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Review Article

Review on pharmacological therapies for management of gestational diabetes

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Abstract

The prevalence of Gestational Diabetes Mellitus (GDM) is increasing and is closely linked to numerous negative pregnancy outcomes. To mitigate these risks, early identification and management of GDM is critical. Treatment for GDM aims to maintain normal blood sugar levels and typically includes glucose monitoring, adjustments to diet, lifestyle changes, moderate physical activity, and medication as necessary. Insulin administration is generally the preferred choice for pharmacotherapy, but oral drugs such as metformin or glyburide may also be appropriate. Compared to glyburide, which has been linked to higher birth weight, neonatal hypoglycemia, raising the risk of shoulder dystocia, and necessitating a caesarean delivery, metformin is seen to be a safe first-line therapy. It should be emphasized that some expecting mothers choose complementary and alternative therapies, such as traditional herbal supplements and treatments. This review article will address present pharmacological options and considerations associated with treating GDM.

Introduction

Gestational Diabetes Mellitus (GDM) is a distinct endocrine disorder resulting in glucose intolerance that may occur during pregnancy. This condition is a consequence of various factors, such as genetics, environmental triggers, and epigenetic changes [1-3]. Pre-existing diabetes comprises only 1% of diabetes cases during pregnancy and is not categorized as GDM [4]. GDM is characterized by impaired insulin synthesis, insulin resistance, and altered fetoplacental vascular function [5]. Additionally, GDM is associated with fetal complications, such as macrosomia, stillbirth, birth trauma, increased C-section delivery rate, and infant hypoglycemia [6]. The risk of these issues increases with significant maternal weight swings [7]. Early GDM screening, even before 20 weeks gestation, is optimal for maternal and fetal outcomes [8]. Novel predictive and diagnostic biomarkers are essential for GDM management [9].

Individualized medical nutrition treatment and mild exercise are the first-line therapy for pregnant women with GDM to avoid hyperglycemia and its negative effects on fetal development. Scientific groups advise a glucose fasting level of 95 mg/dL and 140 mg/dL at 1h postprandial [10]. However, recent research suggests that a lower threshold for blood glucose levels at 1h after meals (less than 120 mg/dL) can reduce the risk of large for gestational age infants and macrosomia without increasing the risk of small for gestational-age infants [11].

Insulin therapy is the most efficacious treatment for GDM and does not cross the placenta, making it the first choice. Oral diabetes medications (OAD) like metformin or glyburide have been adopted in recent times, mainly because of the drawbacks of insulin therapy in GDM, such as lack of precise dosage level, the requirement for several daily injections, the possibility of increased maternal weight gains and hypoglycemia [12]. Oral drugs are straightforward to use and highly effective in treating women with GDM. However, approximately 20% of women fail to achieve glycemic control, requiring novel therapeutic optimization [13]. The most recent results from meta-analyses reveal that metformin is the superior treatment over insulin or

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glyburide for most adverse neonatal outcomes, while glyburide administration is predominantly linked to the risk of poor outcomes for pregnant women [14]. The use of these diverse medications needs extra care [8].

Although screening for GDM and quick treatment have made tremendous strides, secondary prevention in GDM-affected mothers and their offspring still poses a huge scientific challenge [15]. The efficacy and safety of other oral hypoglycemic medicines and insulin used to address GDM are emphasized in some studies. It also looks at dietary supplements and complementary medical approaches.

Current pharmacological options for GDM

A. Insulin and its analogues

Pharmacological use and properties: Insulin is considered a safe and effective treatment for Gestational Diabetes Mellitus (GDM) due to its inability to pass through the placenta unless administered in high doses. Insulin is also not teratogenic and does not appear to be excreted in human milk. There are several insulin formulations that may be used to treat GDM at the moment, including rapid-acting analogues (like lispro and aspart), short-acting conventional insulins, intermediate-acting NPH insulins, and longer-acting insulin analogues (like detemir and glargine) [16].

Insulin is advised as the first-line medication for female patients who have not reached their glycemic treatment objectives by lifestyle modifications alone [17]. Those who are unable to tolerate the negative effects of other oral anti-diabetic medicines (OADs) may also utilize insulin. Based on variables such as gestational age, body weight, and the onset of hyperglycemia, insulin dose and timing are chosen. Throughout the course of the pregnancy, dosages may be adjusted in accordance with blood glucose levels, nutritional intake, infection, physical activity, and compliance [18].

Depending on when recurrent hyperglycemia occurs, either split doses or a single daily dosage of insulin may be given. Women who only experience hyperglycemia when fasting are permitted to take intermediate insulin in a single dosage at night [19]. Women experiencing postprandial hyperglycemia should receive rapid-acting insulin before a meal. A combination of short-acting insulin and intermediate- or long-acting may be used to control hyperglycemia throughout the day. Regular self-monitoring of blood glucose levels is essential for adjusting insulin dosages and avoiding hypoglycemia or hyperglycemia [20].

Rapid-acting insulin analogs are often used to mimic the body's natural response to meal intake and are administered shortly before meals. To control lipolysis and stop hepatic gluconeogenesis, basal insulin is used continuously to provide a small quantity of insulin [21]. Although women with GDM have historically used insulin to treat hyperglycemia, some find it difficult to give the drug because of weight gain, dosage concerns, and hypoglycemic episodes [22,23]. Metformin is an insulin replacement that is as effective but less likely to result in hypoglycemia. In diabetics who are not pregnant, detemir has been associated with a lower risk of hypoglycemia, but short-acting insulin has been associated with a high risk of hypoglycemia and changes in glycemic control in GDM [24,25].

B. Oral anti-hyperglycemic drugs (OAD)

i. Metformin

Pharmacological use and properties: The oral biguanide metformin reduces gluconeogenesis in the liver, boosts peripheral insulin sensitivity, and encourages glucose uptake in peripheral tissues while inhibiting gut glucose absorption [26]. Higher insulin sensitivity is achieved by increased insulin receptor tyrosine kinase activity, increased glycogen synthesis, decreased glycogenolysis, decreased hepatic glucose-6-phosphatase activity, and increased recruitment and activity of GLUT4 glucose transporters [27]. Additionally, it causes an average weight loss of 5.8% and a 40% reduction in fasting serum insulin, which decreases the risk of hypoglycemia [28]. Despite identical glycemic control, a long-term prospective study of type 2 diabetes found that metformin was associated with lower cardiovascular and all-cause mortality than insulin and sulphonylureas, which may be explained by the activation of the RISK pathway through increased AMPK activity [29,30].

Metformin is transported across the mitochondrial membrane via Organic Cation Transporters (OCTs) in cells. Metformin can easily pass the placenta while a woman is pregnant because the placenta has a variety of OCT isoforms. However, placental transfer raises questions regarding potential harm to fetal development. Pre-implantation human embryos have a constrained mitochondrial capacity that makes them resistant to metformin, while it is unclear whether OCTs are expressed in human embryos [31,32]. Compared to children who got insulin throughout pregnancy, children who received metformin for gestational diabetes had equal levels of total body fat, but higher subcutaneous than intra-abdominal fat. Accordingly, metformin therapy may provide a better pattern for the distribution of fat than insulin [33].

Metformin has been used for years in the first trimester and throughout pregnancy for different purposes, despite the fact that it has just recently been demonstrated to be an effective therapy for gestational diabetes. When administered throughout the first trimester, it can lessen the probability of spontaneous abortion in women with polycystic ovarian syndrome and help them develop regular ovulation [34]. Early studies have supported the usage and effectiveness of metformin for insulin-dependent T2DM in pregnancy [35,36].

Efficacy and safety: Metformin or insulin was given to women (n = 100) in a random order as the standard treatment for gestational diabetes. Compared to women using insulin as a monotherapy, a significant portion of metformin-using women required additional insulin at substantially lower dosages. Both treatment groups had a comparable main outcome, which included newborn hypoglycemia, respiratory distress, the need for phototherapy, a 5-minute Apgar score of 7, or a preterm delivery before 37 weeks. Compared to women using insulin,

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those taking metformin acquired less weight from enrollment through term [37]. Other factors, such as birth weight, neonatal anthropometrics, and probabilities of being big for gestational age, were comparable between the two treatment clusters. However, the incidence of severe hypoglycemia was reduced in the metformin group as compared to insulin treatment. Metformin was far more well-tolerated by patients than insulin. Although metformin did have some gastrointestinal adverse effects, only 8.8% of women had to reduce their doses, and just 1.98% had to stop taking it altogether [38].

In a different case-control observational research, 100 GDM women receiving just metformin treatment were compared to 100 GDM women receiving only insulin treatment. In both groups, maternal risk factors were comparable. Preeclampsia, gestational hypertension, and Caesarean section rates were all equal, but the metformin group's average maternal weight increase from enrollment to term was much lower. When compared to women who got insulin therapy, those who got metformin had a reduced risk of preterm delivery, newborn jaundice, and admission to a neonatal unit, as well as a general decrease in baby morbidity [39].

A meta-analysis of three randomized controlled studies in GDM women found that post-prandial glucose levels were lower in metformin-treated patients than in insulin-treated patients, albeit these differences did not achieve statistical significance. Metformin did not increase the likelihood of premature deliveries, caesarean sections, or small-for-gestational-age babies. The risk of preterm delivery, infant hypoglycemia, admission to neonatal intensive care units, and the incidence of pregnancy-induced hypertension were all found to be reduced in association with the use of metformin [40].

Metformin doesn't promote the release of insulin, therefore it doesn't cause maternal hypoglycemia, a side effect of glyburide that is still a worry. The likelihood of severe neonatal hypoglycemia following metformin therapy is lower than it is after insulin administration for the same reason. Taking insulin carries a higher risk of developing hypoglycemia than taking oral diabetes medications. Metformin rapidly penetrates the placental barrier, however, the fetus's quantities are probably quite low, and there haven't been any reports of any fetal adverse effects such as congenital abnormalities. No cases of neonatal lactic acidosis have been reported, and it is not believed to be teratogenic. Neonatal hypoglycemia has been connected to maternal hyperglycemia after birth rather than being a side effect of metformin directly. Metformin is a Pregnancy Category B drug according to the FDA [41].

Patients should be told about the possibility of deleterious effects on the mother before beginning metformin medication. Although the drug's method of action does not directly cause hypoglycemia, 0% - 10% of women who take it have symptoms [42]. Gastrointestinal side symptoms such as nausea, flatulence, vomiting, and diarrhea were reported by 5% - 15% of women. The most concerning possible adverse effect, lactic acidosis, was avoided by slowly increasing the dosage.

There is not much research in the last 10 years about how metformin and insulin work better together in GDM. According to their findings, insulin monotherapy and concurrent metformin treatment in GDM women resulted in similar obstetric and neonatal adverse outcomes. However, when both medications were taken at the same time, there were no positive effects on weight gain or insulin dosage that were anticipated [43,44].

ii. Glyburide

Pharmacological use and properties: A second-generation sulfonylurea, glyburide mainly increases pancreatic and peripheral tissue insulin sensitivity. The receptor of sulfonylurea, which is a part of the ATP-sensitive potassium channels in pancreatic beta cells, is blocked by the medication as part of its mechanism of action. Glyburide binds mostly to albumin and has a high degree of lipophilicity.

Glyburide was first thought to be incapable of crossing the placenta. To contradict earlier *in vitro* research, Langer, et al. [13] found that umbilical cord serum samples taken from newborns whose mothers had taken glyburide during pregnancy did not contain glyburide. The detection threshold used by the authors for liquid chromatography was 10 ng/ml. However, another research showed that glyburide was detectable in umbilical cord serum samples using an extremely sensitive liquid chromatography-mass spectrometry method, which could do so at sub-ng/mL levels. According to these findings, glyburide can cross the placenta [45].

An effective substitute for glyburide is insulin injection. Despite being an FDA category C medicine, glyburide is nevertheless often used since it is less dangerous than the insulin analogues detemir, lispro, and aspart, which are all pregnancy risk factor B medications. When self-monitoring of blood glucose levels and storage of insulin is not possible or if a patient has a fear of needles, glyburide may be the better option. In addition, glyburide is less expensive than insulin or metformin, has fewer side effects, and is simpler to administer. Glyburide's safety and effectiveness for individuals with gestational diabetes mellitus are not yet apparent, and further study is required to make these determinations [46].

Efficacy and safety: In 2000, a clinical trial contrasting glyburide and insulin for the management of GDM was reported in the New England Journal of Medicine. The first randomized and controlled research on the topic was carried out by Langer, et al. The study split 404 GDM-afflicted women into two groups, giving 201 of them glyburide and the rest 203 insulin. The study found no discernible difference in the two groups' newborn outcomes, such as macrosomia, high blood glucose levels, hospitalization to the neonatal critical care unit, etc. The degree of glycemic control between the two groups, according to the authors, was likewise comparable. In another study, two groups were evaluated, and there was no proof that using glyburide rather than subcutaneous insulin increased the risk of perinatal issues. A retrospective cohort study, however, discovered that babies delivered by glyburide-treated mothers were more likely to experience difficulties than babies born

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to moms who were on insulin [47]. The problems identified were preterm delivery, Caesarean section, respiratory distress hypoglycemia, large for gestational age, jaundice, birth damage, and admission to the neonatal ICU. A recent meta-analysis looked at seven trials to calculate the efficiency and security of Oral Anti-Diabetic (OAD) drugs for GDM. Regarding glycemic control, the researchers found no distinction between glyburide and insulin.

However, glyburide medication was associated with an increased risk of macrosomia, high maternal weight gain, high neonatal birth weight, and newborn hypoglycemia. Another meta-analysis compared 457 pregnancies handled with glyburide against 467 pregnancies treated with insulin. The researchers discovered that glyburide significantly increased the risk of macrosomia compared to insulin and was also linked to a higher likelihood of infant hypoglycemia. Glyburide had the poorest ranking in the most recent meta-analysis due to its high incidence of hyperbilirubinemia, macrosomia preeclampsia, and neonatal hypoglycemia. Use of glyburide should be treated cautiously because it has been linked to weight gain and hypoglycemia in pregnant women, especially when taken on an empty stomach [48].

iii. Acarbose

Pharmacological use and properties: The alpha-glucosidase inhibitor acarbose stops the digestive enzymes of the small intestine from breaking down starches into simple sugars. Postprandial glucose concentrations are consequently decreased. Nevertheless, using it could result in intestinal issues. While 34% of acarbose's metabolites are found in circulation, the amount that is actually absorbed as medicine is only 2%. Due to a lack of well-established research on its effects during pregnancy, it is not recommended to use acarbose to treat gestational diabetes. Instead, safer and more advantageous alternatives like insulin and metformin should be taken into account [49].

Efficacy and safety: In Brazil, a 70-person randomized prospective research assessed the effectiveness of glyburide, acarbose, and insulin in the management of GDM. Though gastrointestinal side effects were more common with Acarbose, the study showed that there were no appreciable differences between acarbose and insulin in fasting or postprandial glucose levels. In contrast to glyburide, which had a failure rate of 21%, acarbose showed a greater failure rate of 42% in achieving glycemic control Neonatal hypoglycemia was reported to occur in just one patient treated with acarbose and one subject treated with insulin, compared to eight subjects treated with glyburide. Only 16% of neonates who received glyburide went on to develop macrosomia [50].

Even other studies indicated that acarbose is less successful than glyburide at establishing glycemic control, it also showed that acarbose had a reduced incidence of hypoglycemia and macrosomia, making it an appealing drug for further investigations on the treatment of GDM. Acarbose was deemed an efficient option for GDM control and appeared to be well-tolerated in a subsequent research by Jayasingh, et al. (2020). In the research trials, feto-maternal outcomes in pregnant GDM patients treated with insulin or acarbose were compared. Recurring infections, preeclampsia, premature membrane rupture, delivery methods, postoperative random levels of blood glucose, fasting blood glucose level at day 7, fasting blood glucose level after six weeks, and mean birth weight of offspring were not significantly changed between the two groups.

Recent investigations have not found a markedly greater risk of liver damage following acarbose medication, despite the fact that acarbose has been associated with hepatic failure and abnormal liver enzymes in diabetic persons [51]. Acarbose can pass the placenta and is not teratogenic at dosages up to 32 times greater than those used in humans, according to animal studies. However, the medication has the ability to induce labour by causing stomach cramping and increasing prostaglandin E levels.

C. Supplementation and traditional treatment options

Research is currently being done to determine whether vitamin and mineral supplements are useful for GDM sufferers. Vitamin E, vitamin D, and magnesium levels have been discovered to be low in GDM patients, despite the fact that these nutrients have been favorably associated with controlled glucose metabolism, anti-inflammatory effects, and decreased oxidative stress when taken as supplements. Li, et al. most recent meta-analysis backs up these conclusions. Additionally, it has been discovered that providing GDM women with Mg-Zn-Ca-vitamin D co-supplements for six weeks reduces oxidative stress and inflammation. According to Wang, et al. vitamin D supplementation can enhance glycemic management and decrease negative feto-maternal outcomes, such as Caesarean sections, postpartum hemorrhages, hospitalization of mothers, newborn hyperbilirubinemia, big children, fetal distress, polyhydramnios, and preterm birth [52].

Most women with GDM can attain normoglycemia with dietary changes and lifestyle changes, especially when it comes to the kind and quantity of dietary carbs. When taken soon after the diagnosis of GDM, myoinositol, a dietary supplement known to lower insulin resistance, has been demonstrated to be useful in establishing glycemic control and lowering the requirement for further medication [53].

Studies are also being done on the possibilities of treating GDM using herbal remedies and conventional Chinese medicine. Herbs like Zuo Gui Wan, red raspberry tea, and Orthosiphon stamineus have all shown promise in decreasing glucose and relieving GDM-related symptoms, with good safety profiles for both mother and infant. The glycyrrhiza flavonoids from traditional Chinese medicine have also been demonstrated to have anti-diabetic potential as adjuvants for insulin therapy [54].

Probiotic supplementation is an area of study that shows promise for enhancing glycemic control and lowering GDM-related adverse events, but more research is required to fully

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appreciate its advantages. Despite the fact that fresh and promising outcomes are frequently published, dependable and long-lasting results in the field of adjuvant GDM therapy require standardized methods and well-designed trials [55].

Conclusion

GDM is a significant issue that needs to be managed effectively to prevent negative consequences on the mother and fetus. This chapter discusses potential pharmacological therapies for GDM, their special traits, advantages, and drawbacks. Oral medications like glyburide and metformin are the most recommended first-line therapies, but if optimal glucose control is not achieved, analogues such as aspart, lispro, and detemir may be required. Patient evaluation is crucial to selecting the best treatment option. Education about the advantages and disadvantages of different treatment modalities is also necessary. Future clinical research will provide more knowledge on the prevention and management of GDM. The conclusion can be further condensed if needed.

Recommendations

Managing gestational diabetes is critical for the healthcare sector to prevent negative outcomes for mothers and infants. This review article on pharmacological therapies provides an overview of treatment options. However, improvements are necessary. There should be more information on early screening and diagnosis, insulin analogues, complementary therapies, nutrition, and long-term effects on health outcomes. Patient education and involvement are critical for optimal glycemic control. The article should also clarify the FDA pregnancy risk categories for the medications discussed, especially glyburide. Incorporating these recommendations can enhance the article's reliability for healthcare providers and expecting mothers.

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