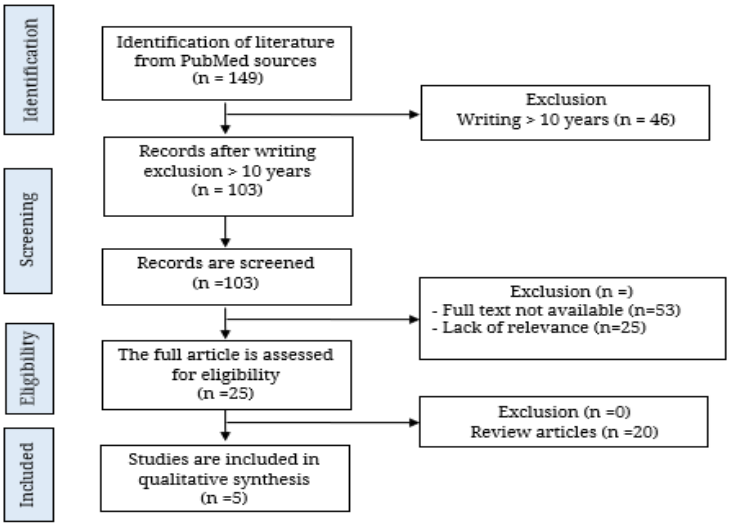

FIGURE 1. Search terms and publication selection process (PRISMA flowchart)

TABLE 1. The outcome of the use of metformin vs sulfonilurea with other antidiabetic drugs for pregnant women

References	Drug use	Patient, population, and problem	Objective	Result	
				Efficacy	Safety
Nachum *et al.*,[13]	Patients receive randomly glibenclamide 2.5–20 mg/day 30 min before a meal and/ or at 22.00. or metformin 850–2,550 mg/day right after meals and/or at 22.00	Pregnant women between the ages of 18-45 years and GDM diagnosed between 13 and 33 weeks gestation that required therapy because lack of glycemic control with diet alone	Evaluate the drug efficacy and safety though seen the treatment failure as patients needing additional oral hypoglycemic or a second-line therapy either because of low glycemic control or adverse effects of the first-line drug and glycemic control according to mean daily glucose charts.	In the glyburide group, the treatment failure in up to 18 (34%) patients was due to a lack of glycemic control in 12 (23%) patients. However, in the metformin group, the drug treatment failed in 15 (29%) patients that 14 (28%) caused by lack of glycemic control. Achievement the target of clinical outcome after given the second-line therapy was higher in the metformin group compare with glyburide group (13 of 15 [87%] vs. 9 of 18 [50%], respectively; p = 0.03).	In the glyburide group, the treatment failure in up to 18 (34%) patients was due to adverse effect (hypoglycemia) that exist in 6 (11%) patients. However, in the metformin group, the drug treatment failed in 15 (29%) patients that 1 (2%) caused by gastrointestinal problem as an adverse effect.
Reynolds *et al.*,[14]	Metformin-glibenclamide vs metformin-insulin combination	Pregnant women with GDM diagnosed between ≥16 weeks or ≤36 weeks gestation, who lack of glycaemic control and have tolerated maximum dose of metformin.	Evaluate drug efficacy and safety between metformin- glibenclamide and metformin-insulin combination	Combination metformin-insulin was superior glycaemic control to metformin-glibenclamide, with fewer blood glucose readings <3.5 mmol/L (median [IQR] difference/ woman/week of treatment 0.58 [0.03–1.87]).	There were no episode of severe hypoglycemia in both groups.

TABLE 1. The outcome of the use of metformin vs sulfonilurea with other antidiabetic drugs for pregnant women (cont.)

References	Drug use	Patient, population, and problem	Objective	Result	
				Efficacy	Safety
Shuster *et al.*,[15]	Glyburide vs metformin vs combination glyburide and metformin	Pregnant women prior to 32 weeks gestation, singleton pregnancy, 18-45 years of age, failed diet therapy and required drug treatment	To characterize the effects of glyburide, metformin, and combination therapy for GDM; to evaluate the effects of gestational age on IS and β-cell responsivity.	The increase in insulin sensitivity was greater in the metformin than in the combination. Glyburide significantly decreased dynamic β-cell responsivity (31%), while metformin and combination significantly increased IS (121% and 83%).	Not reported
Guo *et al.*,[16]	Metformin vs glyburide; Glyburide vs Insulin; Metformin vs insulin	Women with gestational diabetes requiring drug treatment	To compare the efficacy and safety of metformin, glyburide, and insulin in treating GDM	Metformin may be a safe and effective for GDM and there was no significant difference between metformin and insulin in terms of glycemic control. Based on the secondary outcome, it can be seen that there is no significant difference between patients taking glibenclamide or metformin.	Metformin had a lower risk in developing pre-eclampsia. Glyburide had a higher risk in neonatal hypoglycemia. Metformin had a lower incidence of NICU. Glyburide caused macrosomia, preeclampsia, hyperbilirubinemia, neo-natal hypoglycemia, preterm birth, and low birth weight. Metformin (plus insulin when required) has the lowest risk of macrosomia, pregnancy hypertension, LGA, RDS, preterm birth, and LBW. Besides, insulin had the highest incidence of NICU admission.

TABLE 1. The outcome of the use of metformin vs sulfonilurea with other antidiabetic drugs for pregnant women (cont.)

References	Drug use	Patient, population, and problem	Objective	Result	
				Efficacy	Safety
George *et al.*,[17]	Glibenclamide 2.5 mg compared to metformin 500 mg.	Women with 3rd trimester of pregnancy (20-33 weeks of gestation), FGP ≥5.5 - ≤7.2 mmol/L, glucose 2-h postprandial after medical nutrition therapy ≥ 6.7 - ≤13.9 mmol/L. The patient does not suffer from T1DM or T2DM, not taking metformin, abnormalities in fetal organ function, does not have cardiovascular and respiratory diseases, does not have gastrointestinal disorders, does not have sepsis, and does not have gestational hypertension	The preferred end result of this study is to look the primary and secondary outcomes. Primary outcome is safety profile while the secondary outcome is efficacy profile.		Based on the primary outcome, it was found that there were no significant differences in macrosomia, need for phototherapy, respiratory distress, neonatal birth or death, birth trauma in patients taking glibenclamide or metformin. However, in patients using glibenclamide showed the occurrence of hypoglycemia in neonates by 12.5%, whereas in patients taking metformin there was no hypoglycemia, which indicated a significant difference in hypoglycemia in neonates due to the use of glibenclamide in pregnant women.

DISCUSSION

The incidence of diabetes is frequent in pregnancy conditions. When a diet intervention, alone or associated with physical exercise, does not enough to control glycemic levels, insulin treatment is often initiated. Insulin treatment is the gold standard, but oral antidiabetics have potential in GDM treatment as well. Several guidelines that suggest the use of oral antidiabetics in pregnancy are clearly non-uniform (TABLE 1).

TABLE 2. Recommendation guidelines on the use of oral antidiabetics in pregnancy

Institution	Recommendations
American Diabetes Association (ADA)[18]	Both metformin and glibenclamide cross the placenta and are associated with increased neonatal hypoglycemia. Metformin is associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin. Oral agents may be an alternative in these women after a discussion of the known risks and the need for more long-term safety data in offspring.
American Diabetes Association, 2018[19]	American Diabetes Association advice insulin as first-line therapy. Several data of efficacy and short-term safety metformin and glibenclamide are obtained by individual randomized controlled trials. However, definitive research are required in this area for long-time period protection both metformin and glibenclamide.
Society of Maternal-Fetal Medicine (SMFM, 2018)[20]	Pregnant women with glibenclamide that can not be controlled by diet intervention alone, Metformin is the first alternative therapy to insulin, though some patients still need insulin. While frequent adverse effect of glibenclamide in neonatal have been raised the evidence based of benefit of one oral antidiabetic over the other still limited.
NICE Guidance 2015[21]	Both glibenclamide and metformin are considered as a first line therapy in gestational diabetes.
Canadian Diabetes Association 2013[22]	For women who are nonadherent to or who refuse insulin, glibenclamide (Grade B, Level 2) or metformin (Grade B, Level 2) may be used as alternative agents for glycemic control. Use of oral agents in pregnancy is off-label and should be discussed with the patient
Endocrine Society 2013[23]	Pregnant women with GDM who failed in nutrition and physical intervention, glibenclamide is a reasonable alternative except for patient with diagnosis 110 mg/dL (6.1 mmol/L), in which case insulin is recommended. Metformin is reasonable used for glycemic control only for women who not cooperative or cannot use glibenclamide or insulin and are not in the first semester

GDM: gestational diabetes mellitus.

Some guidelines support the use of glibenclamide and metformin as antihyperglycemic agents in GDM. However, the evidence-based of one oral antidiabetic agent over the other is still limited. Therefore, several RCT of metformin compared with glibenclamide to control hyperglycemia in pregnancy were presented. A RCT conducted by Nachum *et al.*[13] evaluate the efficacy and treatment failure of metformin over glibenclamide. The results showed that both metformin and glibenclamide were similar in safety as indicated by mean daily, preprandial, and postprandial glucose values during the study period. The treatment failure, defined as patients needing additional oral hypoglycemic or second-line therapy due to low glycemic control, had no differences in both glibenclamide and metformin groups. In addition, Reynold *et al.*[14] conducted a study that compared the addition of insulin or glibenclamide in pregnant women that have tolerated maximum doses of metformin. In the glibenclamide-metformin group, four women need to be switched to insulin due to hyperglycemia and the result showed combination metformin-insulin superior glycaemic control to metformin-glibenclamide, with a fewer blood glucose rate of excursions.

The combination treatment using insulin as second-line treatment with oral hypoglycemic medication as first-

line treatment was always a good option in the management of GDM.[13] Insulin combined with metformin shows superior glycaemic control with a lower incidence of glucose excursions <3.5 mmol/L (compared with glibenclamide in combination with metformin). Insulin can increase the achievement of glycemic control and diminish the rate of treatment failure compared with using an oral hypoglycemic agent. In addition, the risk of neonatal hypoglycemia was an increase when patients consume an additional therapy of glibenclamide to insulin when compare with insulin monotherapy.[14]

A study related to the therapeutic effects of glyburide, metformin, and combination metformin-glyburide conducted by Shuster *et al.*[15] found that metformin showed the improvement of insulin sensitivity (SI) and β-cell responsivity, whereas glyburide has the main effect in increasing the responsiveness of β-cells and produces a disposition index with a small mean value. Combination of glyburide-metformin increased the average effect on β-cell responsivity but had less effect on SI than the metformin group. It is indicated that metformin can be used to maximize SI then followed by increasing β-cell responsivity using glyburide or supplementing with insulin than using monotherapy to reach the optimal strategy of GDM management.

A study conducted by Guo *et al.*,[16] compared the efficacy and safety of metformin, glyburide, and insulin in GDM management showed that metformin (plus insulin when required) has the lowest risk of macrosomia, pregnancy hypertension, large for gestational age (LGA), respiratory distress syndrome (RDS), preterm birth, and low birth weight (LBW). However, it should be aware of insulin use that may give the highest incidence of NICU admission. Meanwhile, the study conducted by George *et al.*,[17] showed that glibenclamide has a higher risk of neonatal hypoglycemia than in metformin groups. It is indicated that metformin is a superior oral hypoglycemic agent in GDM.

A study related to profile pharmacokinetic conducted by Liao *et al.*,[24] found that there was a significant increase in bioavailability (F), clearance (CL), and β-distribution volume (Vβ) in pregnant women. During pregnancy there is an increase in the hormone progesterone which leads prolong intestinal transit time, thereby increasing the absorption of metformin. This results in a significantly higher bioavailability of metformin in pregnant women with GDM. The Vβ metformin is significantly higher during pregnancy. This is due to the presence of the fetus and placenta and the increase in total body fluids during pregnancy. The process of renal excretion of metformin is mediated by organic cation transporters (OCT) and multidrug and toxin extrusion protein (MATE) in renal tubular. Metformin is a substrate for several OCTs, namely OCT1, OCT 2, OCT3, PMAT, and MATEs. Several studies have suggested that OCT2 and MATEs have a major role in the repair of metformin by the kidneys. The presence and variability of OCT2 in the placenta is influenced by epigenetic factors that cause an increase in OCT2 in pregnancy. However, further research is needed on the increase in OCT2 levels in pregnant women. Increased levels of OCT2 and MATE in pregnant conditions are the cause of increased excretion in pregnant women compared to non-pregnant women.

CONCLUSION

Metformin is superior compared with glyburide or glibenclamide administration as antidiabetic oral drugs in GDM. Metformin showed significant effect to lowering preprandial and postprandial glucose level, elevating insulin sensitivity, while glibenclamide administration decreased dynamic β-cell responsivity significantly and had higher risk compared with insulin and metformin.

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