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Review Article

Metformin: A Drug of Choice for Gestational Diabetes Mellitus in Near Future- Hope or Despair ?

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Abstract

Pregnancy is a potentially glucose intolerant condition. Insulin sensitivity decreases as the pregnancy advances. At the later stage of pregnancy, some women develop Gestational Diabetes Mellitus (GDM) particularly obese with pre-existing insulin resistance. Insulin is recognized as the "gold standard" for the treatment of GDM. However, difficulty in administration with multiple daily injections, potential for hypoglycemia, and increase in appetite and weight, make this therapeutic option troublesome for many pregnant patients. Oral hypoglycaemic drugs have been viewed with suspicion for many years in the management of women with diabetes during pregnancy or breastfeeding. However, recent data from well designed trials and meta-analysis may contribute a visible change in practice in terms of oral agents, especially metformin in gestational diabetes. Some cohort data are available and randomized trials are currently in progress to compare metformin with insulin. Evidence is emerging that metformin may improve insulin sensitivity during pregnancy. This may be beneficial in GDM. Use of metformin in pregnancy has opened a new horizon for GDM management. The aim of this article is to review the safety, efficacy and future of metformin in diabetic pregnancy, thus contributing meaningfully in safe motherhood.

Key words: Gestational Diabetes Mellitus (GDM); Insulin; Oral hypoglycaemic drugs; Metformin.

BACKGROUND

The incidence of GDM depends on the diagnostic criteria used and varies widely between racial groups[1]. Overall incidence is reported as 3-6%, but has steadily increased over time, ranging from 2% in South America to 5%[3] in the United States to 15% in the Indian subcontinent[2-4]. GDM has long been recognized as a risk factor for a number of adverse outcomes during pregnancy, including excessive fetal growth, an increased incidence of birth trauma and cesarean delivery, and neonatal metabolic abnormalities such as polycythemia, hyperbilirubinemia and hypoglycemia[5]. Maternal complications include risk of hypertensive disease, pre-eclampsia, cesarean delivery [6-8] and a greater risk of developing diabetes mellitus later on[6,7,8].

Gestational Diabetes Mellitus (GDM) is classically defined as "Carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy"[9]. It does not rule out a prior unidentified glucose intolerance, and in fact several studies have found 10% to 15% of cases of undiagnosed type 2 diabetes mellitus among GDM patients[10]. Insulin resistance increases in normal pregnancy due to progressively rising levels of feto-placental hormones such as progesterone, cortisol, growth hormone, prolactin, and human placental lactogen[11]. The pancreas normally compensates by increasing insulin secretion, but when it fails to do so, or when insulin secretion declines due to a beta-

cell function impairment, then GDM develops[11,12,13]. Maternal hyperglycemia, which is classical for GDM, causes increase transfer of glucose to the fetus, causing fetal hyperinsulinemia an overgrowth of insulin-sensitive (Mainly adipose) tissues, with consequent excessive, unbalanced fetal growth, causing more trauma at birth, shoulder dystonia and perinatal deaths[7,8,14].

Presently, there is consensus that the recommendations of the Fourth and the Fifth International Workshop Conference (FIWC) on GDM to maintain maternal capillary whole blood glucose concentrations below 96 mg/dl (< 5.3 mmol/l) in the fasting state and either below 140 mg/dl (< 7.8 mmol/l) at 1 hour or below 120 mg/dl (< 6.7 mmol/l) at 2 hour after starting the meal should be the treatment targets[15,16]. The goal of glucose management in GDM is to keep glucose values as near normal as possible. The reference plasma glucose levels suggested by the American Diabetes Association (ADA) are below 105 mg/dl (< 5.8 mmol/l) before meals and either below 155 mg/dl (< 8.6 mmol/l) 1 hour afterwards, or below 130 mg/dl (< 7.2 mmol/l) 2 hour afterwards[17].

Measuring glucose levels after meals is more important than pre-prandial levels in GDM patients because it correlates better with certain adverse neonatal events, e.g., malformations, macrosomia, hypoglycemia and shoulder dystocia[18,19].

History of Metformin

Metformin is a dimethylbiguanide, first described in scientific literature in 1957[20]. This compound originates from the French lilac (Galega officinalis) a plant known for several centuries to ameliorate the symptoms of DM[21]. Metformin has a multiple mechanism of actions, comprising decreasing hepatic glucose output, increasing insulin sensitivity and insulin-mediated glucose uptake in the peripheral tissues (Muscle and liver) lowering serum-free fatty acid concentration through antilipolytic effect and increasing intestinal glucose use[22-26]. The activation of the enzyme AMP mediated protein kinase is an important mechanism by which Metformin lowers the blood glucose levels[27]. These effects of Metformin make it an attractive choice in diabetic pregnancy because it decreases peripheral insulin resistance, does not cause hypoglycaemia nor increase insulin secretion[28].

Metformin is a category B drug, indicating that there is no evidence of fetal or animal teratogenicity[29]. Metformin smoothly crosses the placenta and henceforth there is concern regarding possible adverse effects on the fetus[30-31]. Despite valid concerns, there have been clinical reports of Metformin use in diabetic pregnancy since 1966.[32-35] In those earlier studies, mainly from South Africa, the authors conclude that Metformin 'appears' to be safe for use in GDM[28].

Pharmacology and Actions of Metformin

The biguanide, Metformin, is the most widely prescribed insulin sensitizer in the therapeutic management of Type 2 Diabetes (T2D)[36]. Although the liver is the primary target organ, metformin acts on a variety of tissues, namely skeletal muscles, adipose tissue, endothelium and the ovary[36].

Function in Liver

The Metformin-induced inhibition of hepatic gluconeogenesis has been postulated to several mechanisms. Potential mechanisms are the direct inhibition of gluconeogenic enzymes (e.g. Phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase) the reduced hepatic uptake of substrate for gluconeogenesis and the increased phosphorylation of Insulin receptor and Insulin Receptor Substrates (IRS)-1 and -2 [37-42]. Metformin stimulates glucose entry into the liver and glycolysis through the activation of glycolytic enzymes, such as hexokinase (Glucokinase) and pyruvate kinase[37,43].

Function in Skeletal Muscle

Skeletal muscle accounts for more than 80% of insulin-stimulated glucose uptake[44]. In cultures of insulin resistant skeletal muscle cells, Metformin was able to restore insulin signaling defects, including the reductions in insulin-stimulated insulin receptor and IRS-1 phosphorylation and in Phosphatidylinositol-3 kinase (PI3K) activity[44].

Function in Adipose Tissue

Adipose tissue has been recognized as an endocrine organ with a dual role in the regulation of insulin sensitivity and energy homeostasis[45]. Metformin was shown to stimulate catabolism in preadipocytes, as reflected by increases in glucose transport and utilization, mitochondrial and peroxisomal FA β-oxidation, basal lipolysis, and aerobic and anaerobic respiration (i.e. Lactate production). More specifically, chronic Metformin treatment of type 2 diabetes significantly enhanced glucose uptake in visceral fat depot[46,47].

Function in the Ovary

Metformin appears to affect ovarian function in a dual mode, through the alleviation of insulin excess acting upon the ovary and through direct ovarian effects[48].

Function on Endothelium

Metformin was reported to improve endothelium dependent vasodilation in insulin resistant patients, thus potentially protecting against atherogenesis[49].

Studies of Metformin in Pregnancy

There have been clinical reports of Metformin use in diabetic pregnancy since 1966 mainly from South Africa[32-35]. In those earlier studies, mainly from South Africa, the authors conclude that Metformin 'appears' to be safe for use in GDM[28]. Data obtained from a small meta-analysis that included 172 women, from 8 studies, who were exposed to Metformin in the first trimester, either due to polycystic ovary syndrome or due to diabetes, did not find an increased risk of major malformations when compared to controls[50]. This meta-analysis, though included a small number of women, suggested that Metformin is not a teratogenic drug and that its use might be extended to pregnant women. However, an earlier study showed that Metformin use in diabetic pregnant women significantly increase the prevalence of pre-eclampsia and the rate of perinatal mortality (32% and 11.6% respectively)[51]. Beside the

probable safety of Metformin use in the first trimester, investigators studied its effects and safety profile when used for the control of GDM in the second and third trimester of pregnancy[52].

1. Metformin in Polycystic Overy Syndrome (PCOS)

The first study reporting the beneficial effects of Metformin on reproductive as well as metabolic aberrations of Poly Cystic Ovary Syndrome (PCOS) was published in 1994 in the United States[53]. This study found that a 2-month Metformin treatment in 26 obese PCOS led to the attenuation of hyperinsulinemia, reduction of androgen levels, and regularization of menses. Two years later, administration of Metformin to women with PCOS was shown to decrease ovarian 17,20-lyase activity and ovarian androgen secretion, while lowering insulin levels[48]. Since then, clinical studies have addressed the impact of Metformin treatment on hyperandrogenemia in women with PCOS[54]. Metformin either alone or in combination with Clomiphene Citrate (CC) is a pharmaceutical option for ovulation induction in women with PCOS[55].

2. Metformin vs Insulin

The first studies on Metformin was done by Coetzee and Colleagues during the 1970s[33]. Initial data on the efficacy of metformin comes from Coetzee's study in the late 1970s of 160 treated patients with established insulin independent diabetes[33]. In this study, 14% of patients were able to maintain good glycaemic control, as defined by a fasting glucose of 5.5 mmol/l and a post-prandial value below 6.7 mmol/l on a combination of diet and Metformin, compared with about 26% of women who needed insulin. In a follow up study, Coetzee was able to achieve glycemic control in women on Metformin within 24 hours compared with 2-3 weeks for insulin[34].

An Australian study (Metformin in Gestational Diabetes-MiG study) conducted by Rowan and colleagues included 751 women (371 received Metformin, and 378 received insulin) who were randomized between 20 and 33 weeks of pregnancy[52]. It was the largest study so far reported of Metformin use in women with GDM[52]. The Metformin failure rate was 7.4%, in which a second diabetic agent was needed to maintain controlled glucose levels. Although there was no difference in mean fasting blood glucose levels between groups, those on Metformin, had lower 2-hour postprandial glucose levels. There was no difference in the rate of pre-eclampsia. Women in the Metformin group had less weight gain compared to women in the insulin group[52]. A comparable, but much smaller, randomized trial of 63 patients found similar results[56].

Historically, some of the earliest reports of the use of Metformin during pregnancy have come from South Africa, where it has been used since the late 1970s for women with both type 2 diabetes and GDM[33]. While perinatal mortality for these women was still higher than that seen in the general obstetric population, it was however lower than in women who had gone untreated and similar to those who were changed to insulin[33]. Infants of women randomized to Metformin experienced a lower rate of hypoglycemia compared with insulin (insulin 8.1% vs. metformin 3.3%, P=0.008). There was no difference in any other perinatal outcome[52].

Metformin has been found to have a maternal-to-fetal transfer rate of 10-16%[57]. Neonatal hypoglycemia is always a concern postnatally. However, in several reports on the infants in the immediate neonatal period, there was no increase in the rate of neonatal hypoglycemia after delivery compared with women who received insulin. In those who did develop neonatal hypoglycemia, it was determined that this outcome was related to maternal hyperglycemia at the time of delivery[33]. There was no case of neonatal lactic acidosis. Preliminary data on the possibility that infants of diabetic mothers exposed to Metformin in utero may experience a reduction in insulin resistance is contained in the article by Rowan et al in the issue of Diabetes Care[58]. In this first follow-up of the MiG study, infants of women with GDM who had been randomized to receive either Metformin or insulin during pregnancy have been examined at 2 years of age. Rowan et al found that the offspring exposed to Metformin in utero had increased subscapular and biceps skinfolds when compared to the unexposed infants, while total body fat was similar. They hypothesized that this represents a possible benefit as this may signal a healthier fat distribution.

3. Metformin vs OHA(Glyburide) vs Insulin

The eight Randomized Controlled Trials (RCTs) were published between 2000 and 2010 and were conducted in different countries and populations. Four trials were conducted in the United states two in Brazil one in India and one in Australia and New Zealand[56,59-61].

Two trials compared glyburide with Metformin, the maximum Glyburide dose was 20 mg daily and that of Metformin was 2500 mg daily[56,60,61].

Moore and colleagues randomly assigned 149 women to Metformin (N=75) or Glyburide (N=74)[62]. 12% participants on Glyburide and 26% on Metformin required additional insulin therapy.

Silva and colleagues randomised 72 to Metformin (N=32) or Glyburide (N=40)[63]. 10% of those receiving Glyburide and 8% of those on Metformin subsequently required insulin therapy.

Moore and colleagues reported significantly fewer caesarean deliveries in the Glyburide group compared with the Metformin group (3% vs. 15%; p=0.02)[62]. By contrast, Silva and co-investigators reported no difference in the caesarean delivery rate between treatment groups (70% vs 69%, p=0.9)[63]. Moore also reported no difference in FBG levels between the two groups (p=0.23). Moore reported no difference in the rate of pre-eclampsia ($p > 0.5$). Two RCTs evaluated neonatal hypoglycemia (Defined as capillary glucose less than 40 mg/dl), macrosomia and infant birth weight. Both reported no significant differences in neonatal hypoglycemia. Moore reported no difference in the proportion of infants weighting more than 4000 g in the Glyburide group compared with the Metformin group (1.3% vs 5.4%; p=0.2). Silva reported no differences between groups in infants weighing more than

4000 g (p= 0.24) or LGA infants (p=0.14). Infants born to mothers receiving Glyburide were, on average, 200 g heavier than infants born to mothers receiving Metformin (3329± 334 vs. 3103 ± 600 g, p=0.02) (Moore, 2010). Silva and colleagues reported a slightly higher mean birth weight in the Glyburide group (103 g), but this difference is not statistically or clinically significant.

Key findings between Metformin and Glyburide

- No difference in FBG level.
- Almost one third of participants receiving Metformin in the study by Moore required insulin.
- Moor reported that infants were, on average, 200 g heavier in the Glyburide group compared with the metformin group, which is statistically significant and clinically relevant.

Five of the six studies compared an oral diabetes medication with insulin and reported the percentage of participants initially placed on an oral medication who ultimately required insulin[56].

Two of the five studies reported no participants requiring supplementation with insulin. Three of the five studies reported a wide range of participants who required insulin, ranging from 4% to 6% to 47%[56,61,62-65]. The average gestational age at screening and diagnosis of GDM varied across studies from 22 to 25 gestational weeks. Six of the RCTs were under randomization scheme[56,61,64]. None was blinded. Four trials reported participant withdrawals or the reasons for loss to follow-up[59,61]. Only two studies reported an intention-to treat analysis[64]. Rowan and colleagues randomly assigned 751 women at 20-33 weeks of gestation to Metformin or insulin[61]. 92% of the participants on Metformin continued to receive Metformin alone. A smaller trial randomly assigned 63 women to Metformin or insulin[56]. Who started Metformin initially, continued to receive Metformin. There was no difference in the mean standard deviation FBG levels between women treated with Metformin and those treated with insulin (FBG 93.6 ± 11 compared with 91.8 ± 13 mg/dl, p=0.24) among participants in the larger study by Rowan. Moore also reported no difference in FBG (92.6 ± 10 compared with 97± 9 mg/dl; p=0.4)[56]. Both trials reported no difference in caesarean delivery rates. Only Rowan trial evaluated maternal weight, pre-eclampsia and pre-term birth[61]. There was no difference in the rate of pre-eclampsia. Maternal weight gain was substantially less in the Metformin group compared with the insulin group ($p < 0.001$). Rowan reported higher rates of pre-term labour in the Metformin group compared with the insulin group ($p = 0.02$). Both Rowan and Moore evaluated neonatal birth weight and neonatal hypoglycemia[56,61]. Rowan reported a higher proportion of infants with hypoglycemia (defined as any blood glucose less than 28.8 mg/dl) with insulin compared to Metformin ($p = 0.008$), whereas Moore reported no substantial differences (p=0.14). Trail by Rowan did not report any differences in birth weights between treatment groups (3372 ± 572 g in the Metformin group vs 3413 ± 569 g in the insulin group, $p = 0.3$). Similar findings found by Moore (3451 ± 727 g vs. 3500 ± 700 g, p= 0.8). There were no differences in birth trauma, respiratory distress or the 5-min Apgar score[56,65].

Key Findings Between Metformin and Insulin

- No difference in FBG between the Metformin and Insulin groups.
- The larger RCT reported a higher proportion of infants with an episode of hypoglycemia with Insulin compared to Metformin, the smaller trial reported no differences, but had limited statistical power to detect meaningful differences.
- No differences in the proportion of infants with a congenital anomaly between treatment groups were reported in the larger RCT by Rowan. Data on congenital anomalies were not collected in the smaller trial.

The larger study by Rowan contributes most of the evidence for the effectiveness and safety of Metformin.

There has been much debate about efficacy and safety of Oral Antidiabetic Drugs (OADs) for use in GDM patients. The National Institute for Health and Care excellence (NICE) clinical practice guidelines recommend use of Metformin and Glyburide instead of insulin if life style interventions fail to control glycemic levels[66]. After a long debate, the new clinical practice guidelines of the American College of Obstetricians and Gynecologists (ACOG) also recommend use of these two agents in GDM patients as alternatives to insulin therapy and consider the combination equally effective[67].

In another study showed no significant difference in the use of Metformin or insulin (p=0.15) when compared the efficacy of Metformin vs human insulin in GDM patients. 84% of insulin group had good Glycemic control whereas in Metformin group, 72%, achieved euglycemic state[68]. 30% of Metformin group underwent spontaneous vaginal delivery whereas only 20% in the insulin group. During postnatal period, it was seen that 2 babies expired in the neonatal period in the insulin group only. No such mishap occurred in the Metfromin receiving group. Hypoglycemia developed in 4 babies of insulin group and 2 cases in Metformin group. There were no cases of RDS in either group. No cases of congenital anomaly in either group were detected. The neonatal outcome was similar in both groups (P=0.33). 80% of the patients felt that the repeated injections were the most difficult part of the treatment. 64% of the entire study group felt taking oral medications was the easiest part of the study.

Key Points

- Glycemic control is similar in both groups.
- Maternal weight gain and neonatal hypoglycemia is prominent in insulin group.
- No congenital anomaly in both groups.
- Pre-term labour rates are high in Metformin group.
- No noticeable difference in the relevant neonatal outcomes between two groups.
- Most patients liked Metformin due to its easier (Oral) route of administration.

4. Metformin in Lactation

Limited amount of Metformin are transferred into breat milk, but the risk of neonatal hypoglycemia is negligible[69]. The milk:serum or milk:plasma ratio varied between 0.18 and 1.00, while the estimated mean infant dose as a percentage of the mother's weight-adjusted dose varied between 0.18% and 1.08%. This dose is much less than the usual 10% level of the concern[70]. There is no risk of neonatal hypoglycemia, in contrast to the use of drugs stimulating insulin release, such as the sulfonylureas. Maintenance of maternal euglycaemia during lactation remains an important principle to reduce the risk of subsequent obesity in the child in future[71].

Comparison of Other Hypoglycemic Drug with Insulin

Glyburide or Glibenclamide vs Insulin

Glyburide or glibenclamide is a second-generation sulphonylurea[72]. Study showed that glyburide significantly

increased the risk of macrosomia (RR, 3.07; 95% CI, 1.14-8.23, p-value= 0.03) and neonatal hypoglycemia (RR, 2.30, 95% CI, 1.28-4.11, p-value = 0.005) compared to insulin[73]. Study showed no difference between insulin and glyburide with regard to risk for LGA birth, preterm births, neonatal mortality, congenital abnormality[73]. Maternal outcomes such as caesarean section, pre-eclampsia, maternal hypoglycemia and glycemic levels displayed no significant difference between glyburide and insulin[73].

Acarbose vs Insulin

Acarbose, an alpha glucosidase inhibitor, preliminary studies have suggested efficacy in reducing postprandial hyperglycemia in GDM, but its use has been limited due to the frequency of abdominal cramping[74].

Use of Metformin in Pregnancy

- **Advantages:** Though insulin is the first choice in GDM, however Metformin definitely can be used in situations where insulin administration is not feasible or not accepte by the patient or in combination with insulin incase of the demand of the situation. Metformin is not responsible for neonatal complications in terms of malformations, birth weight or neonatal hypoglycemia[75]. Metformin has been associated with fewer cases of GDM among women with polycystic ovary syndrome[76]. It is a safe and effective alternative in women with GDM and those with Type 2 diabetes who become pregnant[77].
- **Disadvantages:** Metformin has been shown to cross the placenta, with fetal level becoming about half those of the mother[78]. The frequently observed gastrointestinal adverse effects include diarrhea, flatulence, nausea, and vomiting, with the incidence ranging from 2 to 63%, but resolve within a few days to weeks after the initiation of therapy[6,79]. Lactic acidosis has been rarely reported with the use of Metformin, mostly in patients with contraindications to the drug or in cases of intoxication after drug overdosage[80]. It has been shown from clinical practice by physicians that fine tuning or accurate dose adjustment (For fasting or 2 hrs post-prandial) is not possible by Metformin alone. Moreover, cases where insulin is required in high dose such as more than 30 to 40 units/ day, Metformin cannot be used alone as a substitute of insulin.

CONCLUSIONS

We believe that in near future accumulation of more evidence will bring a change in clinical practice towards using Metformin in diabetic pregnancy as an efficacious alternative to insulin therapy especially in patients with mild form of disease, shifting the "mind setup" against the use of oral hypoglycemic drugs in gestational diabetes under normal circumstances[73]. This will be particularly beneficial for the developing countries, where rates of diabetes are greatly increasing and the expense of insulin treatment can be minimized. Metformin currently is approved by the US Food and Drug Administration (FDA) for use in the treatment of type2 diabetes[81]. Its off-label use in the treatment of infertility caused by Poly Cystic Ovary Syndrome (PCOS) has been growing over the past decade[50]. Further long term outcome data will add more positive impacts for Metformin use in GDM.

DISCLOSURE

All the authors declared no competing interest.

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