Glucose Homeostasis in Pregnancy and Risk Factors for Gestational Diabetes Mellitus

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Pregnancy represents a unique state of maternal metabolic changes that serves one and only one purpose – to enable a fetus to grow and develop from a mass of cells into a complex living organism by the time of its birth. It is logical to expect a continuous and progressive change in maternal metabolism throughout pregnancy in order to achieve this end. The changes in carbohydrate metabolism are therefore only one of these important changes that are by and large a part of a physiological event. However, at the extreme end of this spectrum, where the diabetogenic effect of pregnancy overwhelms the body's ability to maintain glucose homeostasis, gestational diabetes mellitus (GDM) will ensue.

MAINTENANCE OF MATERNAL GLUCOSE HOMEOSTASIS

Glucose is the primary fuel for the growing fetus. Its supply must be readily available and continuously transferred across the placenta to the fetus, since the fetus has practically no fuel reserve such as glycogen in the liver. On the other hand, glucose absorbed in the maternal small intestine will be transported first to the liver, where a proportion of it will be taken up by the hepatocytes through the action of insulin, before the rest is transferred to the other organs, including the uterus. Thus, in a sense, the fetal supply of glucose is dependent on the function of the maternal pancreatic islet cells.

In order to guarantee a constant and ready supply of glucose to the placenta even when the mother has not been eating, the placenta degrades insulin and produces hormones with varying degrees of insulin antagonism which induce an insulin-resistant state in the mother. However, for a normal individual, maternal blood glucose level is maintained within the normal range of 4.0 to 7.0 mmol/L before and after meals.[1] Indeed, throughout pregnancy, maternal postprandial plasma glucose levels remain quite constant despite the progressive increase in the plasma concentration of placental hormones. This is achieved by the concomitant increase in maternal plasma insulin concentration, which reaches a peak in the third trimester that is about threefold the concentration in the first trimester.

Nevertheless, despite the maintenance of normal postprandial glucose level, the mother becomes progressively less glucose tolerant. When challenged with either an oral[2] or intravenous glucose load,[3] there is a significant increase in the glucose level in the third trimester. In clinical practice, the oral challenge, in the form of an oral glucose tolerance test (OGTT), is usually performed for diagnostic purposes. Although the majority of pregnant women will have normal plasma glucose concentration after glucose challenge, a certain proportion will have high glucose levels which fulfil the criteria of GDM. It is now understood that there is much phenotypic and genotypic heterogeneity in GDM.[4] However, in simple terms, the problem lies with an inadequate insulin response to maintain mater-

nal euglycaemia when the mother has taken food, and the glucose challenge in the OGTT is one form of stimulus to elicit this abnormality. In some cases, the features are compatible with those of the metabolic syndrome (Syndrome X), which include hypertension, insulin resistance and hyperlipidaemia, and GDM may represent one phase or one manifestation of this syndrome.[5] The factors leading to the development of GDM are summarized in Table 1.

RISK FACTORS FOR GESTATIONAL DIABETES MELLITUS

The development of GDM tends to occur in women who are at increased risk because of certain underlying or predisposing factors. The distribution of these risk factors can vary in different populations, and within each population, they can be found in different combinations in different individuals. Thus, in different studies, the risk factors identified might not be the same, or for the same risk factors, the odds ratio might be different. This phenomenon is related in part to the heterogeneity of GDM.[4]

Some of these factors are well known and documented. There are other less well-known or recently described risk factors. The risk factors can be categorized into groups that are related to maternal characteristics, obstetric history, family history, and problems with the index pregnancy. The risk factors described in the following discussion have all been shown to be independent risk factors and are summarized in Table 2.

Table 1. Factors Leading to the Development of Gestational Diabetes Mellitus

- Undetected pre-gestational diabetes (type 1 and type 2).
- Increased insulin antagonists.
- Increased insulin degradation.
- Increased peripheral insulin resistance.
- Decreased/inadequate insulin secretion.
- Part of the Metabolic Syndrome (Syndrome X) presenting in pregnancy.

Table 2. Independent Risk Factors for Gestational Diabetes Mellitus

Maternal Characteristics	• Ethnicity • Advanced age (≥35 years) • Weight excess/obesity • Short stature • Multiparity • Chronic hypertension • History of infertility • Cigarette smoking
Obstetric History	• Stillbirth and fetal loss • Congenital malformations • Large and small infant • Gestational diabetes mellitus
Family History	• First degree relatives, especially mother, with type 2 diabetes • Gestational diabetes in mother or sister(s) • Other relevant family history
Index Pregnancy	• Uterine size > date • Polyhydramnios and oligohydramnios • Multiple pregnancy • Recurrent/significant glycosuria • Recurrent urinary infection • Pregnancy-induced hypertension/ pre-eclampsia

Maternal Characteristics

This group of risk factors is generally the most useful and reliable because the relevant information can usually be elicited with confidence or confirmed clinically. All these factors can be, and often are, routinely ascertained during the antenatal clinic visits. While these are often used individually as indications for performing a screening test or an OGTT, they can also be formulated into a scoring system. Recently, a scoring system based on ethnicity, maternal age, and body mass index (BMI) has been proposed to improve the efficiency and cost-effectiveness of screening for GDM.[6]

Ethnicity

Studies conducted in multi-ethnic communities have demonstrated, irrespective of the form of the OGTT, that Asian/Chinese women have the highest incidence of GDM.[7-14] (Table 3) This phenomenon can also be found in recent Asian immigrants in the West.[15] While changes in the environment and lifestyle, improved nutrition, and easily accessible antenatal care have undoubtedly contributed to this phenomenon, Southeast Asian/Chinese women probably have increased risk due to differences in glucose metabolism and insulin secretion,[10,12] as well as a shorter interval between the presentation of GDM and type 2 diabetes mellitus, compared with Caucasian women.[9] Indeed, the highest risk score is assigned to the Asian women in the study of Naylor et al.[6] In this study, calculated on the basis of adjusted odds ratio, Asian women were assigned a score of 5, compared with age ≥35 years (score of 2) and BMI ≥25.1 kg/m^2 (score of 3).

Advanced Maternal Age

The incidence of GDM increases progressively with advancing maternal age.[10,11,14,16-22] In Hong Kong, the incidence of GDM was 5.3% in teenage (<20 years old) women,[23] and in women ≥40 years of age, the incidence was as high as 35.3% and 30.0% in nulliparas and multiparas respectively.[24] In general, the risk of GDM is significantly increased after 35 years of age.

Weight Excess/Obesity

Excess weight or obesity is a classical risk factor for GDM,[14,18,20] but excessive weight as defined by an arbitrary cut-off is quite inappropriate for Asian women because of their smaller frame and shorter stature. Hence, categorization by means of the calculated BMI is more useful. While the cut-off for a high BMI varies between 25 kg/m^2 and 26 kg/m^2 in the literature, it should be realized that the risk increases with increasing BMI. Naylor et al[6] have demonstrated that when BMI ≤22.0 kg/m^2 was used as the reference category, the

Table 3. Prevalence of Gestational Diabetes Mellitus in Multi-Ethnic Communities

			Prevalence (or RR*) of GDM			
City/Region	Reference	OGTT	Chinese	Asians	Black	Caucasian
Melbourne	Beischer et al 1991[7]	50g	13.9%	—	9.4%	4.0-5.2%
Melbourne	Beischer et al 1996[8]	50g	—	10.6%	10.9%	2.9%
New South Wales	Yue et al 1996[9]	75g	15.0%	—	—	3.0%
London	Dornhorst et al 1992[10]	50g	—	7.6*	3.1*	1.0*
London	Koukkou et al 1995[11]	75g	—	5.8%	2.7%	1.2%
San Francisco	Green et al 1990[12]	100g	7.3%	—	1.7%	1.6%
Chicago	Dooley et al 1991[13]	100g	—	10.5%	3.3%	2.7%
New York	Berkowitz et al 1992[14]	100g	—	4.5%	3.7%	2.3%

RR: relative risk.

adjusted odds ratio (OR) for GDM was 1.8 for BMI between 22.1 and 25.0 kg/m^2, and 3.2 if the BMI was ≥25.1 kg/m^2. The importance of high BMI as a risk factor is also illustrated by a recent study[25] in which two thirds of Chinese women with a pre-pregnancy BMI of >26 kg/m^2 developed GDM, even when all the women requiring insulin therapy had been excluded.

Short Stature

Attention has been drawn to the role of maternal short stature, which has been shown to be an independent risk factor for GDM.[19,26] This association persists after adjusting for the effect of BMI, and can be found in Asian[19] as well as European[26] women. In this regard, the cut-off for short stature depends on the population, and is more helpful by referring to the quartile rank for the index population[19] than an absolute measurement.

Multiparity

Multiparity in general has often been referred to as a risk factor for GDM, but when analysed by the exact parity, only a parity >3 appeared to be a significant independent risk factor after adjusting for other confounding factors.[10,20]

Chronic Hypertension

Chronic hypertension has now been shown to be associated not only with non-insulin dependent diabetes mellitus (NIDDM or type 2 DM),[27] but also with GDM.[20,28] The underlying mechanism is attributed to hyperinsulinaemia.[28] Some of the cases are probably examples of the metabolic syndrome or Syndrome X,[5] especially in women with polycystic ovarian syndrome (PCO syndrome).[29]

History of Infertility

Women with a history of infertility have been found to have an increased risk for GDM.[14] However, part of this could be related to associated factors such as advanced age, obesity, and PCO syndrome.[29]

Cigarette Smoking

Women who are smokers during the course of pregnancy have been found to have an increased risk of GDM compared with both women who have never smoked and women who have stopped smoking.[18] This increased risk was significant only among women who smoked five or more cigarettes per day.

Obstetric History

History of Stillbirth and Abortion

A history of stillbirth, especially 'unexplained', has been associated for some time with increased risk of GDM in subsequent pregnancies, and recently, both a history of stillbirth as well as abortion were found to be associated with increased risk of GDM.[20,30] While in some women with such a history, persistent or pre-gestational diabetes could be excluded by a postnatal OGTT with normal result, such a finding cannot exclude GDM with certainty. Thus, all patients with previous unexplained fetal loss should be tested for GDM in subsequent pregnancies.

History of Congenital Malformation

The association between fetal congenital malformations with GDM is controversial, and it appears incomprehensible that a condition that usually develops in the third trimester would result in fetal malformations that should have developed before 20 weeks of gestation. Nevertheless, a history of major congenital malformation has been reported to be a significant independent risk factor.[30] It is possible that a certain proportion of the cases of GDM with previous children affected by congenital malformation have in fact had pre-existing diabetes mellitus that was asymptomatic and missed in the previous pregnancy. Hence, an OGTT can provide the definitive answer and facilitate management.

History of Large and Small Infants

The association between the birth of a macrosomic infant and GDM is well known, but GDM is only one of the causes of a macrosomic infant. However, it has been shown that a history of macrosomia, even

in the absence of GDM, is associated with increased risk of GDM in subsequent pregnancies.[30] This is probably related to the fact that there is an increased risk of large-for-gestational age and macrosomic newborns in women with glucose intolerance below the diagnostic threshold.[31,32] In such cases, the increased age, and, as is often the case, increased maternal obesity, in subsequent pregnancies can lead to a deterioration of the glucose intolerance into frank GDM. A recent study not only confirmed that a history of high birth weight infants is a risk factor, but also reported that a history of previous low birth weight infants is associated with similar risk.[20]

History of Gestational Diabetes
The relevance of such a history is obvious. However, only a proportion of gestational diabetic women will develop recurrent GDM in subsequent pregnancies. The likelihood of recurrent GDM is related to factors such as the time of diagnosis and the need for insulin in the previous pregnancy, weight gain between pregnancies, and other demographic factors like age and parity.

Family History
A positive family history of type 2 diabetes mellitus in first degree relatives, especially in the patient's mother, is a very significant risk factor.[14,18,30] The same also appears to apply to a history of gestational diabetes in the patient's mother.

Problems with the Index Pregnancy
Uterine Size Greater Than Date
This is often the first sign of GDM in a low-risk patient, and may be related to a large-for-gestational age fetus, polyhydramnios, or both. Assessment of uterine size under the circumstance is facilitated by the measurement of symphysio-fundal height.

Abnormal Amniotic Fluid Volume
There are a number of causes for polyhydramnios, but in a singleton pregnancy in which fetal anomalies have been excluded by previous ultrasound scanning, diabetes mellitus, especially poorly-controlled, is a well documented cause of the polyhydramnios. A recent study[20] has confirmed the association between polyhydramnios with GDM, with an adjusted OR of 5.94 (95% CI 3.87-9.10). In addition, this study also reported for the first time that oligohydramnios has a similar association, with an adjusted OR of 1.71 (95% CI 1.10-2.67).

Multiple Pregnancy
There are few reports on GDM in multiple pregnancies, but the association between multiple pregnancy and increased risk of GDM has been documented.[33] The rate of GDM is increased in proportion to the number of fetuses, being 9.1%, 15.5%, and 30.0% in singleton, twins and triplets respectively. This is probably related to the increased level of placental hormones that antagonize the action of insulin.

Recurrent/Significant Glycosuria
Due to the reduced renal threshold in pregnancy, glycosuria is a common finding and the majority of women with glycosuria do not have GDM. However, if glycosuria is recurrent or persistent, then GDM must be excluded. The association between glycosuria and GDM has been confirmed in a recent report.[30]

Recurrent Urinary Infection
Pregnancy increases the risk of urinary tract infection (UTI), and the majority of women with UTI, especially cystitis, do not have GDM. However, the persistence or recurrence of UTI should always alert one to the possibility of underlying GDM, and a significant association between GDM and UTI has been demonstrated.[20]

Pregnancy-Induced Hypertension/Pre-Eclampsia
The association between hyperinsulinaemia and increase in blood pressure also extends to pregnancy. It has been shown that the risk of GDM is increased in women with pregnancy-induced hypertension/pre-eclampsia, both de novo as well as superimposed on chronic hypertension.[20,30]

CONCLUSION

The diabetogenic effect of pregnancy affects each and every pregnant woman. While the risk of GDM is increased in high-risk groups, with the prevalence rate increasing with increasing number of risk factors, the absence of risk factors does not protect a woman from the risk of GDM entirely. Indeed, the rate of GDM for 'low-risk' women (defined by age <30 years, white ethnicity, pregravid BMI <20.0 kg/m^2, no family history of DM, weight gain from age 18 years of <5 kg, and non-smoker) was a substantial figure of 2.9% compared with the 5.1% in 'high-risk' women.[18] Only vigilance and a high index of suspicion will minimize the adverse effects of GDM in 'low-risk' women, unless universal screening is undertaken for all pregnant women.

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