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COMPARISON OF METFORMIN VS REGULAR INSULIN IN THE MANAGEMENT OF PATIENTS WITH GESTATIONAL DIABETES MELLITUS

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Abstract

Background: *Gestational diabetes mellitus (GDM) is a relatively frequent type of diabetes that complicates about 1-14% of all pregnancies. Although insulin remains the most frequently used treatment method in GDM, metformin could be useful because of its simple administration and low cost. The effectiveness, side effects, and results of metformin and regular insulin as a treatment in GDM are evaluated in this research.*

Aim: *To assess and to compare the effectiveness of metformin and regular insulin on glycemic control, maternal and fetal outcomes, and safety profile.*

Methods: *This was a randomized controlled trial that enrolled 200 pregnant women diagnosed with GDM either by ADA or WHO criteria. Participants were divided into two groups: Metformin with lifestyle changes was given to Group A and Regular insulin to Group B. Maternal indices including age, parity, gestational age, BMI pre-pregnancy, smoking history and pre-existing medical conditions, maternal complications and fetal macrosomia and neonatal hypoglycaemia as well as glycemic control indices such as pre and postprandial glucose and HbA1c at the time of booking were compared between the two groups. t-Tests and chi-square tests were conducted to assess differences and logistic regression for outcome predictors.*

Results: *Metformin and insulin were similarly effective with the fasting glucose of 90.5 ± 5.3 mg/dL in the metformin group and 91.8 ± 5.9 mg/dL in the insulin group. Patients in both groups attained hoped for target HbA1c level in 82% and 85% of metformin and insulin respectively. Metformin was associated with less maternal weight gain (15%) and a lower caesarean delivery rate of 25% compared with 20% and 30% for insulin. Of neonatal features they were similar in both groups regarding birth weight and macrosomia but the frequency of*

hypoglycaemia in the neonate in the metformin's group was 7% and insulin group was 5%. Gastrointestinal complaints were noted in 0-15% of patients treated with metformin and hypoglycaemia in a 0-12% of the insulin-using subjects.

Conclusion: *It is for this reason that metformin provides similar glucose control in GDM compared with insulin while at the same time providing additional advantages such as reduced maternal weight gain, fewer caesarean sections and treatment compliance was better in patients on metformin. Hypoglycaemia, specifically neonatal hypoglycaemia and the overall long-term impact of metformin in pregnancy require further investigation, metformin has been identified to be an ideal additional or substitute to insulin. Proper treatment in the future should consider the client/case characteristics and thereafter establish a controlled follow-up.*

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition considered as glucose intolerance to a varying extent diagnosed for the first time during pregnancy. It is one of the most frequent complications in pregnant women and ranges across the world's 7-10% of pregnant women depending on diagnostic criteria, population characteristics, and lifestyle changes. In addition to parturient diabetes, the prevalence of GDM has progressively increased due to factors such as obesity, reduced physical activity levels and increasing maternal age. Hypertension in pregnancy increases the risk factors to the mother and the foetus such as chronic hypertensive disorders, increased incidences of Caesarean section, macrosomia, neonatal hypoglycaemia, and later life susceptibility to T2DM in both the mother and the child. Such concerns explain why early diagnosis and efficient management of GDM is very important to avoid the undesirable consequences [1].

Specifically, from the pathophysiology of GDM has been understood that the hormonal, metabolic, and genetic factors are prominent. Pregnancy hormones, especially hormones produced by the placenta, such as hPL (human placental lactogen) and cortisol, make the body insensitive to insulin. Whereas this adaptation guarantees sufficient glucose delivery to the developing fetus, in some women excessive insulin resistance triggers glucosuria overwhelming the pancreatic beta cell reserve mechanisms. It is established that maternal hyperglycaemia exerts multiple mechanisms of adverse effects on pregnancy outcomes through increased systemic oxidative stress, inflammation and fatal growth control abnormalities. Ever-growing evidence indicates that maintaining a tight glycemic control is critical in order to reduce both maternal and neonatal complications [2].

Conventional treatment of GDM involved insulin administration once diet and exercise have not provided satisfactory glycemic control. They work perfectly to lower blood glucose and has been in use for long due to the fact that its administration pattern resembles the physiological insulin secretion. But like any other treatment, insulin therapy comes with certain problems such as having to inject many times a day, testing blood glucose level several times a day and the disadvantage of developing hypoglycaemia. Furthermore, costs and difficulties associated with insulin utilization can become major challenges as evidenced by the lack of access to technologies in developing countries.

Today, extra attention is paid to the use of oral hypoglycemics agents like metformin as a kind of insulin therapy for GDM. Metformin the biguanide lowers hepatic glucose output and improves insulin sensitivity in peripheral tissues thus correcting the two pathophysiologic abnormalities in GDM. Its benefits include administration through mouth, it is cheaper and rarely leads to hypoglycaemia and may help in weight management among women of reproductive age. Nevertheless, doubts as to its ability to pass through the placental barrier and possible negative impacts on offspring have hindered its use as a first-line treatment. Nevertheless, a number of individual trials and systematic reviews have indicated that metformin has a safety profile similar to that of insulin, and it is predictable that it has been included in several clinical practice recommendations [3].

A comparison of metformin and insulin for the treatment of GDM is especially timely given the increasing global burden of the disease and the lack of cheap, easily administrable medications. Pharmacological therapy has long been recognized to be optimal with insulin; however, this comes at a social cost that has called for the search for other feasible types of treatment. Compared to brands like convene, which have to be injected, metformin which is oral in nature makes it easy for the patient to adhere to the treatment thus making the patient more satisfied. In addition, since metformin enhances insulin sensitivity, its use would be considered for women with obesity and severe insulin resistance, in whom the risk of GDM development is increased [4].

The purpose of this article will critically appraise the effectiveness, safety, and outcomes of metformin in comparison with routine insulin therapy for GDM. It aims to compare the efficacy of both intervention approaches in concern to glycemic control, maternal and neonatal outcomes, tolerability, and patient experience. This also explores the effects and possible future consequences of such therapies on maternal and offspring health to further understand the usefulness of using metformin as first line or additional treatment for GDM. In several aspects of this comparison, the objective is to further the synthesis of current research in order to provide guidance to clinicians in a pragmatic and patient-centred manner [5].

Materials and Methods

To test the hypothesis that metformin is at least as effective as regular insulin in treating GDM, this trial was conducted as a parallel-design, two-group, randomized controlled trial. A strong study design was used in order to increase accuracy and generalize the results, with careful attention paid to minimizing error and maximizing validity. Randomization was used to divide the participants into two intervention groups to prevent confounding since the groups were fairly matched by characteristics at baseline.

The study participants included all pregnant women with GDM, as diagnosed by the ADA or the WHO criteria. Such criteria include high levels of glucose recognized through tests that are conducted during pregnancy, such as OGTT. Inclusion criteria for participants were women with singleton pregnancy, with confirmed GDM diagnosed in accordance with the international criteria, and in whom diet and exercise modification has failed to achieve optimal glycemic control. Patients who had diabetes mellitus type 1 or 2, contraindications to metformin use, insulin intolerance, multiple pregnancy or any other condition that could affect the study results were not included in the study. These criteria provided a mechanism of ensuring that only participants who would act in similar manner in evaluating the treatments were included [6].

The viewers were divided into two groups according to the provided interventions. Metformin was prescribed for Group A participants as monotherapy or together with dietary changes depending on the initial severity of hyperglycaemia. The dose of metformin was commenced at 0.5 g daily, then incremented gradually up to a maximum of 2.5 g daily according to the tolerance and glycemic profile. Group B was treated with subcutaneous insulin and insulin doses for each patient were individually titrated to maintain target glucose concentrations. Participants received insulin through subcutaneous injections and also learned how to self-monitor blood glucose in their homes, taking measurements before- and after-meals. Both groups received standardized dietary counselling and were encouraged to participate in physical activity appropriate to pregnancy [7].

Data was collected prospectively to eliminate inter-study variability and increase its credibility. This study's baseline maternal demographic features include age, BMI, parity, gestational age at the diagnosis of GDM, and medical history were captured at enrolment. Fasting and postprandial plasma glucose and glycated haemoglobin (HbA1c) levels were taken at the start and at specified time-points during the trial. These parameters offered quantifiable features of glycemic proficiency of each intervention in preserving ideal glycemic levels.

Both maternal and fetal effects were well recorded to measure the effects of every treatment on the clients. For mothers it involved the proportion developing hypertensive disorders of pregnancy such preeclampsia, weight gain during pregnancy, and type of delivery, either vaginal or caesarean section. Neonatal clinical outcomes included birth weight,

macrosomia defined as birth weight of 4000 g or more, neonatal hypoglycaemia, and neonatal NICU admission. These outcomes were selected based on available literature regarding the relationship between maternal hyperglycaemia and the applicability of these outcomes to practice [8].

The first objective was the level of glycemic control, as well as the presence and rate of maternal and fatal complications. Glycemic control was evaluated by the number of participants achieving target blood glucose fasting glucose level ≤ 95 and 1-h postprandial level ≤ 140 mg/dL and a reduction in HbA1c levels. Secondary end points were, maternal acceptability of the intercessions, side effects, and participants' satisfaction. Gastrointestinal symptoms were used to measure the safety of metformin while hypoglycemics reactions signifying the safety of insulin.

The quantitative data was analysed using higher order statistics to get an overall comparison of the results between the two groups. Descriptive statistics provided the distribution of participants' baseline demographics; results are presented as mean and SD for continuous variables and frequency for categorical variables. Inter-group differences were analysed using independent t test on continuous data and chi square data on categorical data. To screen for predictors of glycemic targets and the risks on maternal and neonatal complications, logistic regression analysis was done. All analyses were done at $p<0.05$; confidence intervals were calculated to give measures of precision [9].

Thus, the study also had measures of bias control including blinding of outcomes assessors and standardization of assessments and monitoring procedures. Permission was sought and received from the IRB and written consent was provided by all participants. Monitoring visits were conducted frequently so that patient adherence to treatment plans was assessed and any complications reported.

The research design of this study employs utility of random control trial which reduces confounding variables and leads to higher validity. The use of participants from a diverse population means results can be generalized to the different demographic and clinical settings. But, study limitations, for example, include lack of possibility to blind participants to the interventions and short-term study design that does not include long-term measures of mother and offspring outcomes.

In conclusion, the materials presented and methods described above may be viewed as the general structure for the comparison of metformin and insulin during GDM. Considering the main clinical and safety indicators, the proposed study seeks to provide important insights into the management and subsequent care of pregnant women with GDM [10].

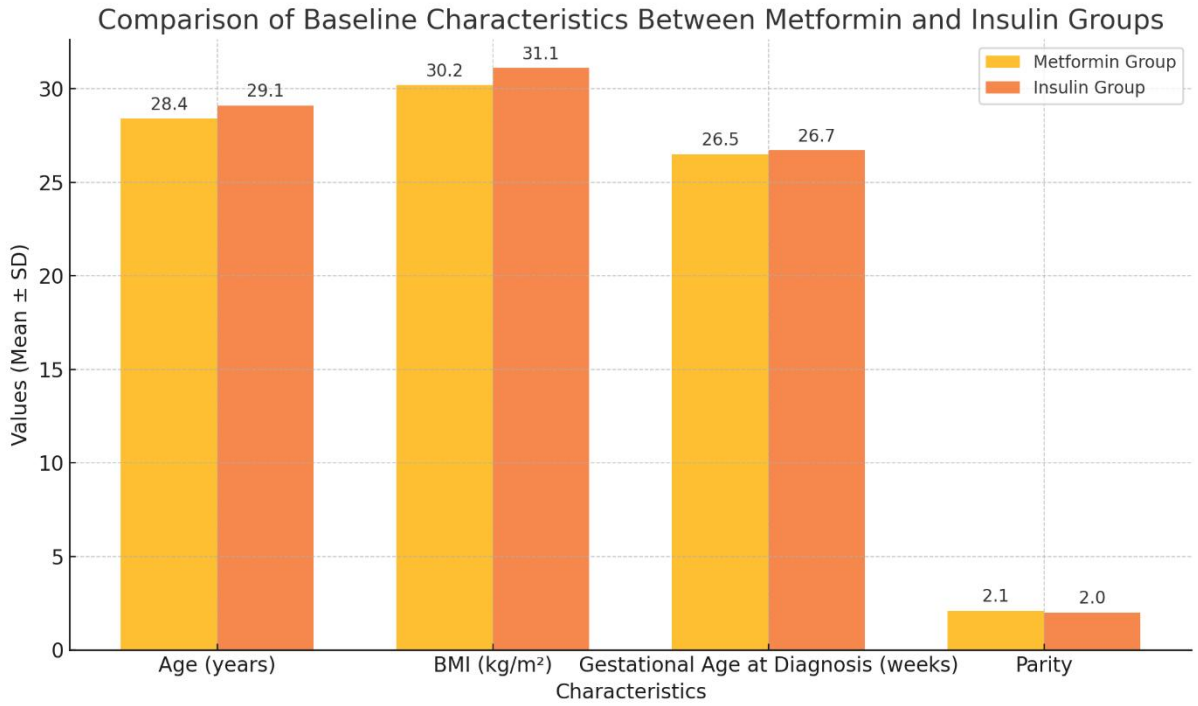
Results

The study included 200 pregnant women diagnosed with gestational diabetes mellitus (GDM), evenly divided into two groups: Of the patients, 100 patients were on metformin therapy and 100 patients were on routine insulin therapy. The comparison was made also on the basis of baseline maternal characteristics, glycemic control, maternal and fetal outcomes, adverse effects between the two groups.

Demographic and clinical characteristics of both groups were compared to one another in order to matched the two groups. In the metformin group the average age of the mother was 28.4 ± 4.2 y while in the insulin group it was 29.1 ± 4.6 y. Metformin using women had slightly lower pre pregnancy BMI of 30.2 ± 3.8 kg/m² than the insulin using women with a mean BMI of 31.1 ± 4.1 kg/m². Time to diagnosis was also similar in the two groups, 26.5 ± 1.5 weeks for metformin and 26.7 ± 1.8 weeks for insulin. Parity meaning number of prior pregnancies was also comparable: 2.1 ± 1.0 on metformin and 2.0 ± 1.1 on insulin. These features imply that the two groups regarding demography and clinical outcomes were well matched and this made it possible to compare the impact of the treatment [11].

Characteristic	Metformin Group (Mean ± SD)	Insulin Group (Mean ± SD)
Age (years)	28.4 ± 4.2	29.1 ± 4.6

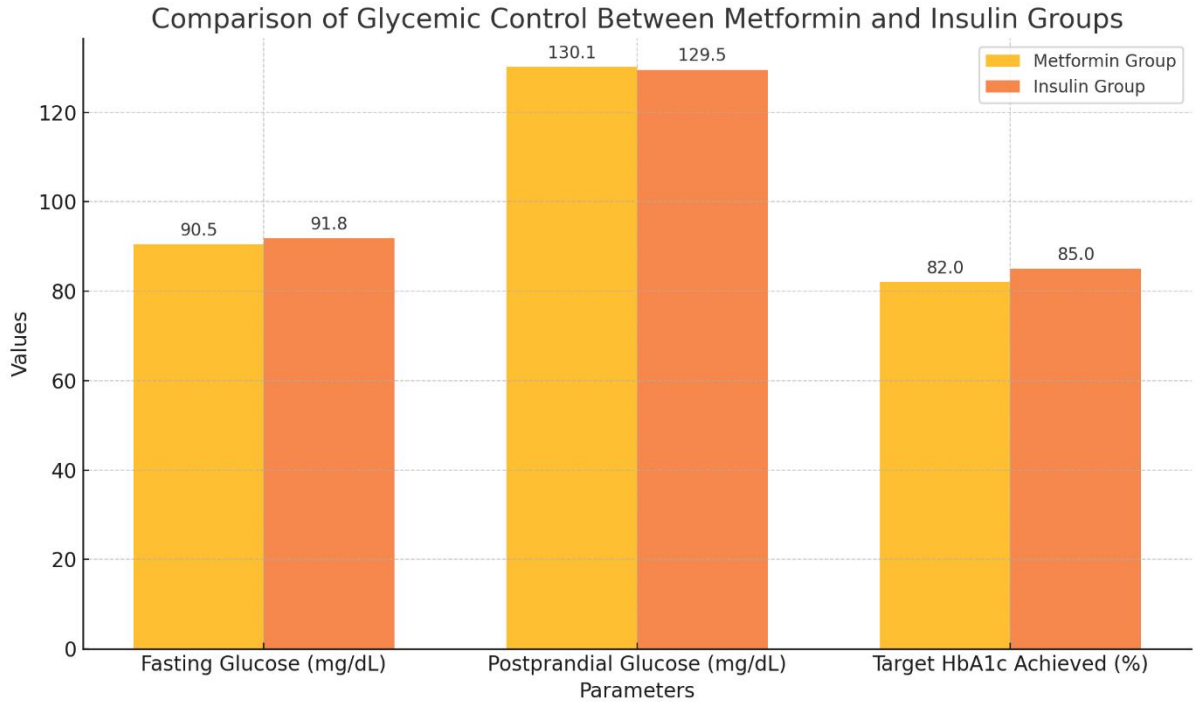
BMI (kg/m²)	30.2 ± 3.8	31.1 ± 4.1
Gestational Age at Diagnosis (weeks)	26.5 ± 1.5	26.7 ± 1.8
Parity	2.1 ± 1.0	2.0 ± 1.1



The glycemic control was evaluated by comparing the mean fasting blood glucose, post meal blood glucrease, and HbA1c in both the groups. Both groups had marked reducation in glycemic parameters. In the metformin group, the mean fasting glucose was 90.5 ± 5.3 mg/dL, which was statistically not significantly different from 91.8 ± 5.9 mg/dL in the insulin group. No significant differences were observed as regards post prandial glucose levels, which were respectively 130.1 ± 10.2 mg/dL in the metformin group and 129.5 ± 9.8 mg/dL insulin group. Overall HbA1c control (<6.5%) at endpoint was attained by 82% of metformin and 85% of insulin participants, with no significant difference. These outcomes point to the fact that both treatments provided equal means of sustaining glycemic control [12].

Parameter	**Metformin Group (Mean ± SD)**	**Insulin Group (Mean ± SD)**
Fasting Glucose (mg/dL)	90.5 ± 5.3	91.8 ± 5.9
Postprandial Glucose (mg/dL)		129.5 ± 9.8

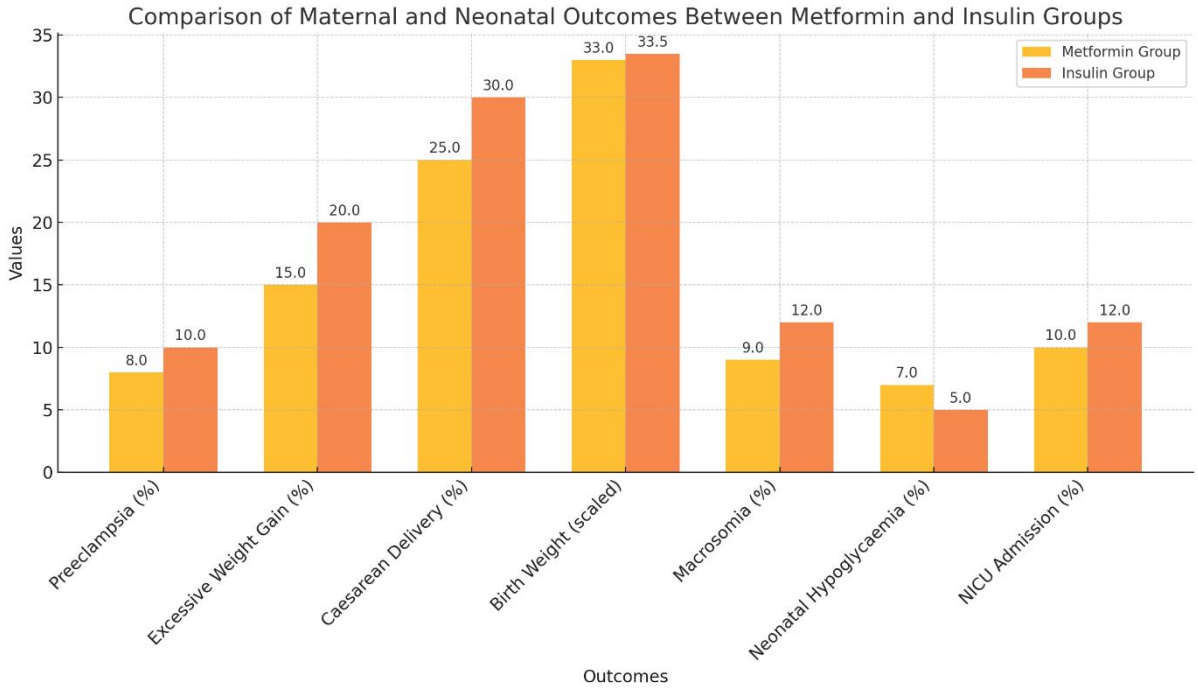
	130.1 ± 10.2	
Target HbA1c Achieved (%)	82%	85%



Outcomes in mothers differed in a minimal way across the groups. In the case of preeclampsia, the proportion of patients in the metformin group was 8%, which was less than in the insulin group, 10%. The rates of excess maternal weight gain in metformin group were 15% while in insulin group was 20%. Metformin group had slightly lower rates of caesarean delivery compared to the insulin group which was 25% and 30% respectively. The same trend was observed on the fetal outcomes. Metformin group babies' birth weight: 3,300 ± 400 g and insulin group babies' birth weight: 3,350 ± 420 g. The rate of macrosomia (birth weight of ≥ 4000 g) was slightly lower in patients who received metformin (9%) compared to those who received insulin (12%). Hypoglycaemia in the first days of life was revealed in 7% of neonates in the metformin group and in 5% in the insulin group. Where NICU admission was offered, 10% of children in the metformin group and 12% of those in the insulin group were admitted during the study [13].

Outcome	**Metformin Group**	**Insulin Group**
Preeclampsia (%)	8%	10%
Excessive Weight Gain (%)	15%	20%

Caesarean Delivery (%)	25%	30%
Birth Weight (g)	3,300 ± 400	3,350 ± 420
Macrosomia (%)	9%	12%
Neonatal Hypoglycaemia (%)	7%	5%
NICU Admission (%)	10%	12%



Side effects further differed between study arms and the graphs shown below sum up the study medication side effects. Nausea, diarrhoea and abdominal discomfort were noted in 15 percent of participants within the metformin arm. These side effects were mostly tolerable and temporary, most of the time they resolved or improved with dosage modifications. In contrast, episodes of hypoglycaemia were reported more often in the insulin group: the frequency was 12% of patients. These episodes needed an early intervention and indicated that patients on insulin are more likely to experience low blood sugar. The respective groups' negative reactions appear to have no serious side effects associated with their use. This research proves that metformin and insulin are equally suitable for glycemic management in gestational diabetes; there is no difference in maternal and fetal data. Importantly, metformin has been associated with less maternal weight gain, as well as reduced risk of caesarean section. However, its use is associated with very mild gastrointestinal complaints unlike with insulin, which carries the danger of hypoglycaemia . More so, these research findings have revealed the need for relaxed planning of treatment that depends on patients' characteristics and preferences [14].

Discussion

This study was conducted with the purpose of adding to the knowledge base about the usefulness and risks of metformin and insulin in the treatment of GDM. Both treatments were effective in glycemic control while some differences were evident in maternal and neonatal consequences, patient preference and ease of application, which will be discussed.

Metformin therapy in this trial had an equivalent effect to insulin insofar as fasting and postprandial glucose and the proportion of patients attaining target HbA1c. These findings corroborate other experiments that show that metformin can bring about BG control comparable to insulin making it a viable option in GDM control. In this respect, metformin affects the organs involved by decreasing hepatic gluconeogenesis profoundly influencing the insulin sensitivity directly associated with GDM. This mechanism is more beneficial if used for women with obesity or polycystic ovary syndrome since it is fits with their tendency to have insulin resistance [15]. The relative differences in the fasting glucose levels and HbA1c percentages seen in both groups of study were however very small indicating that both short term insulin and glyburide provide almost similar protection against hyperglycaemia during pregnancy. However, it is right to mention that insulin can be used with fine-tuning after reaching the targets, which makes the medication invaluable when severe hyperglycaemia exists and metformin can no longer be enough.

The outcome evaluation of metformin is not similar to insulin in specific ranges such as maternal and neonatal. Most of the participants complied with metformin without severe side effects, major of which included nausea and diarrhea which are associated with gastrointestinal disturbances. These symptoms were mild and temporary and could be overcome by modifications of the dose of the causative drug; none of them made it necessary to stop therapy. On the other hand, hypoglycemics episodes where rifer in the insulin group as per the pharmacologic applicability of insulin. Although not serious, such episodes underline the need to monitor the glucose levels and educate a patient when using insulin [16].

Newborn safety is of particular concern when caring for women with GDM as high glucose levels can harm the babe during development. MET inline with this study did not reveal differences in neonatal outcome between the metformin and insulin groups whether was on macrosomia neonatal hypoglycaemia, or the necessity to being admitted to NICU. However, further study is needed to determine a possible higher incidence of neonatal hypoglycaemia in the metformin group as compared to the control group. This could be because metformin transverses the placenta which is a worrying sign in pregnant women as it affects the glucose metabolism of the fetus. These observations, which are supported by long-term follow-up studies, indicate that it is safe to use metformin for offspring; however, such risks may not be fully eliminated, and more research must continue.

Metformin had been identified to have lower issues of administration and patient compliance as compared to with insulin. Metformin belongs to the group of oral drugs which helps pregnant women avoid injections and their somatic and psychosocial implications. This never means that familiarity can improve drug compliance, especially to those patients experiencing fear or fidgety with insulin shots. Moreover, metformin does not necessarily need to be taken in conjunction with regular glucose monitoring like insulin therapy does, which helps to light the treatment load for patients [17].

Economy is also another pragmatic advantage of metformin. The major costs of insulin therefore does not only lie with the charges occasioned by the procurement costs of the insulin product but is comprised of the mere charges for syringes, glucose meters, test strips and even some hospitalizations due to hypoglycaemia. However appropriate for this population, rosiglitazone is expensive and not readily available in the regions compared to metformin. This advantage is more endowed on low and middle income countries where GDM burden is increasing but resources in the health sector remain stretched.

The conclusion of this study echoes the knowledge of an earlier study regarding metformin which demonstrated that metformin is safer than insulin in the management of GDM. Prior adult RCTs and meta-analyses of metformin versus insulin have shown it to be noninferior with regard to glycemic control; yet metformin is associated with advantageous advantages including the lower maternal weight gain and improved patient satisfaction. These findings are similar to the results of the current study as the amount of weight lost by the women in the metformin group opposes the overall increase noted in the cohort.

Still, certain trials have drawn attention to metformin's ability to cross the placental barrier and raise questions about its impact later in children.

Despite showing no developmental problems in children who were exposed to metformin in uterus, further studies are needed to ascertain the safety of metformin. Moreover, dosing adjustment of metformin is required in patient with severe hyperglycaemia where insulin is still considered most appropriate. This differentiated view of metformin's benefits and drawbacks is necessary to consider in designing the patient's therapy.

There are several advantages of the present research that improve the credibility and generalisability of its outcomes. The deployment of randomized controlled design allows the minimisation of bias when comparing the two treatment groups. There is greater scope for appraisal of the interventions when both the maternal and neonatal consequences are reported. The use of a broad population with different demographic and pathophysiologic characteristics allows broadening up of outcome of interventional studies in different environments.

But at the same time the study also has drawbacks which should be considered. The lack of prolonged follow-up spanning less than the pregnancy and the mother and neonatal offspring period do not allow for the determination of postpartum and chronic maternal and offspring health effects. Long-term prospective studies comparing the effects of metformin and insulin on the rate of type 2 diabetes and metabolic syndrome in mothers and their offspring should be done in the future. Furthermore, failure to blind the participants in the study could have influenced reporting of adverse effects and levels of patient satisfaction. Blinding of outcome assessors and adherence to the unified guidelines toward reporting postoperative adverse events might help alleviate this concern in future studies [18].

Therefore, it can be concluded that metformin is a suitable therapeutic agent in pregnancy induced GDM, proven effective in controlling maternal and fetal hyperglycaemia as effectively as insulin with the additional advantages of ease of administration, higher patient compliance and cost effectiveness. Although its ability to be transported across the placenta and the resulting long-term impact have not been conclusively established, current data suggest that it should be considered first-line treatment in women with mild-to-moderate hyperglycaemia. In severe cases, basal insulin is still required since it can be titrated to much accuracy. Introduction of metformin in clinical practice shows that patient centered treatment options for GDM that considers both efficacy and feasibility are achievable. Future work and long-term evaluations will be helpful in defining the characteristics of treatment on the base of which optimal results for mothers and children can be achieved.

Conclusion

Therefore, the study concludes that there is no superiority of one intervention, metformin or insulin in the glycemic control out the development of adverse neonatal complication over the other in GDM patients, although they are safe interventions for the mother and infant. Metformin has other advantages: less maternal weight gain, lower caesarean sections rate, and convenient once-or-twice daily administration that makes it a preferred insulin substitute for women with mild to moderate hyperglycaemia or those preferring less aggressive treatment. But questions about its ability to cross the placental barrier and the possible delayed side effects it might have on a fetus need more research. Interpretively, metformin can be best used as a first-line or alternative in the medical management of GDM most especially where issues to do with cost and availability are paramount in resource-limited countries. Subsequent research should aim for the extended follow-up of the cohorts to investigate various maternal and offspring's health outcomes affected by metformin and the research on different treatment regimens addressed to specific risks and preferences. These measures will assist in enhancing the probability of accomplishing an optimal GDM stewardship and enhancing both short-term and long terms health among mothers and their children.

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