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GESTATIONAL DIABETES MELLITUS – IS STILL A "MYSTERIOUS DISEASE" IN 2016?

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Abstract

Overview of necessity of universal screening as the tool for adequate diagnosis of GDM in 2016. Identifying of gestational diabetes mellitus (GDM) overpasses the medical discussion of utility, both for the mother and child, both for the short term and long term possible complications.

Key words: Gestational Diabetes Mellitus, Diabetes in Pregnancy, Screening, Diagnosis.

INTRODUCTION

Pregnancy is a specific challenging metabolic period in a woman's life, unique from many points of view for the human body capacity of adaptation to sustain the development of the embryo and fetus. The physiological changes of the maternal environment during pregnancy create a medium characterized by insulin resistance. These metabolic changes advance with advancing gestational age, and that is why, even if they begin together with the pregnancy start, they progress through to the third trimester (1).

Pregnancy becomes a challenge for the mechanism of glycemic control, pushing up to the limits of the maternal carbohydrate metabolism capacity. If this capacity is overwhelmed by increased demand, the result is activation of secondary regulatory mechanisms as reduced insulin stimulation of glucose uptake in skeletal muscle, decreased insulin suppression of lipolysis and limitation in insulin suppression of glucose release done by the liver. In this way, not only the insulin resistance but also insulin secretion is tested during pregnancy. In these cases, obesity and weight gain might exacerbate the insulin receptor defects, and these firsts revealed by pregnancy "low resistance" points in glycemic control might be the key point in preventing and postponement of major pathology to be installed and give the awareness about the risk in developing a DM type II in an apparently normal woman during her pregnancy. The maternal adiposity and the maternal weight gain during pregnancy play also a role in creating an insulin resistance environment during pregnancy. In this way, pregnancy itself can be view as a "physiological" test for further risks related to glycemic disturbances in women.

Gestational diabetes mellitus (GDM) can be diagnosed only during pregnancy, because of the specific changes, and also is a risk of further impairments of glucose metabolism, both for mother and fetus. It is also a time for interventions – nutrition and life style changes, and if it is necessary, medication, meant to prevent or postpone the appearance of future diabetes mellitus.

As research and clinical studies provided more insight on the carbohydrate metabolism adaptation and possible pathological status, the notion of gestational diabetes needed a definition and a consensus for diagnostic. Since year 2000 several definitions and glycemic cut-offs were discussed from many points of view: maternal and fetal outcome, health care efforts, percent of disease identification in population, burden of perception from the pregnant women of the pregnancy, and last but not least - cost efficiency.

For a long time, gestational diabetes was defined as any degree of glucose intolerance with onset or first recognition during pregnancy, whether the condition preceded the pregnancy or not. This approach was simpler to use, offering a unified definition to classify and detect glucose intolerance in pregnancy and to integrate all glucose metabolism disturbances in pregnancy. The major problem with this definition was the lack of differentiation between the women with pre-existing diabetes, present at the moment of conception and aggravated by pregnancy, and by this, it was not possible to make the difference between morbidities associated with preexisting diabetes in pregnancy and gestational diabetes. Therefore renewed efforts have been made to improve the definition and classification of hyperglycemia during pregnancy.

The increasing prevalence of diabetes and GDM

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and more data about greater prevalence of maternal and fetal complications resulting from diabetes mellitus antedating pregnancy (2) prompted the need for a new, more precise definition of GDM.

Therefore, hyperglycemia first detected at any time during pregnancy should be classified either as diabetes mellitus in pregnancy (DIP) or GDM (3, 4).

Global GDM prevalence rates show wide variations due to ethnicity and ethnic heterogeneity among different populations tested, which are further exacerbated by the different screening and diagnostic criteria used. GDM prevalence has been reported to vary between 1%-28%, while the International Diabetes Federation (IDF) estimates that one in six live births (16.8%) are to women with some form of hyperglycemia in pregnancy; 16% of these may be due to DIP, while the majority (84%) is related to GDM (5). In Romania the incidence of type 2 Diabetes Mellitus is mentioned to be 12%, but the lack of universal screening made GDM incidence to be difficult to be assessed, despite the existence of the clinical guideline sustained by specialists in diabetes, metabolic diseases and nutrition (6).

Diabetes in Pregnancy (DIP) is:

Pregnant women with previous known diabetes;

Hyperglycemia diagnosed for the first time during pregnancy that meets WHO criterion for diabetes mellitus in the nonpregnant state:

Fasting plasma glucose (FPG) ≥7.0 mmol/L or 126 mg/dL,

and/or 2-hour 75-g oral glucose, tolerance test (OGTT) value ≥11.1 mmol/L or 200 mg/dL,

or random plasma glucose (RPG) ≥11.1 mmol/L or 200 mg/dL, associated with signs and symptoms of diabetes.

It may occur any time during pregnancy including the first trimester.

From the obstetrical point of view, the importance of diagnosis in the first trimester is given by the possible hyperglycemia effects at conception and during embryogenesis, preexisting undiagnosed diabetic complications including retinopathy and nephropathy, which markedly increase pregnancy risks. Hyperglycemia during the first 12 weeks of pregnancy in which the organogenesis might be influenced, may lead to a high risk of spontaneous abortions and congenital anomalies. Diabetes in pregnancy, because of the attendant greater risk of hyperglycemia, may also result in aberrations in fetal growth, both *in utero* restriction and macrosomia, with possible short-term complications, as preterm birth, still birth, obstructed labor, shoulder dystocia, neonatal hypoglycemia, or risk of neurological damage. From the maternal point of view, the risk of pregnancy complications as pre-eclampsia, is higher in this form, but also, risk of onset or exacerbation of microvascular complications, such as retinopathy or nephropathy during pregnancy can be taken into consideration. In these cases, assessing, evaluation and treatment of the hyperglycemic status is very important in avoiding the complications.

Gestational Diabetes Mellitus (GDM) is:

Hyperglycemia during pregnancy that is not diabetes;

Hyperglycemia diagnosed for the first time during pregnancy;

It may occur any time during pregnancy but most likely after 24 weeks.

The diagnosis of gestational diabetes mellitus at any time during pregnancy should be based on any one of the following values:

Fasting plasma glucose = 5.1-6.9 mmol/L (92 -125 mg/dL);

1-h post 75g oral glucose load >=10.0 mmol/L (180 mg/dL);*

*2-h post 75g oral glucose load 8.5 – 11.0 mmol/L (153-199 mg/dL). (*there are no established criteria for the diagnosis of diabetes based on the 1-hour postload value) (3).*

The impact on the fetal formation is less, because of the later onset in the pregnancy and less severe hyperglycemia. In general, GDM implies a relatively milder form of hyperglycemia compared with that of DIP, but it is also associated with risk of poor pregnancy outcome, both from fetal and maternal point of view, which involve for both future risk of diabetes and cardiovascular disease, and must be managed appropriately (7).

The moment of testing during pregnancy, the test itself and among the same test, the cut-off values are widely discussed. And, if in 2011, at the pregnancy and Diabetes Conference in Salzburg Austria, the official representative of WHO said that GDM has less importance in low resources countries where the poverty and under-nutrition are the main causes of pregnancy complication, today there are WHO guidelines published in 2013 and FIGO guidelines published in 2015, which both support, more or less, the universal screening options for diagnosis of gestational diabetes mellitus based on resource settings and the 1-step 75-g OGTT in all women is endorsed by the IDF, and many other organizations that agree with

the recommendations of the IADPSG (3, 4).

The new definition gives a very large gap of the first trimester and 24 weeks of gestation, in between the two entities, which can be covered by individualizing each case from the point of view of personal risks. In this case, the presence of high values of the glycated hemoglobin A1c (HbA1c) in the first trimester, as well as other maternal complications might be an argument for the preconception presence of diabetes mellitus. Otherwise, ADA, IADPSG, ACOG and other medical guidelines do not recommend use of the glycated hemoglobin A1c (HbA1c) to diagnosis or monitor of the GDM in pregnancy due to very low glycosylation process, high dilution secondary to the maternal physiological blood volume increase and lower levels of Hb accepted as normal during pregnancy (10.4 – 10.9 g/L).

Another important step of this diagnosis, is done by the window of opportunity of prevention of pre-eclampsia and its complications (IUGR, maternal morbidity and mortality and other) with starting before 16 weeks of gestation of acetylsalicylic acid in low dose (150 mg seems to be the choice in the latest studies). Some guidelines included as criteria of risk also GDM, Diabetes Mellitus and Obesity as factors with high risk for gestational hypertension and preeclampsia (8).

The universal screening of women considered at low risk or the women who came first in the second trimester between 24-28 weeks of gestation is the recommended way to test. But also, to test again a woman at high risk with a negative 2-h 75g OGGT test in the first trimester is important. And again, in a pregnancy with a fetal growth around 90 -95% percentiles and/or with oligohydramnios and/ or an abdominal circumference above 95 percentiles developed in growth and without other fetal known complications or malformations should be retested even later in pregnancy, between 28-36 weeks of gestation.

Once a diagnosis of GDM was made, close perinatal surveillance is warranted. The goal of treatment is reducing fetal-maternal morbidity and mortality related with GDM. The exact glucose values needed are still not absolutely proved. The decision whether and when to induce delivery depends on gestational age, estimated fetal weight, maternal glycemic control and bishop score.

Future research is needed regarding prevention of GDM, treatment goals and effectiveness of interventions, guidelines for pregnancy care and prevention of long term metabolic sequel for both the infant and the mother.

The new definition and introducing of the disturbances of the carbohydrate metabolism during pregnancy in the universal screening programs were imposed by the impact of the results of treatment with minimal interventions, only diet, or diet and metformin, the increase obesity and diabetes prevalence over the world, and emerging research results regarding the importance of the *in utero* environment and growth and later onset of adulthood diseases – hypertension, stroke, cardiovascular disease, lipid and coagulation disorders, obesity, being among the first causes of morbidity and mortality in the world. It was proved the relation between maternal insulin sensitivity and glucose-induced changes in fetal brain activity. Lower maternal insulin sensitivity is associated with slower fetal brain responses, being the first evidence of a direct effect of maternal metabolism on fetal brain activity and suggests that central insulin resistance may be programmed during fetal development (20).

In September 2015, at the 51st European Association for the Study of Diabetes (EASD) Annual Meeting, in session 47th Claude Bernard Lecture which was hold in Stockholm, Sweden, professor Häring HU presented the lecture upon "Understanding phenotypes of prediabetes: essential to influencing progression to type 2 diabetes", in which, lifestyle intervention according to the phenotype and the sub phenotype are the future steps in preventing type 2 Diabetes Mellitus to develop and/or postponing. There are described two new independent pathways to the development to glycemic disturbances: fatty liver and brain insulin resistance. Because brain insulin resistance starts so early in life, we have to focus very much on gestation and on very early prevention.

The aim of this very short essay on updates in GDM diagnosis was to underline the importance of the screening during pregnancy, as the only way to diagnose it. Even if in the next years one may expect more updates on cut-off levels or values, in 2016 it is clear that identifying of gestational diabetes mellitus (GDM) is important for the mother and child, and treatment is important in preventing the short term and long term possible complications.

In terms of cost effectiveness, the ethical problems of costs are done by the limitation of the estimation of the long term impact and evaluation of quality of life. By contrary, some tools which asses the costs, made impossible to see as efficient an intervention which prolongs the life of a person, as long as each year of life is viewed as a cost of care, not as a value of life (10).

Starting in 1824 – when Heinrich Gottleib Bennewitz described in his thesis for Doctor of Medicine at the University of Berlin a case report of a 22 years old women Frederica Pape, the first recorded case of diabetes in pregnancy, saying that it is "… one aspect of a wider kind of disease not yet adequately researched" – and going to 2016 when the research has made enormous steps to discover the pathology which induces and is associated with Gestational Diabetes Mellitus – still the study of the "mysterious disease" holds the potential of bringing more surprises in the near future as well as the hope for improved health and quality of life for the next generations.

Conflict of interest

The author declares that he has no conflict of interest concerning this article.

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