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Chapter

Pharmacotherapy of Gestational Diabetes Mellitus: Current Recommendations

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Abstract

The incidence of gestational diabetes mellitus (GDM) is still rising, and this pathological condition is strongly associated with some serious adverse pregnancy outcomes. Therefore, GDM must be timely recognized and adequately managed. Treatment of GDM is aimed to maintain normal glycemia and it should involve regular glucose monitoring, dietary modification, lifestyle changes, moderate physical activity, and pharmacotherapy, when necessary. As for the pharmacotherapy, needed in approximately one-third of GDM women, insulin administration is the first choice of pharmacological treatment, although oral hypoglycemic drugs, for example, metformin (a biguanide agent) or glyburide (a second-generation sulfonylurea drug), could be indicated, too. Metformin is considered as a reasonable and safe first-line alternative to insulin. If comparing two oral agents, metformin seems to be safer than glyburide, since glyburide was found to be linked to neonatal hypoglycemia and higher birth weight, which can for example increase the hazard for shoulder dystocia and a necessity for Cesarean delivery. Finally, it should be underlined that many pregnant women turn to complementary and alternative medicine for health maintenance or symptom relief, including traditional herbal medicine and the use of supplements. Given the previous facts, this chapter will address current pharmacotherapy options and challenges related to GDM treatment.

Keywords: gestational diabetes mellitus, treatment, insulin, metformin, glyburide, oral antidiabetics

1. Introduction

Gestational diabetes mellitus (GDM) is well-described endocrinopathy, referring to any degree of glucose intolerance that develops or else is initially recognized during pregnancy. Today, it is recognized that GDB is most probably a consequence of complex and quite diverse interactions between genetic-epigenetic-environmental factors [1–3]. This diagnosis of gestational diabetes does not include pregnant women who have unrecognized pre-existing diabetes, which today accounts for about 1% of diabetes cases during gestation [4].

GDM is characterized by aberrant fetoplacental vascular function, insulin resistance, and impaired insulin production [5]. Numerous fetal issues have been

linked to GDM, for example, macrosomia (birthweight over 4000 g), a higher stillbirth risk, birth trauma, a higher percentage of Cesarean delivery, and newborn hypoglycemia [6]. Most of these have been particularly positively linked to considerable maternal weight fluctuations in GDM [7]. Although today it has become very clear that timely screening and diagnosis (even before 20 weeks gestation) of GDM in at-risk women is more than required for clinically desirable maternal and fetal outcomes [8], in this context, new predictive and diagnostic biomarkers for GDM represent a critical state-of-the-art topic [9].

To circumvent hyperglycemia and its negative effects on fetal growth, pregnant women diagnosed with gestational diabetes are initially managed with individualized medical nutrition therapy and light exercise. Although the majority of scientific associations propose the thresholds for fasting glucose levels of 95 mg/dL and 140 mg/dL at 1-h postprandial, recent findings suggested that decreasing a threshold for blood glucose at 1 h after a meal to less than 120 mg/dL in GDM women lowers the risk of large for gestational age infants and macrosomia, and at the same time without the increased occurrence of small for gestational age infants [10, 11]. This promising finding certainly requires further elucidation.

Insulin has generally been recognized as the first-line drug because it is effective and does not cross the placenta. Other treatment strategies, oral antidiabetic drugs (OAD) such as metformin or glyburide, have been used in recent years given that insulin therapy has several downsides in GDM. Some of them are the absence of a clear dose definition, the need for multiple daily injections, the risk of hypoglycemia, and elevated maternal weight gain [12]. Although oral medications are easy to use and even though they have a high efficacy in the treatment of women with GDM, failure to attain glycemic control appears in around 20% of women, leaving opportunities for new therapeutic optimization [13]. In accordance with previous facts, up-to-date results of available meta-analyses on the effects of antidiabetic pharmaceuticals estimated that if we look to the majority of adverse neonatal outcomes, metformin was ranked to be the superior treatment over insulin or glyburide, whereas the lower risk of adverse maternal outcomes was primarily linked to glyburide administration [14]. These divergent effects require additional caution in their use [8].

Lots of knowledge has been accumulated regarding GDM screening and timely treatment; however, the secondary prevention in women following GDM, as well as in their offspring, represents an important scientific challenge for all of us in many years to come [15].

In this review, we look at how insulin and other oral hypoglycemic medications are used to treat women with GDM, emphasizing on their efficacy and safety. Supplement-related and other alternative pharmacotherapy will be addressed, as well.

2. Current options of pharmacotherapy in GDB

2.1 Insulin and insulin analogs

2.1.1 Pharmacological properties and use

Insulin, due to its huge molecular size, does not pass the placenta unless at extremely high doses [16]. It has a great fetal safety profile; it attains tight maternal glucose control and is therefore recommended as a gold standard, and the first-line

treatment for women with GDM. Insulin is not teratogenic, and there is also no evidence that any of them are excreted in human milk [17].

Currently, available insulin analogs are rapidly acting analogs, including aspart and lispro, short-acting regular insulin, intermediate-acting NPH insulin, or longer-acting insulin analogs, such as glargine and detemir [18, 19].

Insulin is the therapy of choice for women who have failed to meet their glycemic treatment goals despite making lifestyle changes—diet and exercise [2]. It can also be used by those who are unable to tolerate the adverse effects of other OADs.

The dose and timing of insulin use are determined by the women's body weight, gestational age, and the time of day when hyperglycemia occurs. Insulin dosage is modified often during pregnancy based on blood glucose values, hypoglycemia, physical activity, nutritional intake, infection, and patient's compliance.

Based on the time of recurrent hyperglycemia, there are two major ways of prescribing insulin. Insulin can be given in divided doses throughout the day or as a single daily dose. Intermediate insulin, such as NPH or detemir, should be given as a single dose at bedtime in GDM women who have hyperglycemia solely in the morning fasting state. Rapid-acting insulin should be administered before a meal in women who have postprandial hyperglycemia. Hyperglycemia during the day should be controlled with a combination of intermediate- or long-acting and short-acting insulin [20].

Close blood glucose monitoring is required while prescribing insulin to avoid hypoglycemia or hyperglycemia. GDM women should bring their self-monitored blood glucose logs to the doctor's office so that the insulin regimen can be adjusted when necessary.

2.1.2 Efficacy and safety

Rapid-acting insulin analogs, often known as bolus insulin, are used to imitate endogenous insulin's response to meal intake. They reach a concentration peak sooner than regular insulin and show a shorter duration of action (3–5 h) [21]. In comparison with human insulin, which must be administered 30 minutes before a meal, rapid-acting insulin analogs can be given 5–10 minutes before a meal, making them more convenient [22]. Basal insulin, also known as intermediate-acting and long-acting insulin, is primarily used to give a constant supply of the modest amounts of insulin to regulate lipolysis and avoid hepatic gluconeogenesis, regardless of meal intake.

Although insulin treatment has traditionally been the drug of choice for treating hyperglycemia in GDM after medical nutrition and physical exercise, it is not without limitations. Many pregnant women face issues with insulin administration, including gaining weight, balancing dosage, diet, and, for some, the frequency of hypoglycemic episodes. For that reason, there are quite a few reports currently suggesting metformin as the first-line agent having an equivalent efficacy *vs.* insulin, yet with less hypoglycemia than insulin [23].

Short-acting insulin has been connected to an augmented risk of hypoglycemia and glycemic control changes in those with GDM. Aspart's recent experience has been positive, although lispro has been linked to higher birth weight and a greater rate of large for gestational age newborns [24]. In randomized clinical investigations comparing detemir to NPH for intermediate- and longer-acting insulin, there was no difference in glucose management or perinatal outcomes. Detemir has been linked to a lower risk of hypoglycemia in diabetics who are not pregnant [25].

2.2 Oral antihyperglycemic drugs (OAD)

2.2.1 Metformin

2.2.1.1 Pharmacological properties and use

Metformin, an oral biguanide, works by reducing liver gluconeogenesis, increasing peripheral insulin sensitivity, and also promoting glucose uptake in peripheral tissues while lowering glucose absorption in the gut [26]. Several mechanisms are responsible for higher insulin sensitivity including the augmented activity of insulin receptor tyrosine kinase, enhanced synthesis of glycogen, reduction of glycogenolysis, decreased activity of hepatic glucose-6-phosphatase, and an increase in the recruitment and activity of GLUT4 glucose transporters [27]. It decreases fasting serum insulin by 40% (thus lowers the risk of hypoglycemia) and leads to a 5.8% weight loss on average [28]. Despite identical glycemic control, metformin was related to lower cardiovascular, as well as all-cause mortality if paralleled to sulphonylureas and insulin in a long-term prospective study of type 2 diabetes. The RISK pathway activation *via* increased AMPK activity may be responsible for this effect [29, 30].

Organic cation transporters (OCTs) transport metformin across the mitochondrial membrane at the cellular level. Since the placenta expresses many OCT isoforms, metformin crosses the placenta easily during pregnancy. Concerns about potential negative effects on fetal development arise from transport *via* the placenta into the developing fetus. Although it is unknown if OCTs are expressed in human embryos, we know that pre-implantation human embryos have limited mitochondrial capacity making them resistant to metformin [31, 32]. In Metformin in gestational diabetes study (MiG), children (aged 2) exposed to metformin during pregnancy were compared to children of the same age whose mothers were on insulin during pregnancy. Children exposed to metformin had comparable overall body fat, yet more subcutaneous fat over intra-abdominal fat compared to children exposed to insulin, thus suggesting that metformin treatment may lead to a more advantageous pattern of fat distribution than insulin [33].

Only recently there has been evidence to support the use of metformin for the management of GDM. It has, however, been used in early pregnancy and all through pregnancy for additional indications for decades. Metformin can help women with the polycystic ovarian syndrome to establish regular ovulation and to enhance conceiving odds, and by using it during the first trimester to lower the incidence of spontaneous abortion [34]. Metformin's use and effectiveness in the management of insulin-dependent T2DM in pregnancy have been supported by early research [35]. Despite this, it was not until the metformin in Gestational Diabetes trial, presented by Rowan et al. in 2008, was widely reported as an effective treatment for GDM [36].

2.2.1.2 Efficacy and safety

In the gestational diabetes trial [36], women were randomly assigned to either metformin or standard treatment, that is, insulin. Supplemental insulin was required by a large percentage of women using metformin (46%), however at much lower doses than GDM-women using insulin as monotherapy. The key outcome was a combination of neonatal hypoglycemia (2.6 mmol/L), respiratory distress, requirement for phototherapy, 5-minute Apgar score of 7, or premature birth (before 37 weeks), and it was similar in both treatment groups. Women who took metformin gained considerably less weight from enrolment to term than those who took insulin. Other parameters considered in the metformin and insulin clusters

were similar, including birth weight, neonatal anthropometrics, and odds for large for gestational age. However, when compared to insulin therapy, the incidence of severe hypoglycemia (1.6 mmol/L) was lower in the metformin group. This research also discovered that patient acceptability for metformin was substantially better than with insulin; when questioned if they would select it yet again for future pregnancies, 77 percent of metformin users replied yes, compared to only 27 percent of insulin users. Metformin's gastrointestinal side effects caused 32 women (8.8%) to cut their dose, although only 7 (1.9%) had to discontinue taking it.

A group of 100 GDM women merely treated with metformin *vs.* 100 women with GDM only treated with insulin were matched for age, weight, and ethnicity in a case–control observational study [37]. Maternal risk factors were similar in both groups. The rates of preeclampsia, prenatal hypertension, and Cesarean section were identical, but an average maternal gain of weight from enrolment to term was considerably lower in the metformin group, just as it was in the MiG study. When compared to women who were treated with insulin, women who were given metformin had a lower rate of preterm, neonatal jaundice, and admission to a neonatal unit, as well as an overall improvement in newborn morbidity [37].

Post-prandial glycemic levels may indeed be of importance when comparing metformin to other treatment options. A meta-analysis of three randomized controlled studies of GDM women found lower post-prandial glucose in metformin as opposed to insulin-treated patients, though these disparities did not meet statistical significance [38].

Metformin did not raise the risk of preterm delivery or Cesarean section, as reported in a latest systematic review, nor did it raise the risk of small for gestational age newborns. Metformin, on the other hand, was linked to a lower risk of preterm birth, newborn hypoglycemia, and admission to neonatal intensive care units, as well as a decreased prevalence of pregnancy-induced hypertension [39].

Because metformin is not stimulating the secretion of insulin, it does not provoke maternal hypoglycemia, which is a side effect that remains a concern with glyburide. For the same reason, severe neonatal hypoglycemia is less likely to occur after metformin administration compared to insulin [14]. Accordingly, hypoglycemia is a greater risk if taking insulin, than with OAD [40]. Metformin, on the other hand, crosses the placental barrier easily due to its low molecular mass, hydrophilic nature, and lack of protein binding [41]. Metformin concentrations in the fetus are likely minimal and no fetal side effects, such as congenital malformations, have been detected [42]. It is not thought to be teratogenic, as evidenced by decades of use in preconception and early pregnancy. There have been no reports of newborn lactic acidosis, and neonatal hypoglycemia has been related to maternal hyperglycemia during delivery rather than a direct side effect of metformin. It belongs to the FDA's Pregnancy Category B.

Before starting metformin treatment, patients should be informed about the potential for maternal adverse effects. Although its mechanism of action does not produce hypoglycemia directly, symptoms are observed in 0–10% of women who administered the drug. A 5 percent to 15% of women experienced gastrointestinal side effects, such as flatulence, nausea, diarrhea, and vomiting. Lactic acidosis, the most worrying potential side effect, was prevented by gradually raising the dose [43].

One final question could be certainly related to the eventual advantageous co-administration of metformin and insulin in GDM. Scarce reports have been published over the past decade; however, Chaves et al. [44] recently addressed this issue through the retrospective investigation with an evaluation of the Portuguese National Registry of GDM (2012–2017) with a very interesting report that in GDM women the concomitant use of metformin and insulin resulted in comparable obstetric and neonatal adverse events if paralleled with insulin monotherapy. Moreover,

the authors reported that expected beneficial effects on weight gain and insulin dose were simply not detected if both drugs were used in a parallel manner [44].

2.2.2 Glyburide

2.2.2.1 Pharmacological properties and use

Glyburide is a second-generation sulfonylurea that acts mainly by increasing the secretion of insulin from the pancreas and improving the insulin sensitivity of peripheral tissues. These actions can be detected after a block of the sulfonyl-urea receptor, which is actually a part of the ATP-sensitive potassium channel in the pancreatic beta cells [45]. Glyburide is lipophilic and significantly bound to albumin [46].

At first, it was assumed that glyburide did not cross the placenta. Langer et al. (2000) did not detect glyburide in umbilical cord serum of neonates whose mothers were taking glyburide during pregnancy, thus confirming *in vitro* investigations that found no glyburide transfer in-between mother and fetus. The reason behind that is that they used liquid chromatography with a limit of detection of 10 ng per milliliter [13]. Newer studies proved that glyburide can be found in umbilical cord serum by using a highly sensitive liquid chromatography-mass spectrometry test for determining glyburide at sub-ng/mL levels, confirming that glyburide is actually transferred transplacentally [47].

There is an obvious option to glyburide and that is insulin administration. Even though glyburide is an FDA category C drug, compared to insulin analogs (lispro, detemir, and aspart) that are all pregnancy risk factor B medications, glyburide is still widely used. The situation where glyburide is a better choice is where self-monitoring of glucose blood levels needed for insulin or insulin storage is not possible or where a patient has a severe needle phobia.

Another benefit of using glyburide is that it is a low-cost oral agent, easy to take with few side effects. Also, glyburide is, as an oral agent just like metformin, easier to use compared to insulin [41]. Nevertheless, the other use of glyburide during pregnancy for GDM patients is still unclear and needs to be comprehensively elucidated [48].

2.2.2.2 Efficacy and safety

The New England Journal of Medicine published a clinical investigation comparing glyburide versus insulin in management of GDM in 2000, which transformed the management of GDM. Namely, Langer et al. (2000) conducted the first randomized, controlled study where they compared glyburide to insulin by dividing 404 women with GDM into two groups, 201 receiving glyburide and 203 receiving insulin [49]. Results did not show any significant difference between the two clusters in neonatal outcomes by measuring high blood glucose concentrations, the incidence of macrosomia, admission to neonatal intensive care unit, etc. The authors also noted that the extent of glycemic control between the two groups was similar. A different study comparing macrosomia, neonatal hypoglycemia, and hyperbilirubinemia in two groups found no evidence that using glyburide instead of subcutaneous insulin leads to a higher rate of perinatal problems [50]. On the contrary, a retrospective cohort study analyzed data from 9173 women diagnosed with GDM and treated with glyburide opposite to insulin 150 days before delivery [37]. It was found that newborns delivered by women treated with glyburide were more expected to have complications than those delivered by mothers who were taking insulin. Complications noted were preterm birth, Cesarean delivery, hypoglycemia,

respiratory distress, jaundice, birth injury, large for gestational age, and hospitalization in the neonatal ICU [51].

Seven trials comparing glyburide (n = 457) to insulin (n = 467) were analyzed in one more recent meta-analyses by Jiang et al. to assess the efficacy and safety of oral anti-diabetic (OADs) medicines for GDM. In terms of glycemic management, the investigators did not find any difference between glyburide and insulin. Glyburide therapy, on the other hand, is linked to a higher risk of neonatal hypoglycemia, high neonatal birth weight, high maternal weight gain, and macrosomia [52].

A group of 457 glyburide-managed pregnancies and 467 insulin-treated pregnancies were evaluated in the Jiang meta-analysis comparing the efficacy and safety of OAD for GDM [52]. Despite no dissimilarity in glycemic control, the authors found that glyburide caused considerably more macrosomia than insulin (OR: 3.09, 95% CI: 1.59–6.04, P = 0.009). Glyburide was also associated with a greater rate of newborn hypoglycemia than insulin (OR: 2.64, 95% CI: 1.59–4.28, P = 0.0002). There was no difference in weight growth, Cesarean delivery rate, or preeclampsia between NICU admissions or premature births.

Finally, it has to be underlined that glyburide was ranked the worst in the recent meta-analysis, with the highest rates of macrosomia, hyperbilirubinemia, preeclampsia, neonatal hypoglycemia, low birth weight, preterm birth, and metformin (plus insulin when needed) had the lowest rates of pregnancy hypertension, macrosomia, LGA, RDS, preterm birth, and low birth weight [53]. Besides, one has to be very cautious with glyburide use, which was shown to be associated with weight gain, as well as maternal hypoglycemia, especially when taken without any food [45].

2.2.3 Acarbose

2.2.3.1 Pharmacological properties and use

Acarbose is an alpha-glucosidase inhibitor, which means it prevents enzymes found on the small intestine's brush border from breaking down complex starches into oligosaccharides and oligosaccharides, trisaccharides, and disaccharides into glucose. As a result, the rise in postprandial glucose concentrations is lowered. Its use is usually linked to gastrointestinal complications. Although just 2% of acarbose is absorbed as an active medication, 34% of its metabolites were found in the systemic circulation [54].

Acarbose is not usually recommended for the treatment of GDM, because it has not been thoroughly researched during pregnancy and considering safer and more acceptable options, with more information regarding treating GDM, such as insulin and metformin.

2.2.3.2 Efficacy and safety

One small randomized prospective study (n = 70) in Brazil compared glyburide and acarbose to insulin in the treatment of GDM and showed the absence of notable differences in fasting or postprandial glucose concentrations with acarbose, although gastrointestinal side effects were higher in occurrence with acarbose [55]. Acarbose showed a higher failure rate (42%) in establishing glycemic control compared to glyburide (21%). Neonatal hypoglycemia occurred in one acarbose-treated subject, one insulin-treated subject, and eight glyburide-treated subjects. Only four neonates (16%) developed macrosomia, which is after receiving glyburide therapy.

Although in this short trial, failure to achieve glycemic control with acarbose was higher if compared to glyburide, the decreased incidence of hypoglycemia and

macrosomia underlines acarbose as an appealing agent to investigate in future GDM treatment studies. Accordingly, in the recent investigation published by Jayasingh et al. (2020), it was proposed that acarbose can be seen as an effective and adequately tolerated choice for the management of GDM [56]. Namely, this prospective, open-label, and controlled study was designed to compare the fetomaternal outcomes in pregnant women with GDM designated to insulin or acarbose group. Thus, no difference was found if the following parameters were paralleled in between the groups: the incidence of recurrent infections, preeclampsia, or premature rupture of membranes; then the modes of delivery, mean postoperative random blood glucose, fasting blood glucose level at day 7 and after 6 weeks; and finally difference in the mean birth weight of offspring born to mothers treated with either of the two pharmacological agents.

Even though using acarbose in diabetic patients has been linked to abnormal liver enzymes and hepatic failure, a newer study did not show a higher risk of liver injury during acarbose treatment [57]. Acarbose can pass through the placenta. In pregnant animal investigations, doses up to 32 times higher than the human dose were not proven to be teratogenic. On the other hand, it induces stomach cramps and may raise prostaglandin E, suggesting that it possess the potential ability to induce labor [58].

3. Supplementation and traditional treatment options

The efficacy of vitamin and mineral supplementation in GDM patients is still under investigation. However, today is known that in GDM, low levels of vitamin D, vitamin E, and magnesium have been detected, whereas glucose metabolism, anti-inflammatory, and anti-oxidative stress have been all positively regulated after vitamin D, vitamin E, magnesium, and selenium supplementation, which was also confirmed in the very recent meta-analysis reported by Li et al. [59]. In the same manner, 6-week-long Mg-Zn-Ca-vitamin D co-supplementation reduced biomarkers of inflammation and oxidative stress in GDM women [60]. To continue, the improvement in glycemic control and decline of adverse fetomaternal outcomes after vitamin D supplementation (including Cesarean section, postpartum hemorrhage, maternal hospitalization, neonatal hyperbilirubinemia, giant children, fetal distress, polyhydramnios, premature delivery) was underlined by Wang et al. [61].

Dietary adjustments accompanied with lifestyle modifications are known to achieve normoglycemia in a majority of women with GDM, especially underlining careful attention to type and amount of dietary carbohydrates [62]. In this context, myoinositol, a dietary supplement knowing to decrease insulin resistance, became extensively investigated [63]. It represents inositol isomer organically present for example in legumes or nuts, but also synthesized in kidneys and liver to a certain extent. Accordingly, recent findings pointed out that, if started shortly after the GDM diagnosis, myoinositol (1000 mg twice daily, *per os*) was shown to be effective in reaching glycemic control and reducing the need for additional pharmacotherapy [64].

Traditional Chinese medicine and herbal products, known to be broadly utilized during human history, now belong to a very interesting field currently investigated in the frame of GDM [65]. So far, herbs such as *Zuo Gui Wan*, red raspberry tea, and *Orthosiphon stamineus* all provided valid possibilities in reducing glucose and alleviating the GDM-related pathophysiology, and at the same time with good safety profile to the mother and neonate [66]. In addition, the antidiabetic potential of glycyrrhiza flavonoids from traditional Chinese medicine, as adjuvants for insulin therapy, could be especially beneficial in GDM [67].

Finally, probiotics supplementation in improving glycemic control and attenuating some of the adverse events related to GDM is a very interesting and appealing scientific issue that needs further elucidation [68, 69].

Even though new and promising results are published every day, novel investigations and, most of all, well-designed standardized protocols are needed for obtaining original, comparable, and sustainable results in this field of adjuvant GDM treatment.

4. Conclusions

In the twenty-first century, GDM poses a significant challenge to health care professionals. The short- and long-term effects of successfully controlling GDM are important for both the mother and the fetus. This chapter provided data related to proposed pharmacological treatment options for GDM, further evaluating each therapy's unique characteristics, benefits, and drawbacks in comparison with the alternatives. Most guidelines recommend oral pharmacological therapy, such as glyburide and metformin, and it is now widely used, with data on efficacy and safety. They can both be used as the first-line option; however, metformin appears to be preferable to glyburide in terms of newborn and maternal outcomes, while it is associated with a higher incidence of failure to achieve appropriate glycemic control. Analogs such as detemir, aspart, and lispro, which have been thoroughly proved for their safety and efficacy during pregnancy, are indicated as first-line therapy or when oral medication fails to achieve optimal glucose control. Glargine can be used during pregnancy, while there is not as much data to back it up as there is for other long-acting analogs and human insulins.

Therefore, the pharmacological treatment for GDM should be adapted to the patient's characteristics, glycemic profile, and preferences, as well as local professional body guidelines. While insulin has typically been used to treat GDM, both metformin and glyburide may be used, but patients should be informed about the risks and advantages.

Pharmacotherapy of GDM is still under investigation, even though much is known about GDB itself. We can witness that the molecular understanding of GMB has been constantly translated to more efficacious and safer therapeutic options. Still, we expect that coordinated and well-focused basic and clinical investigations will provide even more precise information regarding future choices for prevention and adequate, as well as timely treatment of GDM.

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References

[1] Rosik J, Szostak B, Machaj F, Pawlik A. The role of genetics and epigenetics in the pathogenesis of gestational diabetes mellitus. Annals of Human Genetics. 2020;**84**(2):114-124. DOI: 10.1111/ahg.12356

[2] McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nature Reviews. Disease Primers. 2019;**5**(1):47. DOI: 10.1038/s41572-019-0098-8

[3] Franzago M, Fraticelli F, Stuppia L, Vitacolonna E. Nutrigenetics, epigenetics and gestational diabetes: Consequences in mother and child. Epigenetics. 2019;**14**(3):215-235. DOI: 10.1080/15592294.2019.1582277

[4] Radenkovic M. Treatment considerations for gestational diabetes mellitus and long-term postpartum options. In: Gestational Diabetes. IntechOpen; 2011. pp. 315-324. DOI: 10.5772/21908

[5] Subiabre M, Silva L, Toledo F, Paublo M, López MA, Boric MP, et al. Insulin therapy and its consequences for the mother, foetus, and newborn in gestational diabetes mellitus. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2018;**1864** (9 Pt B):2949-2956. DOI: 10.1016/j. bbadis.2018.06.005

[6] Singh KP, Rahimpanah F, Barclay M. Metformin for the management of gestational diabetes mellitus. The Australian & New Zealand Journal of Obstetrics & Gynaecology. 2015;**55**(4):303-308. DOI: 10.1111/ ajo.12311

[7] Gou BH, Guan HM, Bi YX, Ding BJ. Gestational diabetes: Weight gain during pregnancy and its relationship to pregnancy outcomes. Chinese Medical Journal. 2019;**132**(2):154-160. DOI: 10.1097/CM9.0000000000000036

[8] Mirabelli M, Chiefari E, Tocci V, Greco E, Foti D, Brunetti A. Gestational diabetes: Implications for fetal growth, intervention timing, and treatment options. Current Opinion in Pharmacology. 2021;**60**:1-10. DOI: 10.1016/j.coph.2021.06.003

[9] Lorenzo-Almorós A, Hang T, Peiró C, Soriano-Guillén L, Egido J, Tuñón J, et al. Predictive and diagnostic biomarkers for gestational diabetes and its associated metabolic and cardiovascular diseases. Cardiovascular Diabetology. 2019;**18**(1):140. DOI: 10.1186/s12933-019-0935-9

[10] Szmuilowicz ED, Josefson JL, Metzger BE. Gestational diabetes mellitus. Endocrinology and Metabolism Clinics of North America. 2019;**48**(3):479-493. DOI: 10.1016/j. ecl.2019.05.001

[11] Żurawska-Kliś M, Czarnik K, Szymczak S, Wójcik M, Cypryk K. 1-Hour postprandial glucose target of < 120 mg/dL is superior to < 140 mg/dL in the treatment for gestational diabetes mellitus in relation to pregnancy outcomes: A retrospective study. Acta Diabetologica. 2021;**58**(5):665-668. DOI: 10.1007/s00592-020-01655-w

[12] Norman RJ, Wang JX, Hague W. Should we continue or stop insulin sensitizing drugs during pregnancy? Current Opinion in Obstetrics & Gynecology. 2004;**16**(3):245-250. DOI: 10.1097/00001703-200406000-00007

[13] Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. The New England Journal of Medicine. 2000;**343**(16):1134-1138. DOI: 10.1056/ NEJM200010193431601

[14] Bidhendi Yarandi R, Amiri M, Ramezani Tehrani F,

Behboudi-Gandevani S. Effectiveness of antidiabetic agents for treatment of gestational diabetes: A methodological quality assessment of meta-analyses and NETWORK META-ANALYSIS. Journal of Diabetes Investigation. 2021. DOI: 10.1111/jdi.13603

[15] Sheiner E. Gestational diabetes mellitus: Long-term consequences for the mother and child grand challenge: How to move on towards secondary prevention? Frontiers in Clinical Diabetes and Healthcare. 2020;**1**:1. DOI: 10.3389/fcdhc.2020.546256

[16] Challier JC, Hauguel S, Desmaizieres V. Effect of insulin on glucose uptake and metabolism in the human placenta. The Journal of Clinical Endocrinology and Metabolism. 1986;**62**(5):803-807. DOI: 10.1210/jcem-62-5-803

[17] Martis R, Crowther CA, Shepherd E, Alsweiler J, Downie MR, Brown J. Treatments for women with gestational diabetes mellitus: An overview of Cochrane systematic reviews. Cochrane Database of Systematic Reviews. 2018;**8**:CD012327. DOI: 10.1002/14651858.CD012327.pub2

[18] Lende M, Rijhsinghani A. Gestational diabetes: Overview with emphasis on medical management. International Journal of Environmental Research and Public Health. 2020;**17**(24):9573. DOI: 10.3390/ijerph17249573

[19] Kautzky-Willer A, Harreiter J, Winhofer-Stöckl Y, Bancher-Todesca D, Berger A, Repa A, et al. Gestational diabetes mellitus (Update 2019). Wiener Klinische Wochenschrift. 2019;**131**(Suppl 1):91-102. DOI: 10.1007/s00508-018-1419-8

[20] Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin no. 190: Gestational diabetes mellitus. Obstetrics and Gynecology.

2018;**131**(2):e49-e64. DOI: 10.1097/AOG.0000000000002501

[21] Toledano Y, Hadar E, Hod M. Safety of insulin analogues as compared with human insulin in pregnancy. Expert Opinion on Drug Safety. 2016;**15**(7):963-973. DOI: 10.1080/14740338.2016.1182153

[22] Pettitt DJ, Ospina P, Kolaczynski JW, Jovanovic L. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. Diabetes Care. 2003;**26**(1):183-186. DOI: 10.2337/diacare.26.1.183

[23] Musa OAH, Syed A, Mohamed AM, Chivese T, Clark J, Furuya-Kanamori L, et al. Metformin is comparable to insulin for pharmacotherapy in gestational diabetes mellitus: A network meta-analysis evaluating 6046 women. Pharmacological Research. 2021;**167**(105546):105546. DOI: 10.1016/j.phrs.2021.105546

[24] Lv S, Wang J, Xu Y. Safety of insulin analogs during pregnancy: A meta-analysis. Archives of Gynecology and Obstetrics. 2015;**292**(4):749-756. DOI: 10.1007/s00404-015-3692-3

[25] Herrera KM, Rosenn BM, Foroutan J, Bimson BE, Al Ibraheemi Z, Moshier EL, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. American Journal of Obstetrics and Gynecology. 2015;**213**(3):426.e1-426.e7. DOI: 10.1016/j.ajog.2015.06.010

[26] Scarpello JHB, Howlett HCS. Metformin therapy and clinical uses. Diabetes & Vascular Disease Research. 2008;**5**(3):157-167. DOI: 10.3132/dvdr.2008.027

[27] Wiernsperger NF, Bailey CJ. The antihyperglycaemic effect of metformin: Therapeutic and cellular mechanisms.

Drugs. 1999;**58**(Supplement 1):31-39. DOI: 10.2165/00003495-199958001-00009

[28] Glueck CJ, Goldenberg N, Wang P, Loftspring M, Sherman A. Metformin during pregnancy reduces insulin, insulin resistance, insulin secretion, weight, testosterone and development of gestational diabetes: Prospective longitudinal assessment of women with polycystic ovary syndrome from preconception throughout pregnancy. Human Reproduction. 2004;**19**(3):510-521. DOI: 10.1093/humrep/deh109

[29] King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): Clinical and therapeutic implications for type 2 diabetes: Therapeutic implications of the UKPDS. British Journal of Clinical Pharmacology. 1999;**48**(5):643-648. DOI: 10.1046/j.1365-2125.1999.00092.x

[30] Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: The evidence today. Diabetes & Metabolism. 2003;**29**(4):6S28-6S35. DOI: 10.1016/s1262-3636(03)72785-2

[31] Ahmadimoghaddam D, Hofman J, Zemankova L, Nachtigal P, Dolezelova E, Cerveny L, et al. Synchronized activity of organic cation transporter 3 (Oct3/Slc22a3) and multidrug and toxin extrusion 1 (Mate1/Slc47a1) transporter in transplacental passage of MPP+ in rat. Toxicological Sciences. 2012;**128**(2):471-481. DOI: 10.1093/toxsci/kfs160

[32] Cho YM, Kwon S, Pak YK, Seol HW, Choi YM, Park DJ, et al. Dynamic changes in mitochondrial biogenesis and antioxidant enzymes during the spontaneous differentiation of human embryonic stem cells. Biochemical and Biophysical Research Communications. 2006;**348**(4):1472-1478. DOI: 10.1016/j.bbrc.2006.08.020

[33] Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestational diabetes: The offspring follow-up (MiG TOFU): Body composition at 2 years of age. Diabetes Care. 2011;**34**(10):2279-2284. DOI: 10.2337/dc11-0660

[34] Kumar P, Khan K. Effects of metformin use in pregnant patients with polycystic ovary syndrome. Journal of Human Reproductive Sciences. 2012;**5**(2):166. DOI: 10.4103/0974-1208.101012

[35] Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. New England Journal of Medicine. 2008;**358**(19):2003-2015. DOI: 10.1056/NEJMoa0707193

[36] Balani J, Hyer SL, Rodin DA, Shehata H. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: A case-control study. Diabetic Medicine. 2009;**26**(8):798-802. DOI: 10.1111/j.1464-5491.2009.02780.x

[37] Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: A meta-analysis. PLoS ONE. 2013;**8**(5):e64585. DOI: 10.1371/journal.pone.0064585

[38] Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: A systematic review and meta-analysis. Diabetic Medicine. 2016;**34**(1):27-36. DOI: 10.1111/dme.13150

[39] Berggren ERICAK, Boggess KIMA. Oral agents for the management of gestational diabetes. Clinical Obstetrics and Gynecology. 2013;**56**(4):827-836. DOI: 10.1097/GRF.0b013e3182a8e0a5

[40] Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics

of metformin in late pregnancy. Therapeutic Drug Monitoring. 2006;**28**(1):67-72. DOI: 10.1097/01. ftd.0000184161.52573.0e

[41] Vanky E, Zahlsen K, Spigset O, Carlsen S. Placental passage of metformin in women with polycystic ovary syndrome. Fertility and Sterility. 2005;**83**(5):1575-1578. DOI: 10.1016/j. fertnstert.2004.11.051

[42] Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: A meta-analysis. Fertility and Sterility. 2006;**86**(3):658-663. DOI: 10.1016/j. fertnstert.2006.02.098

[43] Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Annals of Internal Medicine. 2007;**147**(6):386. DOI: 10.7326/0003-4819-147-6-200709180-00178

[44] Chaves C, Cunha F, Martinho M, Garrido S, Silva-Vieira M, Estevinho C, et al. Metformin combined with insulin in women with gestational diabetes mellitus: A propensity score-matched study. Acta Diabetologica. 2021;**58**(5):615-621. DOI: 10.1007/ s00592-020-01665-8

[45] Blair RA, Rosenberg EA, Palermo NE. The use of non-insulin agents in gestational diabetes: Clinical considerations in tailoring therapy. Current Diabetes Reports. 2019;**19**(12):158. DOI: 10.1007/ s11892-019-1243-1

[46] Malek R, Davis SN. Pharmacokinetics, efficacy and safety of glyburide for treatment of gestational diabetes mellitus. Expert Opinion on Drug Metabolism & Toxicology. 2016;**12**(6):691-699. DOI: 10.1080/17425255.2016.1187131

[47] Naraharisetti S, Kirby B, Hebert M, Easterling T, Unadkat J. Validation of a sensitive LC–MS assay for quantification of glyburide and its metabolite 4-transhydroxy glyburide in plasma and urine: An OPRU Network study. Journal of Chromatography B. 2007;**860**(1):34-41. DOI: 10.1002/ bmc.3314

[48] Guo L, Ma J, Tang J, Hu D, Zhang W, Zhao X. Comparative efficacy and safety of metformin, glyburide, and insulin in treating gestational diabetes mellitus: A meta-analysis. Journal Diabetes Research. 2019;**2019**:9804708. DOI: 10.1155/2019/9804708

[49] Langer O, Yogev Y, Xenakis EMJ, Rosenn B. Insulin and glyburide therapy: Dosage, severity level of gestational diabetes, and pregnancy outcome. American Journal of Obstetrics and Gynecology. 2005;**192**(1):134-139. DOI: 10.1016/j. ajog.2004.07.011

[50] Sénat MV, Affres H, Letourneau A, Coustols-Valat M, Cazaubiel M, Legardeur H, et al. Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes. JAMA. 2018;**319**(17):1773. DOI: 10.1001/ jama.2018.4072

[51] Camelo Castillo W, Boggess K, Stürmer T, Brookhart MA, Benjamin DK, Jonsson Funk M. Association of adverse pregnancy outcomes with glyburide vs insulin in women with gestational diabetes. JAMA Pediatrics. 2015;**169**(5):452. DOI: 10.1001/jamapediatrics.2015.74

[52] Jiang YF, Chen XY, Ding T, Wang XF, Zhu ZN, Su SW. Comparative efficacy and safety of OADs in management of GDM: Network meta-analysis of randomized controlled trials. The Journal of Clinical Endocrinology & Metabolism. 2015;**100**(5):2071-2080. DOI: 10.1210/jc.2014-4403

[53] H-Ling L, S-Juan M, Y-Ni X, H-Zhuan T. Comparative efficacy and safety of oral antidiabetic drugs and insulin in treating gestational diabetes mellitus. Medicine (Baltimore). 2017;**96**(38):e7939. DOI: 10.1097/MD.0000000000007939

[54] Simmons D. Safety considerations with pharmacological treatment of gestational diabetes mellitus. Drug Safety. 2014;**38**(1):65-78. DOI: 10.1007/s40264-014-0253-9

[55] Bertini AM, Silva JC, Taborda W, Becker F, Bebber FR, Viesi JM, et al. Perinatal outcomes and the use of oral hypoglycemic agents. Journal of Perinatal Medicine. 2005;**33**(6):519-23. DOI: 10.1515/JPM.2005.092

[56] Jayasingh S Sr, Nanda S, Misra S, Baliarsinha A, Das S, Patil A. Comparison of fetomaternal outcomes in patients with gestational diabetes mellitus treated with insulin versus acarbose: Results of a prospective, open label, controlled study. Cureus. 2020;**12**(12):e12283. DOI: 10.7759/cureus.12283

[57] Chao CT, Wang J, Huang JW, Chien KL. Acarbose use and liver injury in diabetic patients with severe renal insufficiency and hepatic diseases: A propensity score-matched cohort study. Frontiers in Pharmacology. 2018;**9**:860. DOI: 10.3389/fphar.2018.00860

[58] Singh AK, Singh R. Oral antidiabetic agents in gestational diabetes: A narrative review of current evidence. Expert Review of Endocrinology and Metabolism. 2014;**10**(2):211-225. DOI: 10.1586/17446651.2015.982090

[59] Li D, Cai Z, Pan Z, Yang Y, Zhang J. The effects of vitamin and mineral supplementation on women with gestational diabetes mellitus. BMC Endocrine Disorders. 2021;**21**(1):106. DOI: 10.1186/s12902-021-00712-x

[60] Jamilian M, Mirhosseini N, Eslahi M, Bahmani F, Shokrpour M, Chamani M, et al. The effects of magnesium-zinc-calcium-vitamin D co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in gestational diabetes. BMC Pregnancy and Childbirth. 2019;**19**(1):107. DOI: 10.1186/s12884-019-2258-y

[61] Wang M, Chen Z, Hu Y, Wang Y, Wu Y, Lian F, et al. The effects of vitamin D supplementation on glycemic control and maternal-neonatal outcomes in women with established gestational diabetes mellitus: A systematic review and meta-analysis. Clinical Nutrition. 2021;**40**(5):3148-3157. DOI: 10.1016/j.clnu.2020.12.016

[62] Mustad VA, Huynh DTT, López-Pedrosa JM, Campoy C, Rueda R. The role of dietary carbohydrates in gestational diabetes. Nutrients. 2020;**12**(2):385. DOI: 10.3390/nu12020385

[63] D'Anna R, Santamaria A, Alibrandi A, Corrado F, DI Benedetto A, Facchinetti F. Myo-inositol for the prevention of gestational diabetes mellitus. A brief review. Journal of Nutritional Science and Vitaminology (Tokyo). 2019;**65**(Supplement):S59-S61. DOI: 10.3177/jnsv.65.S59

[64] Kulshrestha V, Balani S, Kachhawa G, Vanamail P, Kumari R, Sharma JB, et al. Efficacy of myoinositol in treatment of gestational diabetes mellitus in Asian Indian women: A pilot randomized clinical trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2021;**260**:42-47. DOI: 10.1016/j.ejogrb.2021.02.017

[65] Wang CC, Li L, Shao YF, Liu XK, Tam WH, Li RM. Chinese herbal medicines for treating gestational

diabetes mellitus. Cochrane Database
Syst Rev. 2019(6):CD013354.
DOI:10.1002/14651858.CD013354

[66] Xu YXZ, Xi S, Qian X. Evaluating
traditional Chinese medicine and herbal
products for the treatment of gestational
diabetes mellitus. Journal Diabetes
Research. 2019;**2019**:9182595. DOI:
10.1155/2019/9182595

[67] Bai L, Li X, He L, Zheng Y, Lu H,
Li J, et al. Antidiabetic potential of
flavonoids from traditional Chinese
medicine: A review. The American
Journal of Chinese Medicine.
2019;**47**(5):933-957. DOI: 10.1142/
S0192415X19500496

[68] Zhang J, Ma S, Wu S, Guo C,
Long S, Tan H. Effects of probiotic
supplement in pregnant women with
gestational diabetes mellitus: A
systematic review and meta-analysis of
randomized controlled trials. Journal
Diabetes Research. 2019;**2019**:5364730.
DOI: 10.1155/2019/5364730

[69] Kijmanawat A, Panburana P,
Reutrakul S, Tangshewinsirikul C.
Effects of probiotic supplements on
insulin resistance in gestational diabetes
mellitus: A double-blind randomized
controlled trial. Journal of Diabetes
Investigation. 2019;**10**(1):163-170. DOI:
10.1111/jdi.12863