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Prevention is better than cure: identifying and dealing with the key features involved in the prevention of gestational diabetes - A bird's eye view

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Abstract. – Gestational diabetes (GDM) is considered to be the most common metabolic problem of pregnancy, which, if not recognized and treated on time, can lead to devastating effects on both the mother's health and the health of the fetus and the newborns. Many studies have revealed that the children born of GDM mothers or grandmothers have higher chances of developing diabetes type I or type II later in their life. Early identification of risk factors can help prevent the appearance of severe GDM and its complications witnessed both in the child and the mother. Obesity is one of the major risk factors that should not be ignored, and obese females should first undergo weight reduction plans in case of planned pregnancies. Other risk factors include a family history of DM arterial hypertension, significant weight gain during pregnancy, short sleep duration, women's exposure to stressful environments, changes in alpha and beta microbiota, and air pollution.

Proper care should be provided to females of reproductive age both before and during pregnancy to avoid complications. Awareness programs for healthy lifestyles and diets, oral hygiene maintenance guides, and regular health check-ups can all be considered as a key to a healthy society. Expanding the analysis of gut microbiota in individuals at a heightened risk of GDM can hold particular value, especially during the preconception phase. The alterations in gut microbiota can serve as crucial factors in enhancing lifestyle modifications prior to conception. Further studies are required in this direction to decrease the prevalence of GDM, and efficient measures should be implemented before the consequences appear.

Key Words:
Gestational diabetes mellitus, Pregnancy, Obesity, Females, Newborns.

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Introduction

Gestational diabetes (GDM) is an important cause of perinatal morbidity for both the mother and the newborn, so its recognition and timely interventions to correct it can significantly improve the overall morbidity related to pregnancy, birth and the immediate perinatal period[1]. Gestational Diabetes, commonly encountered as an asymptomatic disease[2], represents the most common metabolic conditions encountered during pregnancy[3]. It usually occurs during the second or third trimester of pregnancy in previously non-diabetic women presenting with high blood sugar levels. In many instances, it can be stated as intolerance to glucose, with its first appearance or its first recognition during pregnancy[4,5]. Indifferent of the type of treatment administered (either only diet, oral antidiabetic drugs, or insulin treatment associated with it), the diagnosis of GDM remains the same[6]. In addition, even if diabetes persists after birth, it will still be classified as GDM[6]. With a worldwide increase in the incidence of obesity and undiagnosed diabetes mellitus (DM) type 2 among women in the fertile period, it becomes important to implement screening for DM in the first trimester of pregnancy (during their first visit to register pregnancy), because these pregnant women will be labeled as having DM type 2[7,8].

According to the Centers for Disease Control and Prevention (CDC) reports, in the United States of America, GDM influences 2-10% of pregnancies[3,9]. At the same time, it is estimated that worldwide, 7% of pregnancies are affected by GDM[4]. The prevalence of GDM varies according to the country, the regions of the respective country and also according to the race. In the United States of America, women of Asian origin are most frequently affected (11.1%), followed by Hispanics (6.6%) and white women (5.3%), and the lowest prevalence was recorded among black women[10]. More than half of GDM patients are likely to develop type 2 diabetes mellitus (DM) in the near future. In many countries like China, GDM has been declared an epidemic[11].

Risk Factors

A sedentary lifestyle with the advancement in technology has increased 100-fold compared to the previous times and hence, deteriorating the health status of people worldwide. Overweight and obesity are the key factors leading to higher chances of developing GDM[4,12].

42.8% of GDM cases are attributed to overweight and obesity during pregnancy[13]. Pre-pregnancy weight as well as pregnancy weight gain are inversely associated with diet quality, with a very poor diet being associated with low weight gain[14]. Poor socio-economic status associated with ethnic/racial discrimination further increases the risk of GDM[15].

The alteration of the intestinal microbiota is also associated with the increased risk of GDM[16-18]. The Firmicutes/Bacteroides ratio is significantly increased in patients with GDM[19]. Moreover, the profile of the intestinal microbiota in patients with GDM starting from the third trimester of pregnancy and up to 8 months after delivery is strikingly similar to that of patients with type 2 DM[20].

Screening and Diagnosis

An easy algorithm for GDM screening is proposed by the International Diabetes Federation (IDF) Figure 1.

The mechanisms involved in the occurrence of GDM are not fully understood yet. New markers but also various pathologies are more and more frequently correlated with the increase in the incidence of GDM.

The genetical transmission is relatively understudied in terms of its impact on the risk of developing GDM, in part due to the small number of diagnosed cases. Newborns born to mothers with gestational diabetes at an older age have a higher risk of developing type 1 and type 2 diabetes. Additionally, there is a higher incidence of type 2 diabetes among maternal grandmothers. Moreover, the involvement of genetic mechanisms goes beyond the risk of occurrence of GDM, being also involved in the risk of subsequent occurrence of DM or cardiovascular diseases both for the pregnant woman and her child as well as for the rest of her relatives[21].

DM was associated with 16 variants in eight loci in or near GF2BP2, CDKAL1, GLIS3, CDKN2A/2B, HHEX/IDE, TCF7L2, MTNR1B, and HNF1A[10].

Decreased expression of Annexin A1 (ANXA1) in the placenta (with impairment of plasma villi) is correlated with increased incidence of GDM as well as increased DNA damage[22]. ANXA1 is a calcium- and phospholipid-binding protein located both in the cytoplasm and in the nucleus but also in the plasma membrane[22]. It has a role

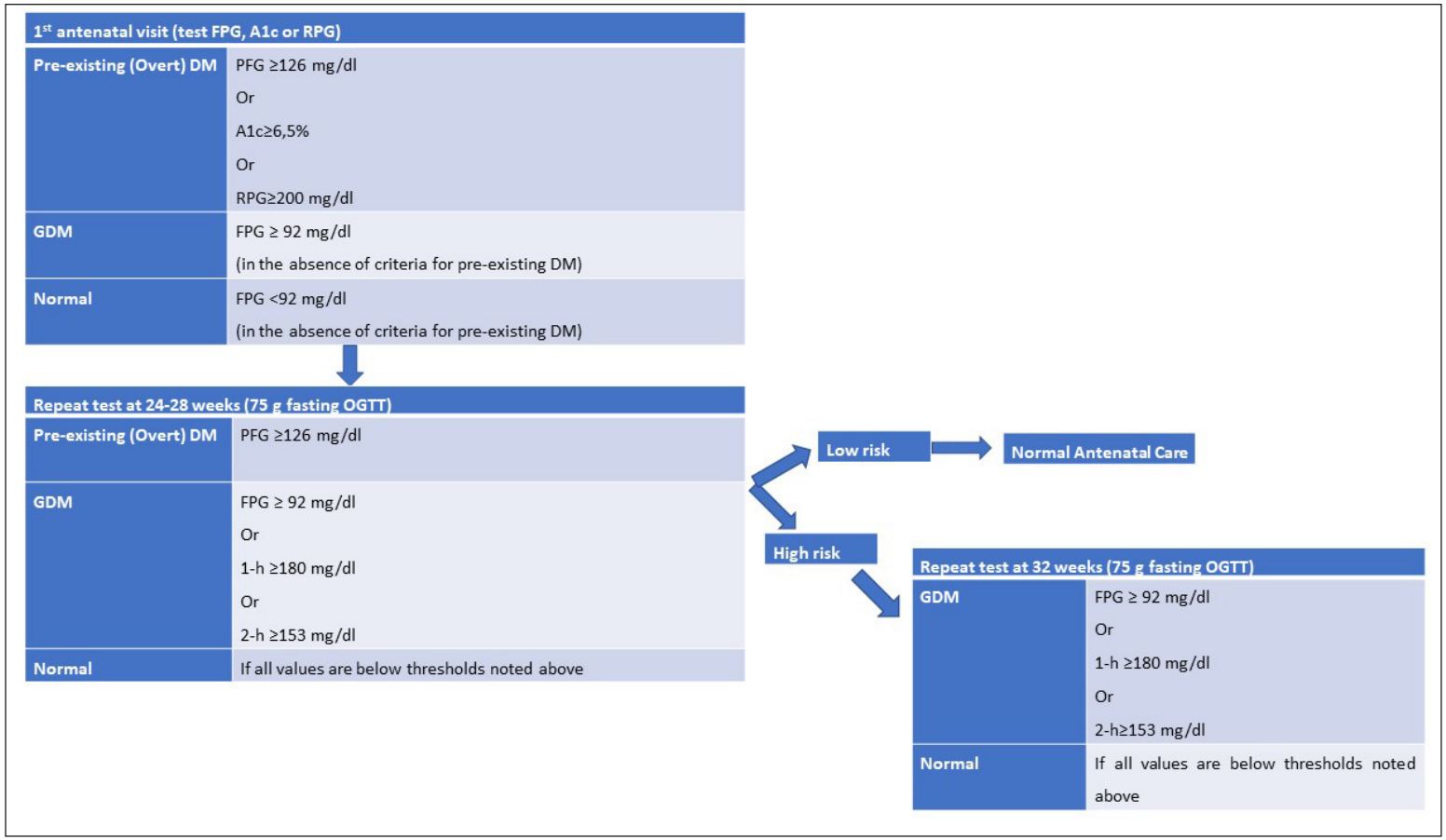

Figure 1. Gestational diabetes mellitus diagnostic algorithm[8].

in cell proliferation, differentiation, and cellular apoptosis[22].

Another mechanism that affects the development of placental villi but also their vasculature being also involved in the development of GDM is represented by the deficiency or absence of human equilibrative nucleoside transporter-1 (hENT1). hENT1 is part of the adenosine family, this being a potent vasodilator with an effect including in the placental circulation, having the role of facilitating the transport of adenosine[23].

The release of soluble factors from the ischemic placenta (on the background of uteroplacental circulatory insufficiency) will lead to the appearance of maternal endothelial dysfunction that will be associated with an increased risk of GDM[24]. In addition, if it is overlapping a pre-existing endothelial dysfunction, it results in an increase in the incidence of GDM[24].

Metabolic disorder in pregnant women seems to be present through the modification of lipid metabolism and the induction of insulin resistance; an important role in this mechanism is given to Betatrophin. Betatrophin is an important marker for increasing postprandial insulin secretion but also for decreasing lipoprotein lipase activity in adipose tissue. Increased Betatrophin levels have been associated with increased incidence of GDM.

Alteration of iron metabolism also appears to be involved in the occurrence of GDM. The risk of gestational diabetes mellitus (GDM) is also increased with a decrease in serum ferritin levels. This association is also observed in girls with low weight for gestational age and is more significant with prolonged periods of low ferritin levels. Increased pethidine plasma concentrations between 15-26 weeks of gestation are associated with an increased risk of developing GDM[25].

Low plasma levels of vitamin D are directly proportional to the risk of GDM. Moreover, a 5 ng/mL increase in plasma vitamin D is associated with a 14% decrease in the risk of appearance of GDM[26].

Gestational Diabetes in the Era of COVID-19

The infection with COVID-19 is responsible for the appearance or modification of the natural course of many pathologies, and sometimes of the normal physiological way. COVID-19 affects almost every system of the body. The effects of this infection, unfortunately, go well beyond the moment of the acute infection, the entity being called the post-acute phase of COVID-19 syndrome that has already been described by many authors[27,28].

Like any infection, the infection with COVID-19 can quickly destabilize the fragile immune balance of pregnant women[29]. Premature births compromised vascular perfusion of the fetus, and premature membrane ruptures have all been reported in pregnancies where the women had a COVID-19 infection in the initial weeks of pregnancies. Inflammatory processes suffered by the developing embryo, are capable of causing long-term postnatal side effects[30,31]. The mechanisms incriminated in the link between the two pathologies are represented by the presence of endothelial dysfunction and immune system deregulation induced by the COVID-19 infection[32]. These two will lead to the installation of pyroptosis, a particular way of cell death produced by the erroneous recognition of some receptors as pro-inflammatory molecules. NLRP3 inflammasome/caspase-1 pathway is the pathway most incriminated in the occurrence of GDM in mothers infected with COVID-19. Involvement of NLRP3 is associated with increased plasma levels of miR-106a-5p and miR-210-3p among pregnant women infected with COVID-19 who developed GDM[29].

Conclusions

Gestational diabetes, one of the most feared complications of pregnancy, is a disease that must be well-known by the medical staff providing antenatal care. The presence of risk factors should alarm both the patient and the doctor, and ways to control the harmful effects should be immediately initiated. Awareness programs for weight control, maintaining good oral hygiene, the importance of a healthy diet, and regular health check-up plans can all contribute to lowering the incidence of GDM or pregnancy-related issues. Healthy mothers and healthy children can lead to a healthy society. Hence, proper measures should be implemented in time, which will further reduce the burden on the healthcare system worldwide.

Conflict of Interest

The authors declare that they have no conflict of interests.

Informed Consent

Not applicable.

Ethics Approval
Not applicable.

Authors' Contributions
S. C.: Data base collection, writing the draft, N. R. K: writing and revising the manuscript, data base search, V. C.: data base search and data collection, M. N. N.: conception and design, D. Serban: final revision, M. A. I.: design and analysis5, D. N: study design, C. B: supervision, study conception.

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