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## **Diabetes and Pregnancy: an Update of the Problem**

**Iracema Mattos Paranhos Calderon<sup>1</sup>, Luciane Teresa Rodrigues Lima Kerche, Débora Cristina Damasceno, Marilza Vieira Cunha Rudge**

Department of Gynecology and Obstetrics, São Paulo State University (Unesp), BRAZIL

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### **Abstract**

*Calderon I MP, Kerche LTRL, Damasceno DC, Rudge MVC. Diabetes and Pregnancy: an Update of the Problem. ARBS Annu Rev Biomed Sci 2007;9:1-11.* Pregnancies complicated by diabetes account for about 7% of all pregnancies attended by the Brazilian Unified Healthcare System (SUS) and are one of the main causes of maternal/perinatal morbidity and mortality in Brazil. Considering the importance of this topic, this article presents an update of diabetes classification, diagnostic criteria, maternal/perinatal outcomes, and both clinical and obstetric prenatal care. Even though there is no consensus about screening and diagnostic standards, the investigation of hyperglycemia in all risk pregnancies is recommended. The importance of adequate metabolic control is emphasized in order to improve maternal and neonatal outcomes. Finally, the development of educational programs is encouraged, viewing not only good gestational outcome but also long-term changes in the lifestyle of these women.

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**Keywords:** diabetes and pregnancy, diagnosis, treatment, perinatal prognosis

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## **1. Introduction**

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta ( $\beta$ )-cells of the pancreas

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### **<sup>1</sup> Correspondence**

Iracema Mattos Paranhos Calderon, Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – Unesp, Distrito de Rubião Júnior s/n, CEP. 18618.000 - Botucatu, São Paulo, BRAZIL. E-mail: [calderon@fmb.unesp.br](mailto:calderon@fmb.unesp.br)

to abnormalities that result in resistance to insulin action. The physiopathological basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues (ADA, 2004).

Pregnancy, a period when maternal pancreatic reserve is tested, should be considered as a risk factor for diabetes (Rudge & Calderon, 2004). Gestational diabetes (GD) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for treatment or whether or not the condition persists after pregnancy (ADA, 2004). However, it does not exclude the possibility that unrecognized glucose intolerance may be classified as gestational diabetes. Thence, six weeks or more after delivery, maternal glycemic status should be reclassified into one of the following categories: 1) diabetes, 2) impaired fasting glucose, 3) impaired glucose tolerance, or 4) normoglycemia. In most GD cases, glucose regulation will return to normal after delivery (ADA, 2004; Gabbe & Graves, 2003).

While planning the management of risk pregnancies, including those complicated by diabetes, two vital questions should be asked: “How will pregnancy affect maternal clinical status?”, and “How will this disorder affect gestational outcome?”. These key points highlight the importance of the early investigation, diagnosis, classification, and treatment of the several types of pregnancy-related diabetes. (Rudge *et al.*, 1995; Rudge *et al.*, 2000; Gabbe & Graves, 2003)

## 2. Historical Background

### 2.1. Classification

Gestational diabetes was first classified in 1949, by Priscilla White, who used classes from A to T, based on severity, age at onset, duration, need for insulin, and presence or absence of vascular diseases resulting from diabetes. This system, initially developed to help at delivery, is still widely used to predict complications during pregnancy and is, therefore, considered an etiologic, prognostic and progressive system (Table 1) (Rudge & Calderon, 2004).

According to some investigators, the revision of White’s classification system in 1978 increased its complexity and reduced its clinical usefulness. Even though, the American College of Obstetricians and Gynecologists (ACOG) adopted this new classification method in 1994. Gabbe *et al.* (1985) suggested aggregating P. White’s classes into three categories according to clinical severity, duration, and presence of vascular complications in target organs as follows:

- classes A and A/B - gestational diabetes
- classes B and C - short-length clinical diabetes
- classes D to FRH - clinical diabetes + vasculopathy

Table 1. P. White’s classification<sup>a</sup>.

Type	Class	Insulin	Onset (years)			Duration (years)			Vasculopathy
			>20	10 - 19	<10	<10	10 - 19	>20	
Gestational	a								
Gestational	a/b	x							
Clínical	b	x	x			x			
Clínical	c	x		x			x		
Clínical	d	x			x			x	
Clínical	e	x						Simple retinopathy	
Clínical	f	x						pelvic arteries	
Clínical	r	x						diabetic nephropathy	
Clínical	h	x						proliferative retinopathy	
Clínical	t	x						hypertensive cardiopathy	
Clínical	t	x						renal transplantation	

<sup>a</sup>modified by Rudge & Calderon, (2004).

Pedersen (1979) defined the prognostic factors considering that the presence of ketoacidosis, coma, pyelonephritis, preeclampsia, and treatment negligence, among others, represent maternal, fetal and neonatal risk. In 1981, Rudge & De Luca added the lack of hospital beds specifically assigned to the treatment of these risk pregnancies as another criterion (cited in Rudge & Calderon, 2004).

The National Diabetes Data Group (NDDG), in 1979, revised the clinical classification of diabetes based on diabetes type:

- insulin-dependent Diabetes mellitus (IDDM) or type I
- noninsulin-dependent Diabetes mellitus (NIDDM) or type II
- gestational Diabetes mellitus (GDM) – diagnosed during gestation

In 1980, WHO (World Health Organization Expert Committee on Diabetes Mellitus) endorsed the recommendations of NDDG and went on to include impaired glucose tolerance, classifying the type of diabetes associated with pregnancy as type I, type II, gestational impaired glucose tolerance and gestational diabetes. This system defined Diabetes mellitus as an etiologically and clinically heterogeneous group of disorders that share hyperglycemia in common. The recognition of this heterogeneity has important implications not only for the individualization of treatment of patients with diabetes but also for clinical research (Calderon & Rudge, 2004).

The American Diabetes Association (ADA), in 1999, reformulated the definition, the classification and the diagnostic criteria for diabetes. They proposed changes in the NDDG/WHO classification system, highlighting the etiology of this disorder, and recommended the use of Arabic rather than Roman numerals. In 2004, ADA retained these changes and recognized two intermediate stages in the disease process – impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG and IGT characterize impaired glucose regulation and represent risk factors for future diabetes as well as cardiovascular disease (Table 2).

Table 2. Etiologic classification of diabetes mellitus<sup>a</sup>.

I. Type 1 diabetes: ( $\beta$ -cell destruction / absolute insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes: insulin resistance/ relative insulin deficiency (predominantly secretory defect)
III. Other specific types
A. Genetic defects of $\beta$ -cell function
B. Genetic defects in insulin action
C. Diseases of the exocrine pancreas
D. Endocrinopathies
E. Drug- or chemical-induced
F. Infections
G. Uncommon forms of immune-mediated diabetes
H. Other genetic syndromes sometimes associated with diabetes
IV. Gestational <i>Diabetes mellitus</i> (GDM)

<sup>a</sup> from ADA (2004).

## 2.2. Diagnosis

There is no consensus regarding the criteria and the tests for the screening and diagnosis of GDM. ADA and ACOG recommend the selective screening of women at risk of GDM. WHO and the Brazilian Study of Diabetes and Gestation (EBDG) Working Group have lately advocated universal screening, that is, screening in all pregnancies (Reichelt *et al.*, 2002).

Women at high risk of GDM have the following characteristics: age > 25 years, pregestational obesity or excessive weight gain during pregnancy, family history of diabetes (first-degree relative), personal history of poor obstetric outcome (fetal death of no apparent cause, polyhydramnios, macrosomia or fetal malformation, preeclampsia or eclampsia), abnormal glucose tolerance, and member of an ethnic

group with a high prevalence of diabetes. In these cases, ADA recommends the undertaking of a 1-h plasma glucose test after a 50-g oral glucose load at 24-28 weeks of gestation (ADA, 2004).

Over the past 25 years, Rudge & De Luca have been investigating, since the first prenatal visit, the combination of fasting glucose with risk factors – personal, family and obstetric history. If fasting glucose < 90mg/dL and risk factors are absent, the patient is considered to be at a normal risk of gestational diabetes. If fasting glucose  $\geq$  90 mg/dL (regardless of the presence of risk factors), or fasting glucose is normal but risk is present, screening is considered positive and the patient is referred to diagnosis confirmation at 24-26 weeks of pregnancy. A comparative study between universal screening, 50-g OGTT, and the fasting glucose with risk factor combination approach, which is simpler and easier to perform, demonstrated their equivalence (Rudge *et al.*, 1994a). The combination of fasting glucose with risk factor showed a sensitivity rate of 83.7% and a negative predictive value of 95.3% when compared with 50-g OGTT (Rudge & Calderon, 2004).

The EBDG Working Group, considering the simplicity of screening using the combination of fasting glucose with risk factors, suggests the assessment of fasting glucose with cut points of 85 mg/dL or 90 mg/dL from 20 weeks of gestation onward. They also stress the importance of having this test performed at the first prenatal visit, especially when diabetes risk factors are present (Reichelt *et al.*, 2002).

ADA supports that: a) a 100-g oral glucose test (100-g OGTT) should be undertaken when glucose threshold values > 140 mg/dL on 1-hour 50-g OGTT in order to establish the diagnosis of diabetes; b) the diagnosis of gestational diabetes is confirmed when two or more measures of plasma glucose levels  $\geq$  95, 180, 155 and 140 mg/dL, under fasting and 1, 2 and 3 h after ingestion, respectively; c) an alternative 75-g OGTT similarly to the detection of diabetes outside pregnancy can be used, but according to the same criteria used during gestation, i.e., two measures  $\geq$  95, 180 and 155 under fasting and 1, 2 and 3 h post load glucose, respectively (ADA, 2004).

WHO recommends the use of a 75-g glucose load with a fasting glucose cut point  $\geq$  126 mg/dL and 2-h post load glucose  $\geq$  140 mg/dL, encompassing two subcategories: impaired glucose tolerance (2-h glucose  $\geq$  140 mg/dL and < 200 mg/dL) and gestational diabetes (2-h glucose  $\geq$  200 mg/dL).

In Brazil, the EBDG Working Group standardized the use of the 75-g OGTT with threshold values of 110 mg/dL for fasting glucose and 140 mg/dL for 2-h glucose, including the subcategory impaired fasting glucose in the classification of gestational diabetes (Reichelt *et al.*, 2002).

In 1983, Rudge used two parallel diagnostic tests, 100-g OGTT and Glucose Profile (GP), to classify pregnant women. GP measures maternal plasma glucose levels every two hours, from 8:00 AM to 6:00 PM while a standard diet of 2840 calories divided into five meals is given. A fasting glucose level of 90 mg/dL and postprandial glucose of 130 mg/dL are considered normal, and a single abnormal value confirms maternal hyperglycemia (Rudge & Calderon, 2004). The combination of 100-g OGTT with GP defined a new classification system for the diagnosis of pregnancies complicated by diabetes (Table 3).

Table 3. Diagnostic classification of Rudge.

Groups	Oral glucose test OGTT	Glucose Profile GP	Clinical category
<b>IA</b>	Normal	Normal	No diabetes
<b>IB</b>	Normal	Abnormal	Mild hyperglycemia
<b>IIA</b>	Abnormal	Normal	Gestational diabetes
<b>IIB</b>	Abnormal	Abnormal	Gestational or clinical diabetes

According to this system, pregnant women in group IA are considered euglycemic, that is, non-diabetic. Those in groups IIA and IIB are diabetic according to the literature that supports the use of a diagnostic 100-g OGTT. The women in group IIA have gestational diabetes (Class A) and those in group

IIB have either gestational diabetes (Class A or A/B) or clinical (Classes B to FRHT) diabetes. Even though OGTT is normal among the pregnant women of group IB, their abnormal GP reveals mild hyperglycemia. No category in White's classification system includes these cases where carbohydrate, protein and lipid intolerance is present and diet plus insulin therapy are required to control mild hyperglycemia (Rudge & Calderon, 2004). Group IB accounts for 13.8% of the women with positive screening. Its perinatal mortality rate is comparable to that observed in women with diabetes and 10-fold higher than the rate found in the nondiabetic population. Moreover, this group shows placental abnormalities compatible with those described in pregnancies complicated by diabetes (Calderon *et al.*, 2000; Rudge & Calderon, 2004).

### 2.3. Maternal and perinatal outcomes

Depending on the timing of diagnosis, prior to or during pregnancy, diabetes is associated with the most adverse maternal and fetal outcomes, increased rates of spontaneous abortion, congenital malformations, intrauterine fetal death, macrosomia, prematurity, and neonatal metabolic and respiratory disorders (ADA, 2004). Over the past decades, diabetes-related perinatal mortality has decreased thanks to the growth of knowledge regarding the physiologic alterations that occur in carbohydrate metabolism during pregnancy as well as to a consensus regarding the necessity of normoglycemia in diabetic pregnancies, and the introduction of methods for the assessment of fetal well being and pulmonary maturity (Rudge *et al.*, 1995).

According to Pedersen, maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia, resulting in fetal overgrowth. Macrosomia is the most frequent complication and is associated with severe outcomes. Birth traumas caused by disproportionately large shoulders and chest, neonatal metabolic and electrolytic disorders, such as hypoglycemia and hypocalcaemia, as well as peripartum hypoxia, are complications directly associated with poor maternal glucose control. In macrosomic fetuses, the risk of shoulder dystocia at pregnancy is twice larger and the risk of intrauterine death over the last 4-6 weeks of gestation is also higher. The rate of large for gestational age (LGA) and macrosomic infants born in our center reduced from 37.8% to 22.6% after the therapeutic protocol was revised and maternal normoglycemia was rigorously maintained (Rudge *et al.*, 1995; Rudge *et al.*, 2000).

Hyperinsulinemia delays pulmonary maturity, inhibits the production of phospholipids, and favors the Respiratory Distress syndrome (RDS) in neonates. Respiratory problems are aggravated by intrapartum hypoxia and prematurity caused by either a poor maternal control or fetal conditions (Gabbe & Graves, 2003; Rudge & Calderon, 2004). Maternal hyperglycemia increases the levels of glycosylated hemoglobin (HbA1C), which has a greater affinity to oxygen, causing inadequate oxygen delivery to the fetus and consequent intrauterine hypoxia. Contributors to hypoxia also include maternal hyperglycemia-related placental abnormalities, placentomegaly, restricted intervillous space, and increased glycogen storage (Calderon *et al.*, 1999), in addition to endarteritis and dysmaturity that reflect delayed placental maturation and development (Calderon *et al.*, 2000). Fetal responses to hypoxia include enhanced erythropoiesis that results in polyglobulia; higher risk of hyperbilirubinemia and all its consequences; increased blood viscosity; and renal vascular thrombosis in the neonate (Rudge & Calderon, 2004).

In developed countries, congenital anomalies are the most important cause of perinatal death in pregnancies complicated by Diabetes mellitus. However, there is no association with a characteristic syndrome. Central nervous system anomalies, characterized by the Caudal Regression syndrome and neural tube defects (anencephaly, encephalocele, meningomyelocele, spina bifida, holoprosencephaly), and cardiovascular disorders (transposition of the great vessels, ventricular septum defects, left ventricle hypoplasia, hypertrophic cardiomyopathy) are the most common. Urogenital and gastrointestinal malformations, among others, are also associated with intrauterine hyperglycemia at embryogenesis. The pathogenesis of these anomalies is still unclear and comprises multiple factors. Hyperglycemia, however, seems to be the major intrauterine stimulus present at the first weeks of gestation, that favors oxidative stress, production of free radicals, and other adverse conditions to embryonic implantation and fetal development. As a result, increased rates of spontaneous abortion and malformations correlate with diabetes-complicated pregnancies (Gabbe & Graves, 2003), as confirmed by experimental studies (Damasceno *et al.*, 2002).

The glycosylated hemoglobin level, which reflects the quality of glucose control over the last gestational months, is closely correlated with the frequency of fetal anomalies. HbA1C levels of no more than 8.5% correlate with a fetal malformation rate of 3.4%; and when glycosylated hemoglobin

> 9.5%, the rate of fetal malformations approaches 22%. Therefore, it is imperative that women with clinical diabetes achieve excellent glucose control, and have access to preconceptional family planning programs (Gabbe & Graves, 2003; ADA, 2004).

Besides the consequences of malformations, the offspring of diabetic mothers are at higher risk of obesity and plurimetabolic disorders, including diabetes in adulthood, and more frequently show abnormal psychomotor development (Rudge & Calderon, 2004).

Maternal clinical complications associated with diabetic pregnancies include hypoglycemia, worsening of pre-existing retinopathy, nephropathy, diabetic ketoacidosis, preeclampsia, recurrent urinary infection, premature labor and polyhydramnios. Other complications may derive from fetal macrosomia, such as birth traumas and canal lacerations, as well as a higher rate of caesarian deliveries (Rudge & Calderon, 2004). Studies have demonstrated that gestational diabetes correlates with an increased risk of future diabetes type 2 that may reach 44.8% twelve years after pregnancy (Kim *et al.*, 2002; Silva *et al.*, 2003).

No difference in retinopathy has been shown between parous and nulliparous women, suggesting that although pregnancy might accelerate the progression of retinopathy, it has no long-term effect on the disease process. Proliferative retinopathy might occur or worsen in pregnancy and should ideally be controlled before conception, carefully screened in the first prenatal visit, and monitored during pregnancy and after delivery. The prevalence of diabetic nephropathy during gestation ranges from 5 to 10%. Pregnancies complicated by this disease are at increased risk of maternal and fetal morbidity and perinatal mortality. Diabetic nephropathy significantly increases the risk of maternal hypertensive complications, including preeclampsia, preterm birth due to worsening of maternal disease, and fetal growth restriction. Renal dysfunction is confirmed by a reduction in creatinine clearance and the presence of proteinuria, predictors of poor perinatal outcome. Gabbe & Graves (2003) recommend that all pregnant women with a prior history of microalbuminuria or diabetes for over 10 years should be screened with a 24-h urine collection for total protein and creatinine both at the initial prenatal visit and after delivery.

Coronary artery disease is a potential contraindication to pregnancy and its association with arterial hypertension and diabetic nephropathy increases the risk of these diseases. The hemodynamic changes characteristic of pregnancy and the adrenaline released in response to hypoglycemia might exacerbate the risk for myocardial infarction. Women with coronary artery disease should undergo preconception counseling and be informed of these risks (Gabbe & Graves, 2003).

Despite the small number of studies and the lack of scientific evidence regarding maternal outcome in pregnancies complicated by diabetes, perinatal outcome is clearly dependent on a tight control of maternal hyperglycemia. Therefore, the specific determination of the type of pregestational diabetes and its complications, and the early recognition of gestational diabetes, are recommended for the adequate planning of the therapeutic regimen and careful assessment of the maternal and perinatal risks and benefits.

## 2.4. Prenatal care

Early and regular euglycemia should be considered the gold standard in any therapeutic protocol to ensure birth at term and improve the chances of a healthy infant of normal weight and no respiratory disorders or malformations (Rudge *et al.*, 1995; Rudge *et al.*, 2000; Rudge & Calderon, 2004). A multidisciplinary approach improves the quality of prenatal care centers, stimulates compliance to treatment, and, above all, improves maternal and perinatal outcomes. Therefore, care to mothers at risk and their infants should be delivered in tertiary centers. Current recommendations support that diet with regular physical activity should be the first step in the treatment of gestational diabetes, followed by insulin therapy when necessary. In cases of clinical diabetes, regardless of type, diet with insulin is the general recommendation that also includes regular physical activity if no contraindications are present.

Although the impact of physical exercise on pregnancy and maternal/perinatal outcomes still awaits rigorous clinical trials, the beneficial glucose-lowering effects of this activity warrant its recommendation as part of the treatment of GDM (Kramer, 2002; ACOG, 2002; ADA, 2004). A randomized clinical trial including diabetic pregnant women who were treated with either diet or insulin revealed that regular walking favored the achievement of mean glucose < 120 mg/dL and correlated with a tendency to need less insulin and better neonatal outcome (Cunha & Calderon, 2004).

Specifically in type 1 diabetes, the deficient secretion of insulin and count-regulatory hormones

determines the response to physical exercise according to the action of exogenous insulin and the quality of metabolic control. In individuals with type 1 diabetes and in good metabolic control, regular physical exercise of moderate intensity has a glucose-lowering effect as it stimulates the use of peripheral glucose, maintains the concentration of circulating insulin, and stabilizes glucose hepatic production.

These desirable effects are not observed in the presence of severe hyperglycemia, usually associated with ketosis, characteristic of poor glucose control. In these conditions, the use of glucose and hepatic and muscle glycogenesis is impaired by the activation of glycogenolysis, lipolysis and ketogenesis that worsen hyperglycemia and increase the risk of metabolic acidosis (Cunha & Calderon, 2004).

In general, regular physical exercise is recommended in gestational diabetes because it exerts beneficial effects on glucose and weight control, insulin requirements and development of diabetes in adulthood. ADA (2004) encourages a program of moderate exercise as an adjuvant in the treatment of GDM; supports the individualized prescription of exercises in type 1 diabetes depending on the patient's compliance to treatment, awareness and ability to promote and assess her own glucose control; and recognizes that 30 minutes of physical activity of moderate intensity 3 times a week favors both metabolic control and weight management in type 2 diabetes mellitus. Finally, they recommend that all diabetic individuals should have the opportunity to benefit from the effects of this activity.

For the successful introduction or adjustment of diet therapy, it is fundamental to have a nutritionist to calculate caloric requirements and consider the preference for and availability of several kinds of food in each case. Glucose, the main source of energy to the fetus, is of paramount importance in maternal diet. The caloric composition currently recommended includes 40-50% from complex carbohydrates, 20% from protein, 30-40% from unsaturated fats, and less than 10% of saturated fats. The caloric prescription is based on the patient's ideal prepregnancy weight with 35 kcal/kg for the average patient with an increase to 40kcal/kg/day for underweight women, and a decrease to 25 kcal/kg/day for the obese (Gabbe & Graves, 2003; ADA, 2004). Total intake should be distributed into at least five meals/day with a higher load (2/7) at main meals, and a smaller load (1/7) at breakfast and at afternoon or evening snacks. Caloric requirements should be adjusted according to the curves of maternal weight gain and uterine height, indicators of fetal development (Rudge et al., 1995; Rudge & Calderon, 2004).

There are several guidelines for the management and control of hyperglycemia in diabetic mothers. Normoglycemia has been characterized by fasting glucose = 90 mg/dL and 1-h and 2-h postprandial glucose = 130 mg/dL as measured by daily GP (Rudge et al., 1995; Rudge et al., 2000). In addition, fasting glucose of 95 mg/dL and 1-h or 2-h postprandial glucose of 140 and 120 mg/dL, respectively, are also proposed (Landon et al., 2002; Gabbe & Graves, 2003). ADA (2004) recommends 105 mg/dL for fasting glucose, 155 mg/dL for 1-h postprandial glucose and 130 mg/dL for 2-h postprandial glucose.

Regardless of variations, all diagnostic standards consider that these threshold values indicate if insulin therapy is required and assess the quality of control during pregnancy.

Rudge et al. (1995) associated mean diurnal and gestational glucose levels (MG) with fasting and postprandial glucose levels where diurnal MG is the mean of all values obtained in the 24-h GP, and indicates whether insulin therapy should be introduced or adjusted during pregnancy; and gestational MG is the arithmetic mean of all glucose measures obtained in all GP tests undertaken during pregnancy, and characterizes the quality of maternal glucose control. When MG > 100 mg/dL and <120 mg/dL, glucose control is considered adequate; when MG > 120 mg/dL, control is considered poor, and when MG < 100 mg/dL glucose control is ideal. According to these authors, gestational MG and the consequent quality of maternal glucose control, are predictors of perinatal outcome (Rudge et al., 1995; Rudge et al., 2000; Rudge & Calderon, 2004).

When a good glucose control cannot be achieved with diet and physical exercise, the introduction of insulin therapy reduces fetal and neonatal morbidity. Human insulin should be used when insulin is required (Gabbe & Graves, 2003; ADA, 2004). The recommended insulin dose is 0.8 U/kg/day in the first trimester, 1.0 U/kg/day in the second trimester, and 1.2 U/kg/day in the third trimester. Appropriate increases in insulin dosage are made on the basis of monitoring glucose levels. Glyburide, a second-generation sulphonylurea that does not cross the placenta, was found to be comparable to insulin in improving glucose control, with less than 10% of the patients randomized to glyberide requiring insulin (Langer et al., 2000). ADA warns that glyburide is not approved by Food and Drugs Administration (FDA) in pregnancy and that further studies in a larger population are needed to establish its safety. Therefore, the use of insulin, rather than oral hypoglycemic agents is recommended during pregnancy (ADA, 2004).

Nowadays, several types of insulin, with different action profiles (onset action, peak of action, duration of action) are available (Gabbe & Graves, 2003) (Table 4).

Table 4. Types and action profile of insulin<sup>a</sup>.

<b>Insulin</b>	<b>Onset</b>	<b>Peak</b>	<b>Duration</b>	<b>Characteristic</b>
<b>Lispro</b>	1 - 15 min	1 - 2 h	4 - 5 h	rapid
<b>Regular</b>	30 - 60 min	2 - 4 h	6 - 8 h	rapid
<b>NPH</b>	1 - 3 h	5 - 7 h	13 - 18 h	intermediate
<b>Slow</b>	1 - 3 h	4 - 8 h	13 - 20 h	intermediate
<b>Ultralow</b>	2 - 4 h	8 - 14 h	18 - 30 h	long
<b>Glargine</b>	1 h	—	24 h	long

<sup>a</sup> adapted from Gabbe & Graves (2003).

Several insulin therapy protocols that usually combine intermediate- or short-acting insulin (NPH) with rapid-acting insulin (regular and lispro) have been proposed in the literature. Regular- or rapid-acting insulins are administered before meals to reduce glucose elevations in the postprandial period. When insulin lispro is used, the desirable effects reported include lower HbA1C levels and higher patient satisfaction. However, its high cost, risk of hypoglycemia and progression of diabetic retinopathy, though not confirmed by recent studies, have been reported as unfavorable effects. NPH is the intermediate-acting insulin most commonly used in pregnancy, usually in association with rapid- or regular-insulin. Two doses are recommended, one before breakfast and the other before dinner or at bedtime. Bedtime administration is preferable for the prevention of nocturnal hypoglycemia. Long-acting insulins should be given at basal doses in order to prevent the hepatic production of glucose between meals and prolonged fasting. The prolonged duration of action might make it difficult to determine the timing of effect, especially if insulin is given twice a day. Glargine, a human insulin analog, was recently developed by the addition of two arginines to the C-terminus of the insulin  $\beta$  chain and replacement of asparagine with glycine at position 21 of the insulin  $\alpha$  chain. Experience with this kind of insulin is limited and no adequate testing has been conducted during pregnancy (Gabbe & Graves, 2003; ADA, 2004).

Rudge & Calderon (2004) recommend the exclusive use of human NPH (intermediate action) administered in 1-3 daily doses, depending on MG and GP hyperglycemic peaks.  $MG \leq 100$  mg/dL is considered ideal and determines the maintenance or, at the most, the redistribution of the insulin daily dose.  $MG > 100$  mg/dL or  $< 120$  mg/dL reflects an adequate control and allows a small increase in dosage. When MG is inadequate or  $> 120$  mg/dL, the total daily dose of insulin should be considerably increased and partitioned. The complications of this regimen, being hypoglycemia episodes the most common, have been associated with mistaken administration, timing of use, food intake, and excessive physical activity. These authors point out that the necessity for reducing insulin daily dosage at the end of pregnancy might indicate placental failure and require the assessment of fetal well being.

Hypoglycemia is common in pregnancy and is observed in 71% of the pregnant women on insulin therapy and in 34% of those with severe hypoglycemia with loss of consciousness. Intensively treated pregnant women with type 1 diabetes mellitus seem to have impaired counter regulatory responses to hypoglycemia, with reduced release of glucagons and adrenaline. In these cases, the patient's diet as well as exercise program and insulin regimen should be reviewed. The ingestion of a glass of skimmed milk is recommended for moderate hypoglycemia and glucagon for severe cases (Gabbe & Graves, 2003).

The obstetric procedure should include more frequent prenatal visits at a 7-day interval from week 30 to delivery. The assessment of pressure levels and the progression of the curves for uterine height and maternal weight gain are important indicators. The association of arterial hypertension with diabetes is common and reaches the average of 30%, resulting in higher risk of perinatal morbidity and mortality. All patients should undergo retinal examinations at the first prenatal visit so that clinical diabetes can be classified. If retinopathy is present, then follow-up examinations are recommended. Ultrasonographic examinations should be performed before 20 weeks of pregnancy to confirm gestational age; around 25

weeks to investigate for malformations; and at every 4 or 6 weeks to monitor fetal development and well being with an obstetric ultrasonography, fetal biophysical profile (BPP), dopplervelocimetry, amniotic fluid index, and placental development evaluation. Fetal well being should be evaluated by counting fetal movement (FM) at 3 daily periods of 1 h, by cardiotocography (CTG) performed daily in inpatients and weekly in outpatients, by BPP and dopplervelocimetry of the uterine, umbilical and fetal cerebral arteries. Assessment should start with FM counting and CTG at 28 weeks of pregnancy, and finish with BPP and Doppler when necessary (Ridge & Calderon, 2004).

According to Gabbe & Graves (2003), nonstress (basal) cardiotocography (CTG), undertaken once or twice a week, complemented by BPP when necessary, is still the most widely applied method in assessing fetal well being. Daily fetal movement counting, a simple and easy technique, should also be considered. Dopplervelocimetry is more useful in monitoring pregnancies with vascular complications and poor fetal growth. However, the most recent findings about dopplervelocimetry in diabetes-complicated pregnancies showed a direct correlation between decreased placental vascularization and increased resistance in the umbilical artery, regardless of the maternal type of diabetes (Calderon, 2003).

Rudge *et al.* (1994b) evaluated 84 pregnant women with gestational and clinical diabetes to establish the relationships between antepartum CTG findings and the type of diabetes, mean gestational glucose level, and perinatal outcome. Independently from the type of diabetes, mean glucose  $\geq 120$  mg/dL correlated with abnormal CTG findings, indicating fetal commitment. Pereira *et al.* (1999) reported specificity indexes superior to 60% and negative predictive value  $> 90\%$ , and considered normal CTG findings as predictive of neonatal health in these risk pregnancies. The accuracy and validity of CTG in ensuring fetal well being have recently been confirmed in our center (Mascaro *et al.*, 2002).

Maternal metabolic control is key in allowing pregnancies complicated by diabetes to progress to term and in favoring vaginal delivery and the birth of healthy infants. On the other hand, confirming fetal well being allows the prolongation of pregnancy or, at least, the taking of measures, vital to the neonate, before birth (Rudge *et al.*, 1994b; Yamamoto *et al.*, 2000).

In preterm diabetic gestations, amniocentesis is still used in the decision-making process. Upon amniotic fluid analysis, Lecithen/Sphingomyelin ratio(L/S)  $> 2$  and presence of Phosphotidylglycerol(PG), with Phosphotidylglycerol/Phosphatidylinositol(PI) ratio  $> 1$  indicate fetal pulmonary maturity and reduced risk for Respiratory Distress syndrome (RDS) (Rudge *et al.*, 1996). Gabbe & Graves (2003), not only point to the usefulness of amniocentesis in this condition, but also recommend corticosteroids to accelerate pulmonary maturity. In these cases, glucose levels should be more frequently monitored and insulin should be increased over the first 5 days of corticotherapy.

Timing of delivery should be determined by balancing the risks of intrauterine fetal death and excessive fetal growth if pregnancy is continued versus the risks of prematurity. The vaginal route is preferable unless fetal weight  $> 4500$ g, maternal history includes two or more caesarean deliveries, and fetal wellbeing is severely affected. During labor induction, fasting is recommended as well as the infusion of 10% glycosylated solution, prescription of 1/3 of the insulin dose used on the previous day, and tight maternal glucose control. When glucose levels  $> 110$  mg/dL, regular insulin should be intermittently or continuously infused. After delivery, women with diabetes type 1 should be given half of the predelivery insulin dose, which should be gradually adjusted according to food intake and glucose levels. Women with diabetes type 2 should resume the use of oral hypoglycemicating drugs while those with gestational diabetes, as a rule, no longer require insulin or any other kind of treatment. Breastfeeding should be encouraged in all women, regardless of diabetes type (Gabbe & Graves, 2003; Rudge & Calderon, 2004).

The women with clinical diabetes are referred back to an endocrinologist and those who had gestational diabetes should undergo a 75-g OGTT four to six weeks after delivery in order to confirm or rule out pregestational clinical diabetes. Because women with gestational diabetes are at high risk for developing future diabetes, they should be tested for diabetes every three years. Family planning should prioritize the smaller number of children at the shorter time interval in cases of diabetes type 1, and stress the importance of glycemic control in the pregestational period. Condoms are still the most commonly used contraceptive method. The intrauterine device (IUD) can be used in well-controlled cases, while the new generation of hormonal contraceptives should be given to women with histories of prior gestational diabetes. Tubal ligation should be considered for women who have completed their families (ADA, 2004; Rudge & Calderon, 2004).

### 3. Concluding Remarks

Despite all physiopathological, diagnostic and therapeutic advances to date, diabetic pregnant women are still at very high risk in Brazil. According to DATASUS (SUS database) latest records, 75 maternal deaths were diabetes-related in the state of São Paulo in 1999, which is equivalent to a specific maternal death ratio (MDR) of 5.162. Even in tertiary centers, diabetes is a severe complication and perinatal death rate is 10-fold higher than that observed in the nondiabetic population (Rudge & Calderon, 2004). The implementation and improvement of centers of reference and, above all, the involvement of the medical class is essential. Investments on diagnosis, adequate treatment and referral of the pregnant women to specialized centers might prevent both maternal and perinatal hyperglycemia-related morbidity and mortality.

Independently from the lack of consensus about screening and diagnostic standards, it is very important to investigate for hyperglycemia in all pregnant women at risk, that is, when there is a family, personal or obstetric history of diabetes. As long as they are well controlled, the patients with clinical diabetes might expect the same outcomes as normal women. Finally, the development of educational programs should not only promote good outcome but also long-lasting lifestyle changes.

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