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RISK FACTORS FOR GESTATIONAL DIABETES – AN UPDATE

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Abstract

Women with gestational diabetes mellitus (GDM) have an increased lifetime risk of developing type 2 diabetes mellitus (T2DM). GDM has a substantial impact on maternal and foetal short and long-term health. Risk factors for GDM may be genetic or nongenetic and have been analysed in numerous studies. Researches in recent years allowed the identification of other risk factors for GDM except for those already known. Knowledge and identification of all risk factors for GDM allows the elaboration of a prevention strategy of T2DM, it may influence the screening, diagnosis, and, subsequently, treatment modalities for this disease.

key words: *gestational diabetes mellitus, type 2 diabetes mellitus, risk factors*

Introduction

Diabetes mellitus diagnosed for the first time during pregnancy was defined as gestational diabetes mellitus (GDM). It has been recognised as a distinct form of diabetes from the World Health Organisation (WHO) classification in 1999 [1], but came back to actuality after the conclusion of some recent studies which clearly established the risk for the occurrence of perinatal events associated to maternal glycaemia in pregnancy: the Hyperglycaemia and Adverse Pregnancy Outcomes Study (HAPO) [2] and the Australian Carbohydrate Intolerance study in pregnant women [3]. In 2009, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), taking into consideration the results of the HAPO study, established new diagnostic criteria for GDM. The diagnosis of GDM is made when any of the following plasma glucose value are met or exceeded: fasting plasma glucose (≥92mg/dl), 1 hour plasma glucose (≥180mg/dl) and 2 hours plasma glucose (≥153mg/dl) during an *oral-glucose-tolerance-test* (OGTT) with 75g glucose. It was decided that only one modified value is enough for GDM diagnosis.

According to the WHO report in 2013, hyperglycaemia first detected at any time in pregnancy is classified into: diabetes mellitus in pregnancy (not diagnosed previously) and GDM [4].

Diabetes in pregnancy will be diagnosed according to the 2006 WHO criteria valid for the general population, i.e. if one or more of the following conditions are met: fasting plasma glucose ≥ 126mg/dl, 2-hour plasma glucose after 75g oral glucose load ≥ 200mg/dl, or any (random) plasma glucose > 200mg/dl in the presence of diabetes symptoms.

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Gestational diabetes should be diagnosed any time in pregnancy if at least one of the following criteria during a 75 g glucose load is met: fasting plasma glucose 92-125mg/dl, 1-hour plasma glucose >180mg/dl, and 2-hour plasma glucose 153-199mg/dl.

The new WHO specifications clarify ambiguities of the IADPSG criteria regarding the intervals of plasma glucose values which may make the distinction between diabetes in pregnancy and GDM. Systematic testing for GDM is usually carried out between the weeks 24 and 28 of pregnancy. Although often hyperglycaemia is less severe in GDM than in overt diabetes, there are studies which showed an increased risk of macrosomia, perinatal events (preterm birth, pre-eclampsia, birth trauma, neonatal hypoglycaemia, hyperbilirubinemia, caesarean section) [2,3], and on the long term risk of T2DM occurrence for mother. In addition, GDM is associated with an increased risk for the child to develop obesity, metabolic syndrome and even T2DM.

Risk factors for GDM

Knowing the risk factors for GDM is extremely important both for clinicians and for women of fertile age. Identifications of persons with risk for GDM may influence the modality of screening, diagnosis and, subsequently, of treatment. Risk factors for GDM may be genetic or nongenetic and may exist previous to the pregnancy or may occur during the pregnancy. The most important risk factors recognised for GDM are the advanced age of the mother, maternal weight, GDM existent in a previous pregnancy, history of macrosomia, family background of diabetes mellitus in first degree relatives, membership to certain ethnic groups with increased prevalence of diabetes [5]. Throughout different studies, other potential risk factors have been identified.

Older maternal age is recognised as the best documented risk factor. Numerous studies asserted that advanced age of mother is a risk factor for DGM with ,,cutoff" interval of the age between 30-35 years old [6-9]. A certain age limit for this risk factor was not precisely set, most of the studies indicating the increase of risk along with the age. Bo *et al.* [8] showed an increase in GDM risk from 0.15% for women under 20 years old, up to 4.2% for women over 30 years old (Odds Ratios (OR) of 2.8; 95% confidence interval-CI: 1.9-4.3). Following the retrospective analysis of the largest cohort of pregnant women (38.5000), Jolly *et al.* reported an average age of women with GDM of 33.0±4.8 years old *versus* 31.8±4.4 years old in the group without GDM [9]. In a recent study, Hedderson *et al.* reported an average age of women with GDM of 35.4±5.1 years, 84.2% of GDM women having the age over 30 years old [10].

Maternal weight. At global level, obesity became a real problem of public health due to its increased prevalence and numerous associated comorbidities. Many studies reported the relationship between maternal weight and the risk for various antepartum complications, at birth and postpartum. One of these complications is GDM. Maternal weight was analysed whether singularly (kg) or as *body mass index* (BMI-was computed as a ratio of weight to the square of height-kg/m²) in different moments, such as weight prior to pregnancy, excessive increase of weight during pregnancy, but also postpartum. Jang *et al.* [6] emphasised a statistically significant difference ($p<0.001$) between average weight prior to pregnancy which complicated with GDM (56.4±9.2 kg) versus 51.6±6.4 kg in the group without GDM. Most studies analyzed the correlation between BMI prior to pregnancy and subsequent occurrence of GDM [11-13]. One of the most recent studies [14] showed the increase of GDM

prevalence by categories of BMI: 0.7% in underweight women (13-18.4 kg/m²), 2.3% in women with normal weight (18.5-24.9 kg/m²), 4.8% in overweight women (25-29.9 kg/m²), 5.5% in women with 1st degree obesity (30-34.9 kg/m²) and 11.5% in women with morbid obesity. Authors also calculated the percentage of overweight and obese females with GDM and identified 46.2% (95%CI: 36.1-56.3) cases. In this original study it was asserted that, if all overweight and obese women would have the risk reduced to that of women with normal weight, almost half of the cases of GDM could be prevented. Thus, reducing the risk of GDM in the category of overweight and obese women would reduce the global prevalence of GDM.

The most important studies in the field of GDM were included in two meta-analyses. The meta-analysis published in 2007 by Chu *et al.* [15] assessed over 50,0000 women from 20 studies, analyzing the relationship between maternal obesity and GDM. The study found a risk for GDM 4 times higher in women with morbid obesity (OR 8.56, 95%CI 5.07-16.04) as compared to overweight women (OR 2.14, 95%CI 1.82-2.53). Another meta-analysis, comprised 70 studies and was published by Torloni *et al.* in 2009 [16]. The lowest risk of GDM (0.75) was reported in underweight women (95%CI 0.69-0.82), 1.94 in overweight women (95%CI 1.77-2.19), 3.01 in case of moderate obesity (95%CI 2.34-3.87) and 5.55 for morbid obesity (95%CI 4.27-7.21) as compared to women with normal weight. For each 1kg/m² increase of BMI was calculated an increase of GDM prevalence with 0.92%.

Another risk factor for GDM is the excessive weight gain during pregnancy. The optimal weight increase in pregnancy was established based on other studies, and is different depending on BMI prior to pregnancy. The American College of Obstetricians and Gynecologists (ACOG) updated its recommendations in 2013 [17]. There are studies which proved that excessive weight gain is a significant risk factor for GDM in all categories of BMI, but the association is more stringent in obese persons [18,19]. Hedderson *et al.* [19] assessed the relationship between weight increase in pregnancy and the risk to develop GDM in a group of 345 women with GDM *versus* 800 women without GDM. They established that the risk increases proportionally to the weight increase rate. As compared to the lowest tertile of gestational weight increase (<270g/week), an increase of 270-400g/week and >400g/week were associated to an OR of 1.43 (95%CI 0.96-2.14), respectively 1.74 (95%CI 1.16-2.60) for the association of GDM. Taking into account the prior results, we may assert that both excessive weight gain during pregnancy and increased maternal weight prior to pregnancy are „modifiable" risk factors on which we may actively intervene in order to prevent the occurrence of GDM.

Complications occurring during a prior pregnancy such as: macrosomia, congenital malformations, preterm birth, caesarean section, but also multiparity were frequently associated with the occurrence of GDM in subsequent pregnancies.

Macrosomia is generally known as an event secondary to maternal hyperglycaemia, but it is also considered one of the risk factors for GDM in a future pregnancy. The predictive value of macrosomia as a risk factor was sustained by the results reported by Jimenez-Moleon *et al.* [20] who found an OR of 5.8 for GDM in women who previously gave birth to a baby with macrosomia. Jang *et al.* [6] found macrosomia in the antecedents of studied women with GDM in 9.3% as compared to 2.5% in women without GDM. They also reported an increased frequency of prior congenital malformations in

women with GDM (20.7%) as compared to those without GDM (OR 5.5; 95%CI 4.1-21.1). In the same cohort they reported that prior preterm birth is associated to an increased risk for subsequent GDM (OR of 8.5; 95%CI 2.35-30.78).

Caesarean section in a prior pregnancy was also reported as an independent risk factor for GDM in a recent study [7]. Thus, Caesarean section was found in antecedents in 14.8% of women with GDM and in 10.1% in the control group (OR 1.55, 95%CI 1.11-1.25). Multiparity was incriminated as an independent risk factor for GDM and was supported by certain studies, but there are also studies which do not support this correlation [21,22]. Over the last years, studies focused also on the analysis of twin pregnancies, as it was assumed that a large placental mass represents an important risk factor in GDM pathogenesis. Thus, the prevalence of GDM was found to be significantly higher in women with twin pregnancy than in singletons, but extended studies to support these assumptions are necessary [23,24].

The excess of amniotic fluid in current pregnancy, the foetus large for gestational age before week 24 of pregnancy, imminent abortion or preterm birth are also more frequently associated with GDM. From the multitude of obstetrical risk factors reported above, the best documented are classified as major risk factors. The International Diabetes Federation (IDF) 2009 Guide and the current recommendations of ACOG maintain macrosomia as a major risk factor for GDM [5,17].

Membership to certain minority groups. Increased prevalence of GDM in certain ethnic groups was well documented by numerous studies that established an increased risk for the ,,non-white" race [25]. For still unclear reasons, nonwhite women who include Afro-Americans, Indian-Americans, Hispanics and persons coming from the area of Middle East and south of Asia (especially India, Pakistan or Bangladesh) are more prone to the occurrence of GDM. An extended analysis which comprised 45 published articles (with 13 studies considered eligible) reported that the most decreased recurrence rate of GDM (30-37%) was found in non-Hispanic white population, and the most increased rate (52-69%) was found in ethnic minorities [26].

The presence of the *polycystic ovary syndrome (PCOS)* was also incriminated as an independent risk factor for GDM. This is explained by the association with an increased degree of insulin-resistance during pregnancy. [27]. Some professional associations, such as the Canadian Diabetes Association, maintain PCOS in the category of major risk factors for GDM [28]. PCOS is a common reproductive disorder of women and a high proportion of women with PCOS have an increased risk for metabolic disorders such impaired fasting glucose (IFG), T2DM and obesity. Pregnancy and its associated high progesterone levels may generate enhanced insulin resistance and secondary GDM.

Family history revealing a first-degree relative with T2DM or GDM. GDM has a recognised familial aggregation. The causes of aggregation in 1st degree relatives with a history of GDM or other form of diabetes are determined by genetic factors of susceptibility, epigenetic influences and shared environmental factors [29,30]. In the last years, Genome Wide Association studies (GWAs) led to a real explosion of knowledge about the genetic risk variants for all major forms of diabetes. The results are important at the same time also for the appreciation of the genetic risk of occurrence of GDM but also of subsequent evolution towards overt T2DM. Some researchers consider that GDM has the same genetic background as

T2DM, but occurs earlier in life, being favoured by the physiological increase of insulin-resistance in the last part of the pregnancy [31]. This theory is supported by the relationship between GDM, maternal obesity and insulin-resistance, associated to the increased risk of diabetes mellitus in women with prior GDM. Although most of women with GDM associate increased risk of developing T2DM, there were described cases of women with GDM who associated a genetic predisposition for autoimmune diseases and a certain structure of human leukocyte antigen (HLA) which is rather correlated with type 1 diabetes mellitus (T1DM) than to T2DM [32,33]. A rare, particular form of diabetes is maturity-onset diabetes of the young (MODY), which affects 1-2% of the persons with diabetes. Because of its insidious onset, not specific as compared to other types of diabetes, if it is present in pregnancy, it may be easily confounded and diagnosed as GDM, and postpartum as T2DM. If the genetic background of T1DM and T2DM involves numerous genes with a complex inheritance, in MODY the transmission is monogenic [34].

„Specific" genetic risk for GDM. Studies which analyzed candidate genes in Caucasian and Asian populations found a correlation between GDM and 14 of the genetic variants found as associated to T2DM in GWAs. (CDKALI, CDKN2A/CDKN2B, FTO, GCK, HHEX/IDE, HNF1A, HNF1B, IGF2BP2, IRSI, KCNQI, MTNRIB, SLC30A8 and TCF7L2) [35]. A recent meta-analysis of 22 studies on genetics of GDM which included 10,336 women with GDM and 17,445 control subjects, found 8 variants significantly associated with GDM (TCF7L2/rs7903146, CDKAL1/rs775484, MTNR1B/rs10830963, IGF2BP2/rs4402960, KCNQ1/rs2237892, KCNQ1/rs2237895, KCNJ11/rs5219 and GCK/rs4607517) [36]. These studies reconfirm the relation between GDM and T2DM, although there were additional genetic variants which were not found as associated to T2DM in GWAs. The risk for GDM has undoubtedly a genetic component which is shared with other forms of diabetes, and the possibility to identify some specific factors for GDM remains unclear. The assessment of genetic risk for GDM and postpartum diabetes is important both to individualise the treatment of women with GDM, and to reduce perinatal outcomes and the risk of transmission between generations.

Other GDM risk factors. Researches carried out over the last years allowed the identification of other risk factors for GDM including the deficit of vitamin D [37,38], diet rich in saturated fats [40,41], lifestyle factors such as physical activity and smoking [39]. Short stature was also reported as an independent risk factor for GDM in several studies [6,40]. A recent case-control study aimed to determine if there is a correlation between sex hormone–binding globulin (SHBG) level measured before the pregnancy and the risk of GDM occurrence. The study assessed 256 women with GDM versus controls and compared the risk for GDM between the highest SHBG level quartile and the other quartiles (OR 1.06; 95%CI 0.44-2.52, respectively OR 2.33; 95%CI 1.07-5.09) indicating a statistically significant difference. A level of SHBG below the average (<64.5 nmol/L) was correlated to a five times higher risk (OR 5.34; 95% CI 3.00-9.49) as compared to women with a level over the average. In conclusion, it was appreciated that the decreased level of SHBG was associated to a GDM risk. By its routine antepartum measurement women at risk may be identified allowing applying prevention measures [10].

Conclusion

In order to determine the practical use of different risk factors, extended studies are still

necessary. While the WHO 2013 report considered that there are not enough arguments for universal screening of GDM, this being limited to women with risk factors, the American Diabetes Association (ADA) recommended even from 2011 [41] the universal screening for GDM with a 75g-OGTT at 24-28 weeks of gestation in all women not known to have prior diabetes. The implication of these recommendations should be considered in the context of each health system.

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