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Gestational diabetes mellitus: Where are we now?

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ABSTRACT

Gestational diabetes mellitus (GDM) is defined as any carbohydrate intolerance first diagnosed during pregnancy. The prevalence of GDM is about 2–5% of normal pregnancies and depends of the prevalence of same population to type 2 diabetes mellitus. It is associated with adverse outcome for the mother, the fetus, neonate, child and adult offspring of the diabetic mother. Detection of GDM lies on screening, followed as necessary by diagnostic measures. Screening can either be selective, based upon risk stratification or universal. Timely testing enables the obstetrician to assess glucose tolerance in the presence of the insulin-resistant state of pregnancy and permits treatment to begin before excessive fetal growth has occurred. 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.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as any carbohydrate intolerance first diagnosed during pregnancy [1]. It is associated with adverse outcome not only for the mother, but also for the fetus, neonate, child and adult offspring of the diabetic mother. Maternal consequences include increased rate of operative and cesarean delivery, hypertensive disorders during pregnancy and future risk for type 2 diabetes mellitus (T2DM) as well as other aspects of the metabolic syndrome, such as obesity, cardiovascular morbidities and recurrent GDM [2–4]. Also, there are maternal implications secondary to a delivery of a macrosomic or large for gestational age (LGA) fetus, such as an increased rate of cesarean delivery, postpartum hemorrhage (PPH), birth trauma and shoulder dystocia [4,5].

As today, GDM is defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy". The definition is applicable regardless of whether insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy [1]. GDM complicates up to 14% of all pregnancies, resulting in approximately 200,000 cases annually in the United States. It is a major cause of perinatal morbidity and mortality, as well as maternal long term morbidity. Of all types of diabetes, GDM accounts for approximately 90–95% of all cases of diabetes in pregnancy [4,6]. The first reference to diabetes in pregnancy was made by Bennewitz in 1823 [7]. He considered diabetes to be a transient symptom of pregnancy and proved his theory when after two pregnancies all symptoms and glycosuria disappeared. The next significant milestone in diabetic research during pregnancy was achieved by Priscilla White. Back in the early 20th century women with diabetes had low chances for successful pregnancy outcome. Pricilla was the first to believe that diabetes is not a contraindication to pregnancy. In 1949, White published the first version of the classification system that had an immense clinical value to practitioners all over the world [8]. In 1979, the White Classification underwent its last revision [9]. In 1952, Jorgan Pedersen pointed out his hyperglycemia [maternal] hyperinsulinism [fetal] hypothesis. According to his hypothesis maternal hyperglycemia results in fetal hyperglycemia, and, hence, results in hypertrophy of fetal pancreatic islet tissue with insulin hyper secretion. The hyperinsulinism in the presence of more than adequate supplies of glucose, abruptly eliminated at birth, explains several of the characteristic features observed in the offspring, [10]. This theory is still in use more than 20 years after Pedersen's death, and is now called the Pedersen Theory. In 1989, Representatives of Government Health Departments and patient organizations from all European countries met with diabetes experts under the aegis of the Regional Offices of the World Health

Abbreviations: BMI, body mass index; DM, diabetes mellitus; GCT, glucose challenge test; GDM, gestational diabetes mellitus; IUFD, intrauterine fetal death; LGA, large for gestational age; OGTT, oral glucose tolerance test; PPH, postpartum hemorrhage; T2DM, type 2 diabetes mellitus.

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Organization and the International Diabetes Federation in Vincent, Italy. They unanimously agreed upon the need to search for the ways to prevent, treat and cure diabetes. The St. Vincent Declaration highlights the importance of diabetes related issues and the necessity to address them on a local, regional and national level. As for today, GDM is a cause of concern to both health providers and patients. In national audits who challenged St. Vincent Declaration poor pregnancy outcome was found.

2. Epidemiology

The prevalence of GDM in the United States is up to 14% and it accounts for 90–95% of diabetes in pregnancy [4,5]. The prevalence of GDM is directly related to the prevalence of type 2 diabetes mellitus (DM) in a given population. Risk factors for GDM are outlined in Table 1, and the risk increases as cumulative factors exist [11,12]. Infants of diabetic mothers are at an increased risk for future insulin resistance. This association, along with the increased prevalence of obesity and type 2 DM, may lead to a significant rise in GDM, throwing future generations to a cycle of obesity, insulin resistance, diabetes and various metabolic complications [13,14].

3. Morbidity and mortality

Adverse maternal outcome can be short term, such as hypertension, preeclampsia and an increased risk of cesarean section. Long term concerns are mainly the increased risk of developing diabetes later in life. There is a higher rate of hypertensive complications in diabetic pregnancies compared to normal pregnancies. The risk for preeclampsia rises from 5–7% to 15–20% [15], and it is influenced by GDM severity, glucose control and pre-pregnancy BMI [16]. Prepregnancy obesity and diabetes independently increase the risk for cesarean delivery [17]. Women with GDM have an increased risk of type 2 diabetes later in life; ranging from 20–80% [18,19].

The infants of GDM women are at an increased risk for stillbirth, aberrant fetal growth, birth trauma and various metabolic and electrolyte disturbances:

- Congenital anomalies and spontaneous abortions are not a major concern as in pre-gestational diabetes. Due to the relatively high rate of undiagnosed type 2 DM (10%), there should be an effort to rule out the presence of congenital malformations.
- Early, albeit flawed studies, showed a 4-fold increase in perinatal mortality in GDM. These studies did not control for variables affecting perinatal mortality such as fetal malformations, maternal history of stillbirth and advanced maternal age. Other studies also showed increased risk for perinatal mortality up to a relative risk of 4.3 over control [20–22].
- Macrosomia and its partner complications (cesarean section, shoulder dystocia and brachial plexus injury) are the most studied perinatal outcomes in GDM. The overall rate of macrosomia for the non-diabetic population is 7–9%, rising to 20–45% in GDM [20,23]. This is chiefly associated with the maternal glycemic profile [24].
- Neonatal hypoglycemia occurs in 25% of newborns, and it depends on maternal glycemic control at time of delivery [25,26].
- Neonatal hypocalcaemia is reported in 10–20% of infants to GDM mothers and it's related to severity of maternal diabetes [21,27].
- Neonatal polycythemia has been reported in 5% of infants of GDM mothers. It is also, partly associated to infant hyperbilirubinemia, which is more common in infants to diabetic mothers [21,28].
- Neonatal respiratory distress is more frequently encountered in infants to diabetic mothers [29] and is caused mainly because of respiratory distress syndrome, but also due to transient tachypnea of the newborn, meconium aspiration syndrome, polycythemia and hypertrophic cardiomyopathy.
- The child of a diabetic mother, mainly prediabetic, remains at increased risk for obesity, impaired glucose tolerance and diminished neurobehavioral capacities [30–32].

Table 1
Risk factors for gestational diabetes mellitus.

Advanced maternal age
Maternal obesity
High parity
Previous delivery of a macrosomic infant
Family history of type 2 diabetes mellitus.
Maternal short stature
Polycystic ovary disease
High levels of saturated fat in the diet
Prior GDM
Prior neonatal death
Prior cesarean delivery
Previous stillbirth or congenital malformations
High blood pressure during pregnancy
Multiple pregnancy

4. Screening & diagnosis

Detection of GDM lies on screening, followed as necessary by diagnostic measures. Screening can either be selective, based upon risk stratification (Table 2) or universal [33]. Risk factors should be determined as early as the first prenatal meeting, and screening for GDM in recommended for all pregnant patients unless they are considered at low risk for diabetes.

4.1. Screening

Approaches for screening tests include either fasting glucose, random glucose or, more commonly, glucose challenge test. The test was developed by O'Sullivan and Mahan in 1950 [34] and involves administration of 50 g glucose load, without consideration from the time of the last meal, and a determination of plasma glucose levels after 60 min. Using a cut-off of 140 mg/dl (7.8 mmol/L) will detect 80–90% of women with GDM and will require that an oral glucose tolerance test (OGTT) be performed for 15% of patients. Lowering the cut off to 130 mg/dl (7.2 mmol/L) will increase the sensitivity to 90–100% but will require OGTT in nearly 25% of all patients. It is generally agreed that a value of 200 mg/dl (11.1 mmol/L) on glucose challenge test (GCT) is likely to be associated with the diagnosis of GDM, and therefore OGTT need not be performed. Women who have positive GCT will need to be diagnosed for GDM, by performing a 100 g or 75 g oral glucose tolerance test (Table 3).

4.2. Diagnosis

Initially, O'Sullivan established the criteria for diagnosis of GDM in 1964 [34]. These cutoffs were established to predict the subsequent development of diabetes and not to identify pregnancies with an adverse outcome. GDM was defined arbitrarily as 2 or more standard deviations above the mean. The National Diabetes Data Group (NDDG) [35] advised in 1979 that plasma should be the preferred sample for glucose analysis and not in whole blood as was measured according O'Sullivan. However, due to measurement concerns, Carpenter and Coustan [36] further modified the cutoffs. In contrast to the 2-step procedures outlined above, the WHO recommended that GDM be diagnosed by a 1-step procedure that uses the same OGTT performed to diagnose diabetes in nonpregnant patient; 75 g of glucose, with only the fasting and 2-h samples analyzed.

Still, even though OGTT is universally used for diagnosis, the exact criteria for OGTT are far from being a consensus. Controversy exists regarding the amount of glucose load (100 g vs. 75 g), the test duration

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