Western European Journal of Medicine and Medical Science
Volume 2, Issue 10, October, 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

GESTATIONAL DIABETES

Candidate of Medical Sciences - **Egamkulov Z.T**
Samarkand, Uzbekistan

Abstract: Gestational diabetes mellitus (GDM), which is defined as a hyperglycemia condition first recognized during pregnancy, is currently the most common medical complication of pregnancy. GDM affects approximately 15% of pregnancies worldwide, which is about 18 million births per year. Mothers with GDM are at risk of developing gestational hypertension, preeclampsia, and termination of pregnancy by cesarean section. GDM increases the risk of complications, including cardiovascular disease, obesity, and impaired carbohydrate metabolism, leading to the development of type 2 diabetes (T2DM) in both the mother and the infant. The increasing incidence of GDM also leads to a significant economic burden and deserves more attention and awareness. A better understanding of risk factors and pathogenesis is becoming a necessity, with a particular focus on the impact of SARS-CoV-2 and diagnosis, as well as effective treatments that can reduce perinatal and metabolic complications. The main treatments for GDM are diet and increased exercise. Insulin, glibenclamide and metformin can be used to intensify treatment.

Background: Gestational diabetes mellitus (GDM) is a state of hyperglycemia (fasting plasma glucose ≥ 5.1 mmol/L, 1 h ≥ 10 mmol/L, 2 h ≥ 8.5 mmol/L during the oral glucose tolerance test of 75 g according to the IADPSG/WHO criteria), which is first diagnosed during pregnancy [1]. GDM is one of the most common medical complications of pregnancy, and its inadequate treatment can lead to serious adverse consequences for the health of the mother and child [1,2]. According to the latest estimates of the International Diabetes Federation (IDF), GDM affects approximately 14.0% (95% confidence interval: 13.97–14.04%) of pregnancies worldwide, which equates to about 20 million births annually [3]. Mothers with GDM are at risk of developing gestational hypertension, preeclampsia, and cesarean abortion [4]. In addition, GDM increases the risk of complications, including cardiovascular disease, obesity, and impaired carbohydrate metabolism, leading to the development of type 2 diabetes (T2DM) in both the mother and the infant [5,6,7]. The increase in the incidence of GDM also leads to a significant economic burden and deserves more attention and awareness [8].

Key words: gestational diabetes mellitus, insulin resistance, complications, behavioral therapy.

Research Materials and Methods: The study is an analysis of data currently available in the literature that relate to the epidemiology, pathogenesis, diagnosis, and treatment of GDM. The study was based on reviews, original articles, and meta-analyses published in English over the past 10 years.

Study results: The growing problem of overweight and obesity worldwide contributes significantly to the steady increase in the incidence of diabetes, including GDM, in the population of women of reproductive age [10]. According to a 2019 report by the International Diabetes Federation (IDF), more than 20.4 million women (14.0% of pregnancies) had carbohydrate metabolism disorders, of which approximately 80% were GDM, that is, about one in six births was affected by gestational diabetes [3]. The incidence of hyperglycemia during pregnancy increases with age. According to Mosses et al., GDM was diagnosed in 6.7% of pregnancies overall, but in 8.5% of women over 30 years of age [11]. Lao et al. showed the highest risk of developing GDM at the age of 35–39 years compared to younger pregnant women (OR 95% CI: 10.85 (7.72–15.25) versus 2.59 (1.84–3.67)) [12]. These observations

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were confirmed by IDF data showing the highest percentage of pregnancies with GDM, reaching 37% between the ages of 45–49 years, which was also due to the lower number of pregnancies with a concomitant overall higher percentage of diabetes in this population [3]. The birth of a child with macrosomia is another important factor that can increase the risk of both GDM and T2DM by up to 20% [13]. Even taking into account the age of the woman, multiple pregnancies remain in linear dependence on the incidence of GDM [14]. GDM in a previous pregnancy increases the risk of recurrence by more than six times [15]. In women with a BMI of at least 30 kg/m2, the incidence of GDM is 12.3%, and in women with first-degree relatives with a history of GDM, it is 11.6%. The combination of these two factors increases the risk of GDM up to 61% of cases [4,16,17]. More than a twofold percentage of pregnancies with GDM was observed in women who had previously been treated for polycystic ovary syndrome (PCOS) [18]. Recent studies have shown that the prevalence of GDM is related to the season and that the prevalence of GDM increases in summer compared to winter [19,20,21]. Moreover, a 50% increase in the incidence of GDM in pregnancies resulting from in vitro fertilization has been described [22]. The greatest hopes are associated with afamine, adiponectin, and 1,5-anhydroglucitol [23,24]. With many countries providing antenatal care by gynaecologists who can consult with other specialists, it is important to develop predictive models to identify women at highest risk of gestational diabetes in early pregnancy. The Benhalim-2 2020 model, which took into account interviews and biochemical data (propensity assessment model: history of GDM, FPG, height, triglycerides, age, ethnic origin, first trimester weight, family history of diabetes, HbA1c), showed the highest sensitivity [25].In the pathogenesis of GDM, as in type 2 diabetes, insulin resistance and a decrease in insulin secretion relative to the patient's needs play a key role. We observe GDM in both obese and thin women [26]. Pregnancy-induced insulin resistance overlaps with pre-pregnancy insulin resistance, which is already present in obese women, whereas in lean women, impaired first phase of insulin secretion also dominates [27]. Insulin resistance during pregnancy is predisposed to the diabetogenic effect of placental hormones (human placental lactogen (LPG), human placental growth hormone (PHG), growth hormone (GH), adrenocorticotropic hormone (ACTH), prolactin (PRL), estrogens and progestogens), increased secretion of pro-inflammatory cytokines (tumor necrosis factor alpha (TNF-α), IL-6, resistin and C-reactive protein (CRP)), adiponectin deficiency, hyperleptinemia and central resistance to leptin, impaired glucose transport in skeletal muscle, impaired insulin receptor signaling, and reduced expression and abnormal translocation of GLUT-4 into the adipocyte cell membrane [28,29,30]. Increased secretion of insulin antagonist hormones (placental hormones, cortisol) during pregnancy leads to increased insulin resistance, which at the end of the third trimester reaches a value similar to that of full-blown type 2 diabetes [9,31]. Subclinical inflammation in pregnant women as a result of the synthesis of pro-inflammatory cytokines in the placenta and adipose tissue also leads to insulin resistance [32,33]. So far, the effects of TNF-α, IL-6 and C-reactive protein on the development of insulin resistance have been best studied. Kirwan et al. stated that the increase in insulin resistance characteristic of pregnancy is most strongly correlated with the increase in TNF-α concentration, given that TNF-α is a marker of insulin resistance during pregnancy [34]. In addition, hyperleptinemia in the first weeks of pregnancy is a predictor of the development of gestational diabetes. According to Qui, the determination of leptin concentration ≥ 31.0 ng/mL at the 13th week of pregnancy causes a 4.7-fold increase in the risk of GDM compared to the risk at a leptinemia level of ≤14.3 ng/mL. For every 10 ng/mL increase in leptin concentration, the risk of GDM increases by 21% [35]. At the same

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time, GDM is characterized by an increased concentration of leptin, which leads to hyperleptinemia [36]. However, BMI before pregnancy is a stronger predictor of leptinemia than GDM itself [37]. Women with gestational diabetes have lower adiponectin concentrations than pregnant women without carbohydrate metabolism disorders, regardless of their BMI before pregnancy [38]. Low adiponectin concentrations in the first and second trimesters of pregnancy have been shown to predict the development of diabetes during pregnancy [39]. Barbour's study found a 1.5- to 2-fold increase in levels of the regulatory subunit p85α PI-3 kinase in both muscle and adipose tissue of obese pregnant women and pregnant women with GDM compared to obese non-pregnant women. In women with GDM, a 62% increase in the phosphorylating activity of IRS-1 serine residues in striated muscle cells was found compared to a control group of pregnant women without GDM, suggesting post-receptor mechanisms of insulin resistance [32]. similar to the population of healthy women. Treatment of GDM is based on consensus and expert opinion. Analyses of reviews of Cochrane's databases have shown that there are no clear data on the correlation between the intensity of glycemic control and obstetric outcomes [40]. Based on a 2014–2019 meta-analysis, Mitanchez et al. indicated that the greatest impact on reducing the number of obstetric complications is achieved by combining dietary treatment with exercise [41].

Conclusions: GDM is one of the most common pregnancy complications and carries lifelong risks for both women and their babies. Observational data have demonstrated a linear relationship between maternal glycemic parameters and the risks of adverse pregnancy and offspring outcomes. SARS-CoV-2 infection will undoubtedly affect the risk of GDM. Many doubts about the diagnostic criteria and treatment of GDM are still debated. But the costs and experience of patients limit its use in clinical practice. The use of metformin as a first-line drug for GDM remains controversial due to its transplacental passage and limited long-term follow-up data. Further clinical trials are needed for the use of other oral hypoglycemic agents for the treatment of GDM. It is very important that patients with GDM receive behavioral therapy and work closely with their doctor. Future work in this area should include research on both clinical and implementation outcomes, exploring strategies to improve the quality of care provided to women with GDM. Screening and treatment of GDM in early pregnancy is highly controversial due to the lack of data from large randomized controlled trials. There is an urgent need for carefully designed studies that could help inform decisions about the best practice for screening and diagnosing gestational diabetes.

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