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# Gestational Diabetes: Evidence-Based Screening, Diagnosis and Treatment

Melania Maria Ramos Amorim and Leila Katz
*Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) – Recife, Pernambuco, Brazil*

## 1. Introduction

Gestational diabetes (GD) is defined as carbohydrate intolerance that begins or is first diagnosed during pregnancy. Hyperglycemia is found only during pregnancy and diagnosis is confirmed when glucose tolerance test results return to normal levels in the postpartum (Metzger et al., 2007). GD occurs in around 4-10% of pregnancies; however, its incidence varies as a function of nutritional habits and differences in genetic patterns between populations (Metzger et al., 2007).

The importance of GD was first described around forty years ago when it was noticed that women with this disorder were more likely to develop diabetes mellitus later on in their lives. The original diagnostic criteria proposed by O'Sullivan and Mahan were in fact never validated for the development of gestational complications or adverse perinatal outcomes (O'Sullivan and Mahan, 1964). Throughout all this time, the importance of this diagnosis for the prognosis of the pregnancy has been the subject of debate (Holt et al., 2011). Whereas some specialists feared that even mild levels of hyperglycemia would negatively affect pregnancy outcome, others have questioned the very existence of GD as a disease (Buchanan and Kjos, 1999).

Recently, however, the harmful effects of hyperglycemia during pregnancy have been demonstrated (HAPO, 2008) and evidence is mounting on the risks of hyperglycemia during pregnancy, not only in terms of adverse perinatal outcome, but also for the future of the infant in adult life (Catalano, 2010; Chandler-Laney et al., 2011; Fall, 2010; Lawlor et al., 2011).

In this chapter, the rationale and current recommendations for the diagnosis and treatment of gestational diabetes will be evaluated based on the best scientific evidence currently available. The MEDLINE, EMBASE, SCOPUS and SciELO databases and the systematic reviews of the Cochrane Library were reassessed using the key words: gestational diabetes, screening, diagnosis and therapy. Preference was given to randomized clinical trials and meta-analyses, with observational studies and review articles being included only when studies with a better level of evidence were unavailable. Guidelines and recommendations established by medical societies for the screening, diagnosis and treatment of gestational diabetes were also consulted.

## 2. Physiopathology

As any carbohydrate metabolism disorder, GD is characterized by insufficient insulin levels for insulin demand (Metzger et al., 2007). The cause of this insulin insufficiency in

pregnancy remains to be fully established; however, it is believed that the occurrence of this event during pregnancy reveals underlying maternal pancreatic disorders that would otherwise only become apparent later on in the woman's life (Metzger et al., 2007).

In a normal pregnancy, fetal and placental growth increases cortisol, growth hormone, human placental lactogen, progesterone, estrogen and prolactin levels. The presence of these stimuli triggers hyperinsulinemia, insulin resistance, fasting hypoglycemia and postprandial hyperglycemia. Consequently, there is a reduction in peripheral sensitivity to insulin and an increase in demand. As a compensatory mechanism, an increase occurs in pancreatic function at the cost of both hypertrophy and hyperplasia. Furthermore, in response to the high insulin levels, peripheral utilization of glucose by the muscles and peripheral glycogen storage increase in an attempt to maintain balance (Metzger et al., 2007; Pridjian and Benjamin, 2010).

As pregnancy advances, these compensatory mechanisms may be insufficient in susceptible women, resulting in an imbalance between insulin production and insulin requirements in pregnancy. Compared to a normal pregnant woman, a woman with GD has pancreatic β-cell dysfunction and a reduction in adaptive β-cell capacity. This results in insufficient insulin secretion and consequent hyperglycemia (Metzger et al., 2007; Pridjian and Benjamin, 2010).

## 3. Consequences for the mother and child

The consequences of gestational diabetes for the mother and child are summarized in Table 1.

| Risks of Gestational Diabetes | | | |
|---|---|---|---|
| **Mother** | **Fetus** | **Newborn infant** | **Child/Adult** |
| Obstetric trauma | Hyperinsulinemia:<br>• Large for gestational age<br>• Macrosomia | Respiratory distress syndrome | Obesity |
| Higher rate of Cesarean sections | Cardiomyopathy | Hypoglycemia | Type 2 Diabetes Mellitus |
| Preeclampsia/ gestational hypertension | Obstetric trauma:<br>• Shoulder dystocia<br>• Fractures<br>• Brachial plexus lesion | Hypocalcemia | Metabolic syndrome |
| Type 2 Diabetes mellitus | Stillbirth | Hypomagnesemia | |
| Metabolic syndrome | | Polycythemia:<br>• Hyperviscosity<br>• Hyperbilirubinemia<br>Cardiomyopathy | |

Modified from Pridjian and Benjamin, 2010

Table 1. Risks of Gestational Diabetes

## 4. Screening and diagnosis of gestational diabetes

The screening and diagnosis of GD is the subject of intense debate and controversy worldwide (Holt et al., 2011; Leary et al., 2010). All aspects of diagnosis (who should be investigated, using which tests and what values are considered diagnostic) have been widely discussed over the past two decades (Holt et al., 2011). Consequently, the guidelines published by the major societies differ with respect to these aspects with the result that the practices of physicians worldwide differ to the same extent (Leary et al., 2010).

The World Health Organization (WHO) recommends screening high-risk women with a 75-gram oral glucose tolerance test in the first trimester of pregnancy and all other women at 24-28 weeks, with fasting glucose measurements of 126 mg/dl and two-hour glucose levels of 140 mg/dl being considered abnormal (WHO, 1999). However, until recently (up to autumn 2010), the American Diabetes Association (ADA) recommended screening only women with risk factors and advocated an oral load of 100 grams of anhydrous glucose (ADA, 2004). The values adopted in each one of the guidelines also differed greatly.

Recently, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) assembled the evidence accumulated over recent years and published new criteria for the screening and diagnosis of GD (IADPSG, Metzger et al., 2010).

### 4.1 Screening

Screening is performed to select individuals to be investigated. Since 1999, the World Health Organization (WHO) has recommended the screening of all women or all women except those considered low-risk (WHO, 1999).

In 2003, a US taskforce was formed to evaluate screening for gestational diabetes. The authors' conclusion was that better-quality evidence was required to determine whether the benefits of screening are greater than the risks. They recommended that until such evidence was available, to screen or not to screen should be left to the discretion of each individual physician according to his/her own clinical judgment and that both options are reasonable (The US Preventive Services Task-Force – USPSTF, Brody et al., 2003-A).

The same taskforce evaluated the risk factors for gestational diabetes and found a strong association with: maternal obesity (body mass index > 25), age > 25 years, personal or family history of a carbohydrate metabolism disorder or a history of gestational diabetes in a previous pregnancy. Some ethnic groups such as Hispanics, Blacks, native American Indians and Asians are also at an increased risk of developing gestational diabetes. If all these criteria are taken into consideration, 90% of all women at risk of developing gestational diabetes will be identified (Brody et al., 2003-A).

A systematic review was conducted of observational studies published in the past thirty years to evaluate the presence and strength of the association between pre-gestational body mass index (BMI) and the presence of gestational diabetes. Seventy studies were included involving 671,945 women (59 cohort studies and 11 case-control studies). Compared to women with normal pregestational BMI, in accordance with the odds ratio (OR) the estimated risk of developing gestational diabetes was 1.97 [95% confidence interval (95%CI) 1.77 – 2.19], 3.01 [95%CI: 2.34 – 3.87] and 5.55 [95%CI: 4.27 – 7.21] for overweight, moderate obesity and severe obesity, respectively (Torloni et al., 2009).

In addition to the principal risk factors, Table 2 provides a detailed list of risk factors from previous pregnancies as well as risk factors that may appear during the course of pregnancy and may merit investigation.

| **Personal characteristics:** |
|---|
| Age > 35 years |
| Obesity (BMI > 25) |
| Arterial hypertension |
| Family history of diabetes |
| **Obstetric history:** |
| Diabetes in previous pregnancy |
| Multiparity |
| Recurrent miscarriage |
| Prematurity |
| Recurrent preeclampsia |
| Fetal death, principally in the final weeks of pregnancy |
| **Neonatal morbidity and mortality:** |
| - Hypoglycemia |
| - Respiratory distress syndrome |
| - Hyperbilirubinemia |
| - Hypocalcemia |
| - Malformations |
| **Complications in current pregnancy:** |
| Excessive weight gain |
| Excessive growth of uterine fundal height |
| Polyhydramnios |
| Fetal macrosomia |
| Glycosuria |
| Use of hyperglycemic drugs (betamimetics, corticoids) |

Amorim and Katz, 2011

Table 2. Risk factors for gestational diabetes

More recently, another systematic review evaluated the available literature, searching for further evidence on screening for gestational diabetes (Tieu et al.,2011). The authors searched for articles which evaluated any individual screening tool or screening program, protocol or guideline for gestational diabetes compared with the absence of screening; or any individual screening tool or screening program, protocol or guideline for gestational diabetes with another. Thirty-one trials were considered for inclusion into the review but after application of eligibility criteria, only four of these trials were included. After analysis the authors found that there was insufficient evidence to determine the effects of screening for gestational diabetes and its subsequent management, or the comparative effects of different protocols for screening. Although women who were routinely screened by 50 g glucose challenge testing were more likely to be diagnosed with gestational diabetes than those screened by their risk factors, effects of subsequent management on health outcome are unclear.

IADPSG recommends investigating "all women or all high-risk women" at their first prenatal consultation (IADPSG, Metzger et al., 2010). Universal investigation is justified by the increase in the prevalence of undiagnosed type 2 diabetes in young women (Leary et al.,

2010) and in the risk factors for the occurrence of GD such as, for example, obesity (Catalano, 2010). In addition, it ensures that cases of early-onset GD will be identified (Leary et al., 2010). Early screening reflects the preference for universal investigation.
In addition, IADPSG recommends **universal** investigation at 24-28 weeks of all women not previously diagnosed as having clinical or gestational diabetes (IADPSG et al., 2010).
The argument used by those who support universal screening is based on the randomized clinical trial entitled the *Australian Carbohydrate Intolerance Study in Pregnant Women* (ACHOIS) trial group (Crowther et al., 2005), which showed a reduction in healthcare costs with universal screening. Nevertheless, criticism to the use of these results for recommending IADPSG's proposal is based on the fact that the ACHOIS study used an oral glucose tolerance test of 75 grams, measuring fasting glucose levels and two-hour glucose levels alone, whereas the IADPSG recommendations also include measurement of glucose levels one hour after overload (Leary et al., 2010). Further studies should be conducted to evaluate the costs and benefits associated with this form of management.

### 4.2 Diagnosis

The origin of all this controversy surrounding the diagnosis of GD lies in the form in which testing was initially developed. The first authors to develop a diagnostic test for GD were John O'Sullivan and Clare Mahan in 1964 (O'Sullivan and Mahan, 1964). The test was developed to predict the risk of developing diabetes mellitus years after the pregnancy rather than the risk of an adverse perinatal outcome.
Although it constituted a watershed in the diagnosis of GD, faults were found in the study conducted by O'Sullivan and Mahan when analyzed from a methodological point of view, particularly with respect to the conclusions drawn and the validation of the test as a diagnostic technique, which was clearly demonstrated by Naylor in a study published in 1989 (Naylor, 1989). One of the questions raised was that gestational diabetes is more important as a predictor of a pregnancy with a higher maternal-fetal risk, whereas the end-point initially evaluated was the presence of carbohydrate intolerance after the end of pregnancy. Since the investigators' objective was to predict the development of diabetes mellitus over the long-term, this characteristic was taken into consideration to select the cut-off points. It was later shown that when pregnant women considered to be diabetic in accordance with the values selected were treated with insulin, the rate of macrosomia decreased when glucose levels returned to normal (O'Sullivan, 1996 and 1973). This is an indirect way of reaching conclusions that is, nonetheless, far from ideal and does not allow the diagnostic technique to be adequately validated. According to Naylor, it would have been more appropriate to try to record the immediate and long-term neonatal complications and test their association using an oral glucose tolerance test.
In the following years, changes were made to the diagnostic techniques used and glucose levels were no longer measured in full blood but rather in venous plasma. Furthermore, enzymatic methods began to be used to measure plasma glucose levels instead of the Somogyi-Nelson technique. These technical modifications led to the mathematical correction of the values initially proposed by O'Sullivan and Mahan with the appearance of different sets of values adopted by different organizations involved in the study of GD (National Diabetes Data Group [NDDG], 1979; Carpenter and Coustan, 1982).
Later, an intense debate ensued among investigators regarding the best form of diagnosing GD. Many investigators suggested the adoption of more rigid diagnostic criteria, including a

reduction in blood glucose levels or the adoption of fewer points on the curve as being sufficient for diagnosis. It was even proposed that the presence of hyperglycemia below the levels established for diagnosis could be sufficient to lead to adverse maternal and perinatal outcomes, or that the hyperglycemia occurring irrespective of an overload should be taken into consideration (Aberg et al., 2001; Jensen et al., 2001; Langer et al., 1987; Rudge et al., 1990; Sermer et al., 1995).

If on the one hand evidence was accumulating to the effect that milder degrees of hyperglycemia, albeit below the levels established for a diagnosis of GD, could lead to unfavorable perinatal outcomes, on the other hand some authors questioned the very existence of this diagnosis as a valid entity and called attention to the possible negative effects of this diagnosis (Buchanan, 1999; Lucas et al., 1993). A diagnosis of GD may result in excessive medicalization of pregnancy, which in itself would be negative. Furthermore, this diagnosis may result in an increase in the number of interventions performed, including even Cesarean sections, in situations in which the need for this type of delivery is questionable, due to the mere presence of a diagnosis of diabetes. In addition, it is important to remember the psychological burden caused by a label of diabetes.

In 2005, an Australian group (ACHOIS) published the findings of a randomized clinical trial in which mild hyperglycemia was treated in women who did not fulfill the diagnostic criteria for GD, but who had measurements of 140 to 199 mg/dl in a 75-gram oral glucose tolerance test (OGTT) and were consequently considered to be carbohydrate intolerant (Crowther et al., 2005). These investigators found a reduction in composite final outcome (perinatal death, shoulder dystocia, fractures and brachial plexus palsy) compared with women managed in the usual manner.

In 2009, a clinical trial was conducted to treat women who were found not to fulfill the diagnostic criteria for GD after being submitted to an oral glucose tolerance test with 100 grams of carbohydrate, but whose glucose levels were not completely normal. Likewise, when this group was treated, a reduction was found in macrosomia, shoulder dystocia, Cesarean section and hypertensive diseases (Landon et al., 2009).

Finally, the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study was conducted to evaluate the risks of hyperglycemia during pregnancy for the mother, the fetus and the newborn infant (HAPO, 2008). A total of 25,505 women were included and followed up prospectively to evaluate a possible association between glucose levels and maternal and perinatal outcome. The women were submitted to an OGTT using 75 grams of anhydrous glucose.

The HAPO results were conclusive with respect to the existence of a linear association between elevated glucose levels in the pregnant woman and the rates of large-for-gestational-age infants, preeclampsia and Cesarean sections. Moreover, an association was found between maternal hyperglycemia and neonatal hypoglycemia, C-peptide in umbilical cord blood, premature delivery, admission to the neonatal intensive care unit (ICU) and hyperbilirubinemia. No association was found between maternal hyperglycemia and neonatal death; however, the sample size may have been insufficient to evaluate this particular outcome.

One of the most important findings of HAPO was the demonstration of an association that is continuous; hence no clear cut-off point can be defined above which adverse events occur (Leary et al., 2010).

The choice of the 75-gram curve to investigate these women has never been validated scientifically. The first glucose overload to be described in pregnancy was performed using

100 grams of anhydrous glucose (O'Sullivan and Mahan, 1964), a procedure that was also recommended by the American Diabetes Association in 2004 (ADA, 2004). Nonetheless, since the WHO proposal in 1980 to use a 75-gram overload, as used in non-pregnant women, this practice became more and more common and even the HAPO study used the 75-gram glucose overload. With the power obtained in the HAPO study showing the adverse perinatal effects of hyperglycemia associated with the levels obtained following a 75-gram overload of anhydrous glucose, this test will probably increase in popularity compared to the 100-gram overload (Leary et al., 2010).

Another interesting outcome of the HAPO study was the recommendation that a finding of only one abnormal value on the glucose curve should also be considered abnormal and diagnostic. This recommendation was made with the aim of increasing the likelihood of identifying milder degrees of hyperglycemia that had been associated with poorer maternal and perinatal prognosis in previous studies.

The cut-off points recommended by IADPSG are arbitrarily defined based on an odds ratio of 1.75 relative to the mean glucose levels at each time-point, i.e. those measurements that result in a 75% greater likelihood of adverse perinatal outcomes. The selection had to be made in this way, since, as previously mentioned, the association between glucose levels and adverse outcome is continuous. These values, however, are subject to criticism and the occurrence of adverse outcomes with glucose levels below the proposed values is to be expected. Nevertheless, use of a lower cut-off point would certainly result in a greater percentage of diagnosed cases and the impact of this excess number of diagnoses on perinatal outcomes has yet to be established (Leary et al., 2010).

The absence of any IADPSG recommendations regarding a category referred to as "carbohydrate intolerance" is noteworthy. According to current criteria, either a woman has normal glucose levels or she has gestational diabetes. However, cases need to be taken into consideration in which women have glucose levels outside the limits considered normal yet without reaching levels that would be considered diagnostic. The adoption of the term "carbohydrate intolerance" is suggested for such cases (Leary et al., 2010).

The findings of the HAPO study appear to indicate that only normal glucose levels would eliminate the risk of adverse perinatal outcome; therefore, it could be argued that any deviation above normal levels should be considered abnormal (Leary et al., 2010). However, the economic and even the psychological impact of so many diagnoses of an "abnormal pregnancy" needs to be taken into consideration and may be immense.

To determine the ideal cut-off point, a cost-benefit analysis has to be performed of different cut-off points. In addition to the cost of the diagnostic test itself, the financial burden caused by the additional cases diagnosed in terms of follow-up and treatment has to be taken into consideration. In addition, it has to be confirmed that treating these diagnosed cases will indeed lead to a reduction in the number of adverse outcomes (Leary et al., 2010) and, furthermore, that this reduction will cause a positive impact that will compensate for the costs of diagnosis and follow-up.

The change in the diagnostic criteria defined by IADPSG will certainly have significant clinical implications for women and for the healthcare system. The number of women diagnosed as having gestational diabetes will rise. This increase in the prevalence of GD may cause a significant impact on all the additional women who will be diagnosed (Holt et al., 2011). In addition to the greater volume of resources required to follow-up and treat these women, the effect on patients of the very existence of a diagnosis should be kept in mind.

Therefore, this change needs to be supported with convincing data showing beyond doubt that its adoption will improve pregnancy outcome. Since the HAPO study was merely observational, it is limited to associating adverse perinatal outcomes with higher glucose levels; however, it does not prove that normalizing glucose levels will necessarily result in any improvement in prognosis (Holt et al., 2011).
Two studies evaluated the benefits of treating milder degrees of hyperglycemia in pregnancy: the ACHOIS study (Crowther, 2005) and the US Multicenter Randomized Trial for Treatment of Mild GMD (Landon, 2009). Despite promising results, it should be remembered that these studies differed in relation to the glucose levels considered treatable and in the number of glucose measurements performed for diagnosis. This hampers extrapolation of these results to the findings of the IADPSG study (Holt et al., 2011).

### 4.3 Investigation

The IADPSG proposal for the screening and diagnosis of GD is shown in Table 3:

| |
|---|
| *First prenatal consultation* |
| Fasting glucose level or hemoglobin A1 (HgA1) or random measurement in women |
| • If clinical diabetes => treatment and follow-up for preexisting diabetes. |
| • If results are non-diagnostic for clinical diabetes: |
| • and fasting glucose level is > 92 and < 126 => diagnosis of GD |
| • and fasting glucose level is < 92 => test at 24-28 weeks with OGTT, 75 grams. |
| *24 - 28 weeks of pregnancy* |
| OGTT, 75 grams: fasting glucose measurement/1 hour/2 hours |
| • Consider clinical diabetes if fasting glucose > 126 |
| • Consider GD if ONE or more measurements are above the cut-off points. |
| • Consider normal if all the values are below the cut-off points. |

| **For a diagnosis of GD (OGTT, 75g)** | |
|---|---|
| Fasting glucose | > 92 mg/dl |
| Glucose level at 1 hour after overload | >180 mg/dl |
| Glucose level at 2 hours after overload | >153 mg/dl |
| **For a diagnosis of clinical diabetes during pregnancy (any one of these tests)** | |
| Fasting glucose | > 126 mg/dl |
| Hemoglobin A1 | > 6.5% |
| Random plasma glucose measurement | > 200 mg/dl |

Table 3. **S**creening and diagnosis of GD according to the IADPSG

It is important, however, to call attention to the fact that controversies persist, despite the enormous number of studies conducted in this field. Analyzing the guidelines drawn up by

the different organizations, it is clear that there is no consensus with respect to the quantity of glucose that should be used in the oral glucose tolerance test (OGTT), to the glucose levels that should be considered abnormal, or to the number of abnormal measurements on the curve that would permit a diagnosis of GD to be made (Holt et al., 2011).
Table 4 shows the different criteria currently adopted for a diagnosis of gestational diabetes.

| Organization | Glucose overload | Number of abnormal values required | Fasting glucose levels | Glucose levels after 1 hour | Glucose levels after 2 hours |
|---|---|---|---|---|---|
| IADPSG | 75g | ≥ 1 | 5.1mmol/l 92mg/dl | 10.0mmol/l 180mg/dl | 8.5mmol/l 153mg/dl |
| WHO | 75g | ≥ 1 | 7.0mmol/l 126mg/dl | | 7.8mmol/l 140mg/dl |
| ADA | 100g | ≥ 2 | 5.3mmol/l 95mg/dl | 10.0mmol/l 180mg/dl | 8.6mmol/l 155mg/dl |
| ADIPS | 75g | ≥ 1 | 5.5mmol/l 100mg/dl | | 8.0mmol/l 144mg/dl |
| CDA | 75g | ≥ 2 | 5.3mmol/l 95mg/dl | 10.6mmol/l 190mg/dl | 8.9mmol/l 160mg/dl |
| EASD | 75g | ≥ 1 | 6.0mmol/l 108mg/dl | | 9.0mmol/l 162mg/dl |
| NZSSD | 75g | ≥ 1 | 5.5mmol/l 100mg/dl | | 9.0mmol/l 162mg/dl |
| ADA: American Diabetes Association (until autumn 2010); ADIPS: Australasian Diabetes in Pregnancy Society; CDA: Canadian Diabetes Association; EASD: European Association for the Study of Diabetes; IADPSG: International Association of Diabetes and Pregnancy Study Groups; NZSSD: New Zealand Society for the Study of Diabetes; WHO: World Health Organization. *The ADA adopted the IAPDSG criteria in the autumn of 2010. | | | | | |

Holt et al, 2011

Table 4. Comparison of diagnostic criteria for gestational diabetes

Until randomized clinical trials are conducted to compare the different strategies for screening and diagnosis and to define possible differences in maternal and perinatal outcome, the ideal test and the ideal criteria remain to be defined. The characteristics of each population should be evaluated, principally with respect to the frequency of gestational diabetes and macrosomia. In populations with a high risk for diabetes, we suggest that the IADPSG criteria be used; however, in low-risk populations in which there is no significant association between macrosomia and gestational diabetes, these criteria may not be applicable (Leary et al., 2010).

## 5. Treatment of gestational diabetes

### 5.1 Rationale for treatment

Normally, the proposal of any strategy for screening and diagnosis of gestational diabetes is aimed at establishing a therapeutic plan for diagnosed cases, since available evidence

suggests that adequate treatment successfully reduces maternal and fetal morbidity, particularly macrosomia (Crowther et al., 2005; Langer et al., 2005; Landon et al., 2009).

Various therapeutic options are available such as diet, physical exercise, blood glucose monitoring and insulin therapy in cases in which diet alone fails to maintain adequate glucose levels (Pridjian and Benjamin, 2010). This chapter does not explore the details of each individual treatment, but simply reviews the available evidence regarding the need for treatment and its effectiveness.

A systematic review in the Cochrane Library specifically deals with the various alternative therapeutic options for gestational diabetes (Alwan et al., 2011). Eight randomized clinical trials involving a total of 1,418 women were included in which any form of treatment was compared with routine prenatal care or different treatments were compared with each other. Except for one large Australian study published in 2005 that included 1,000 women (ACHOIS trial) (Crowther et al., 2005), the sample sizes were small in all the other studies. When the treatment of mild hyperglycemia was compared with routine prenatal care, a significant reduction was found in the risk of preeclampsia and an increase in the risk of induced labor in the group that received treatment. There were no differences in Cesarean section rates, rates of hospital admission, instrumental delivery or postpartum hemorrhage or in the duration of hospital stay. With respect to perinatal outcome, the treatment of diabetes resulted in a significant reduction in composite perinatal morbidity (death, shoulder dystocia, bone fracture and nerve palsy), as well as in the frequency of macrosomia (birthweight > 4000 grams) and shoulder dystocia. Although in the ACHOIS study the rate of admittance to a neonatal intensive care unit was higher for the infants of mothers who received treatment for hyperglycemia, in the meta-analysis this difference was not found to be statistically significant. There were no significant differences between the two groups with respect to gestational age at delivery, incidence of bone fracture in newborn infants, incidence of nerve palsy in the newborn, perinatal death, neonatal hypoglycemia, incidence of respiratory distress syndrome in the newborn infant or in the need for mechanical ventilation. The conclusion reached by these reviewers was that specific treatment for mild gestational diabetes, including diet and insulin, reduces the risk of maternal and perinatal morbidity; however, the risk of labor induction increases. Further studies need to be conducted to evaluate the effect of the different therapeutic modalities, including oral hypoglycemic drugs and insulin, on infant short and long-term outcomes.

Specific analysis of the findings of the ACHOIS trial reveals a frequency of severe neonatal morbidity of 1% in the treated group compared to 4% in the group that received routine care. The incidence of neonatal admission to hospital was 71% versus 61%, respectively, whereas rates of labor induction were 39% in the treatment group versus 29% in the group receiving routine care. The rate of Cesarean sections was similar in both groups, 31% versus 32%. In addition, lower rates of depression and better quality of life scores were found in the treated women in the ACHOIS trial at three months postpartum (Crowther et al., 2005).

Another large randomized clinical trial conducted in the United States was published in 2009 and has yet to be included in the Cochrane systematic review (Landon et al., 2009). The study included 958 women. There was no statistically significant difference in composite outcome (32.4% in the treated group and 37% in the control group) and no perinatal deaths occurred in either group. Nevertheless, birthweight was significantly lower in the treated group (3302 grams versus 3408 grams), as was the frequency of large-for-gestational-age infants (7.1% versus 14.5%), fetal macrosomia (5.9% versus 4.0%), shoulder dystocia (1.5%

versus 4.0%) and Cesarean sections (26.9% versus 33.8%). The rates of preeclampsia and gestational hypertension were also lower in the treated group (8.6% versus 13.6%).
A more recent systematic review on the treatment of gestational diabetes included 18 studies, five of which compared the specific treatment of diabetes with routine treatment (including the 2009 US trial). Modest effects of treatment were found, including a reduction in the risk of fetal macrosomia and shoulder dystocia and a trend, albeit non-significant, towards a reduction in the rate of Cesarean sections. Different levels and intensity of treatment were compared in 13 trials, with findings showing a significant reduction in risk only with respect to shoulder dystocia in the group receiving intensive treatment (Horvath et al., 2010).
Based on the results of these more recent studies, we believe that it is important to diagnose and treat gestational diabetes in order to reduce maternal and neonatal morbidity. Data from the Hyperglycemia and Adverse Pregnancy Outcomes study (HAPO, 2008) reinforce this recommendation, since findings showed a significant association between increasing glucose levels and maternal complications such as preeclampsia, and neonatal complications such as macrosomia and metabolic alterations (Leary et al., 2010), leading, as previously discussed, to changes in the diagnostic criteria for gestational diabetes, as defined by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (Metzger et al., 2010). Nonetheless, some criticism remains with respect to the comparability of the HAPO study with the more recent clinical trials, since different screening strategies were used (Horvath et al., 2010).

### 5.2 Treatment strategies

#### 5.2.1 Diet

The universal recommendation has been that all women with a confirmed diagnosis of gestational diabetes should receive dietary counseling and initiate an appropriate diet with the aim of normalizing glucose levels, preventing ketosis, ensuring adequate weight gain and contributing towards fetal well-being. The number of calories will depend on the woman's current weight, with an allowance of 30 kcal/kg of current weight for women with a normal body mass index (BMI), 24 kcal/kg for overweight women and 12-15 kcal/kg for obese women. Carbohydrates (preferably complex carbohydrates) should correspond to 33-40% of the total number of calories, with protein corresponding to 20% and fat to 40%, provided in the form of three main meals and three snacks. Moderate use of sweeteners such as aspartame is permitted. Following these dietary guidelines, glucose levels will normalize in around 75-80% of women with gestational diabetes (ADA, 2004).
Nevertheless, the most adequate strategy for the control of gestational diabetes still remains to be defined, since diet alone may fail to prevent macrosomia. A systematic review available in the Cochrane Library included four studies with 612 women with gestational diabetes and failed to find any differences in the rates of macrosomia (OR = 0.78; 95%CI: 0.45 – 1.35) or Cesarean section (Walkinshaw, 2011). However, the clinical trials included in this review were all small and old, with variations in quality and very wide confidence intervals that did not permit evaluation of the validity of dietetic therapy. The reviewers concluded that there is insufficient evidence to evaluate the use of primary dietetic therapy for women with impaired glucose metabolism in pregnancy. They recommended that larger studies should be conducted to evaluate the effects of diet on maternal outcome (particularly Cesarean sections) and perinatal outcome.

Compliance with treatment and weight gain constitute factors capable of modifying response to dietetic treatment. One large retrospective study including more than 30,000 women with gestational diabetes showed that in the women in whom weight gain was adequate maternal and perinatal outcomes were favorable, whereas those in whom weight gain was excessive had a higher risk of large-for-gestational-age infants, premature delivery and Cesarean sections (Cheng et al., 2008).

### 5.2.2 Physical exercise

Physical exercise has been proposed as part of the treatment for gestational diabetes based on the fact that, in adults, an improvement in physical fitness increases insulin sensitivity, improves glucose control and reduces the need for insulin (Colberg et al., 2010).

A systematic review available in the Cochrane Library evaluated the effects of exercise programs alone or in association with other therapies on maternal and perinatal morbidity in pregnant women with diabetes. The review included four small, randomized clinical trials involving 114 women with gestational diabetes recruited during the third trimester of pregnancy. The intervention (exercise) was performed over six weeks. There were no statistically significant differences between the group that performed exercise and the controls for any one of the endpoints evaluated. The authors' conclusion was that the evidence was insufficient to either recommend or contraindicate exercise for pregnant women with diabetes and that larger randomized clinical trials should be conducted to further evaluate this form of intervention (Ceysens et al., 2011).

Despite the consistent lack of evidence on the effects of exercise on maternal and perinatal prognosis in women with gestational diabetes, the American Association of Diabetes (ADA) suggests a program of moderate exercise as part of the therapeutic management of women with gestational diabetes as long as there are no medical or obstetrical contraindications to this level of physical activity (ADA, 2004).

### 5.2.3 Monitoring glucose levels

Monitoring glucose levels may also alter the progression of the condition in women with gestational diabetes. One study showed that daily monitoring of pregnant women treated with diet allows identification of those who could benefit from treatment with an anti-hyperglycemic agent, which may lead to a reduction in the rates of macrosomia (Hawkins et al., 2009; Hawkins, 2010). Nevertheless, the ideal frequency of self-monitoring in women with diet controlled gestational diabetes remains to be established and there is insufficient evidence regarding the ideal glucose levels and the duration of control that would allow longer intervals between capillary glucose measurements (Metzger, 2007).

With respect to the timing and frequency of capillary glucose monitoring, although there are still some controversies between investigators, most of them currently recommend measuring fasting levels immediately after waking and one hour after meals. The proposal for self-monitoring made by some specialists is to test capillary glucose levels four times a day in cases of diet controlled gestational diabetes (fasting and one hour after each meal) and six times a day in gestational diabetes requiring the use of insulin (fasting, one hour prior to and one hour after each meal) (Jovanovic, 2008).

A clinical trial comparing monitoring with schedules that involve either the measurement of pre-prandial glucose levels or fasting glucose and postprandial levels (one hour after meals) in patients with gestational diabetes using insulin therapy showed a better control of

glucose levels, a lower rate of large-for-gestational-age infants and a lower rate of Cesarean sections with the latter protocol (deVeciana et al., 1995). Comparing monitoring one hour postprandial with two hours postprandial, a prospective, observational study found less need for insulin therapy and a trend towards lower rates of fetal macrosomia and Cesarean sections with one-hour postprandial glucose measurements (Weisz et al., 2005). There is insufficient evidence to determine the role of continuous glucose monitoring in patients with gestational diabetes, although this may be useful in women who require insulin and who have difficulty in achieving adequate control of glucose levels (Hawkins, 2010).

### 5.2.4 Pharmacological treatment

#### 5.2.4.1 Insulin therapy

With respect to insulin therapy, there is no consensus on the glucose levels that would indicate that insulin should be initiated after the implementation of dietetic therapy. The American College of Obstetricians and Gynecologists (ACOG) suggests that insulin should be administered to reduce the risk of macrosomia with fasting glucose levels ≥ 95 mg% OR one-hour postprandial glucose levels > 130-140 mg% OR two-hour postprandial glucose levels ≥ 120 mg% (ACOG, 2001). There are no randomized clinical trials available in which different glucose levels were compared with the objective of determining the cut-off point for the implementation of insulin therapy. Three randomized clinical trials suggest initiating insulin therapy irrespective of glucose levels if ultrasonographic measurement of fetal abdominal circumference exceeds the 75$^{th}$ percentile (Bonomo et al., 2004; Kjos et al., 2001; Rossi et al., 2000). The doses and types of insulin will not be discussed in this chapter.

#### 5.2.4.2 Antihyperglycemic drugs

Oral hypoglycemic drugs are classically contraindicated in pregnancy. First generation drugs such as chlorpropamide and tolbutamide cross the placental barrier and may potentially cause prolonged and profound states of hypoglycemia, leading to fetal malformation. Nevertheless, the newer hypoglycemic drugs such as glibenclamide do not enter fetal circulation (Langer, 2007).

Furthermore, considering that in patients with gestational diabetes, the need for treatment initiates after embryogenesis (Langer, 2007), the newer oral hypoglycemic drugs were seen as a practical therapeutic option for this group of patients. Patient satisfaction with this route of administration may result in better compliance with treatment. Interest in evaluating these drugs as an option for the control of gestational diabetes has been intense and various randomized clinical trials using these agents have been published over the past ten years (Langer et al., 2000; Moore et al., 2010; Rowan et al., 2008).

In 2008, a systematic review was published that included a meta-analysis of all the clinical trials in which the use of insulin was compared with glibenclamide in women with gestational diabetes. Nine clinical trials were included involving 1,382 women with gestational diabetes. The use of glibenclamide was not found to be associated with any increased risk of macrosomia nor with differences in relation to fetal weight or the frequency of large-for-gestational-age infants, admission to the neonatal ICU or an increased risk of neonatal hypoglycemia. These findings suggest that there is no increased perinatal risk with the use of this drug; however, the effectiveness and safety of its use still need to be confirmed, since the majority of the studies included were not randomized (Moretti et al., 2008).

Another systematic review published by the Johns Hopkins University Evidence-Based Practice Center for the Agency for Healthcare Research and Quality evaluated oral hypoglycemic drugs in women with gestational diabetes. Nine studies were selected, four of which consisted of randomized clinical trials involving 1,229 participants, while five were observational studies involving 831 participants. Two clinical trials compared insulin with glibenclamide, while one compared glibenclamide with acarbose and another compared insulin with metformin. No statistically significant differences were found with respect to glycemic control, the weight of the newborn infant or in the rate of Cesarean sections when insulin was compared with glibenclamide. There was a greater proportion of newborn infants with hypoglycemia in the group that used insulin (8.1% versus 3.3%; p = 0.008). No statistically significant difference was found in the rate of congenital malformations when the pregnancies treated with insulin were compared with those treated with oral hypoglycemic drugs. The authors concluded that there are no substantial differences in maternal and neonatal outcomes between women with gestational diabetes using insulin and those using oral hypoglycemic drugs (glibenclamide and metformin) (Nicholson et al., 2009).

The most recent systematic review on oral hypoglycemic drugs for the treatment of gestational diabetes showed no difference either in glycemic control or in the outcome of pregnancy when insulin was compared with hypoglycemic drugs in six randomized clinical trials involving a total of 1,388 pregnant women. There was no increased risk of neonatal hypoglycemia, macrosomia or Cesarean section, and maternal glucose levels were similar (Dhulkotia et al., 2010).

Results with the use of glibenclamide for the treatment of gestational diabetes are encouraging and although the ADA and ACOG consensuses recommend not prescribing glibenclamide for women with gestational diabetes (ACOG, 2001; ADA 2004), it would appear that there is already sufficient and consistent evidence confirming its safety and effectiveness in this condition. Another issue to be evaluated with respect to glibenclamide is its cost, which is significantly lower compared to treatment with insulin (Melamed and Yogev, 2009). Nevertheless, the United States Food and Drug Administration (FDA) has not approved these drugs for this purpose.

### 5.2.5 Obstetric treatment

#### 5.2.5.1 Evaluation of fetal vitality

Randomized clinical trials have yet to be conducted to evaluate the need for antenatal testing or the type of antenatal tests for the assessment of fetal well-being. Nonetheless, the fetuses of women with gestational diabetes, depending on glycemic control, may be at an increased risk of macrosomia (Durnwald et al., 2011) and intrauterine death (Yogev and Visser, 2009), and some observational studies have reported a reduction in the risk of fetal loss with various protocols for evaluating vitality (Graves, 2007; Kjos et al., 2005).

In 2001, the ACOG concluded that there is insufficient evidence to determine the ideal scheme for monitoring antepartum fetal vitality in women with gestational diabetes controlled by diet and in whom there are no additional perinatal risks (ACOG, 2001). The evaluation of fetal vitality in cases of gestational diabetes may include fetal biophysical profile and antepartum cardiotocography. Doppler blood flow measurement is not useful for evaluating fetal vitality in this context (Graves, 2007). The frequency with which these tests should be performed depends on the classification of diabetes and is not routinely recommended in cases controlled with diet (ACOG, 2001; Conway, 2007). In women who require insulin or antihyperglycemic

drugs, it has been suggested that monitoring should be performed twice weekly beginning at 32 weeks (ACOG, 2001). The method of evaluating vitality and the periodicity of this evaluation, however, remains to be determined and varies in accordance with the protocol implemented in the service and the clinical situation (Conway, 2007).

#### 5.2.5.2 Screening for fetal macrosomia

Macrosomia may be investigated by performing a single ultrasonography scan in the 36th week of pregnancy or by serial scans from 28 weeks onwards (Ben-Haroush et al., 2007). Nevertheless, the poor accuracy of ultrasonography for the prediction of fetal weight limits its use for this purpose (Wong et al., 2001). Based on specialist opinion, it has been suggested that fetal growth monitoring and the investigation of macrosomia is unnecessary in cases of gestational diabetes controlled by diet, principally because false-positive results may lead to unnecessary Cesarean sections (Melamed et al., 2010). Fetal weight estimated by ultrasonography would have to be ≥ 4,800 grams to have at least a 50% chance of predicting an infant being born with a birthweight of 4,500 kg or more (McLaren et al., 1995).

#### 5.2.5.3 Anticipating delivery

Treatment of gestational diabetes may include anticipating delivery through induction or by elective Cesarean section. In a systematic review of the Cochrane Library, the policy of electively interrupting pregnancy by inducing labor in full-term diabetic women was evaluated (Boulvain et al., 2011). Only one study involving 200 women was included. Results showed that induction at 38 weeks reduced the frequency of newborn infants weighing > 4000 grams and above the 90th percentile, which is not surprising, since gestational age at delivery was lower in the induction group. This intervention, however, failed to reduce the risk of Cesarean section or of neonatal morbidities. Therefore, the authors concluded that further studies involving larger sample sizes are required in order to confirm the advantages of this intervention. Up to the present moment, there is insufficient evidence to enable this practice to be recommended.

More recently, a systematic review including five studies (the same clinical trial included in the Cochrane review plus four observational studies) compared active management at term (induction or Cesarean section) with expectant management. The results of the randomized clinical trial were similar to the findings of the previous systematic review. When the four observational studies were analyzed, however, a potential reduction was found in the rate of macrosomia, of shoulder dystocia in induced deliveries and in Cesarean sections indicated because of fetal macrosomia. The authors concluded that active management appears to reduce the rates of macrosomia and its complications; however, further clinical trials are clearly necessary to strengthen the evidence and support clinical practice (Witkop et al., 2009).

The ACOG suggests performing elective Cesarean sections as a means of reducing the risk of shoulder dystocia in cases of gestational diabetes when estimated fetal weight is ≥ 4,500 grams (ACOG, 2001). In diabetic pregnant women in whom estimated fetal weight is below 4,000 grams, Cesarean section is unjustified on the basis of fetal weight alone (Hawkins and Casey, 2007). On the other hand, the management of cases in which estimated fetal weight is between 4,000 and 4,500 grams remains controversial. In addition to estimated fetal weight, the size of the mother's pelvis and the progression of labor should also be taken into consideration when deciding on the type of delivery (Hawkins and Casey, 2007). It should also be noted that the limited accuracy of ultrasonography for adequately estimating fetal weight leads to unnecessary Cesarean sections because of the suspicion of macrosomia (Chauhan et al., 2005).

In the absence of macrosomia, specialists suggest that patients with gestational diabetes controlled by diet may be able to reach 40/41 weeks and recommend induction at this gestational age. In patients in use of insulin or oral antihyperglycemic drugs, labor should be induced at 39 weeks. In diabetic patients in use of insulin or those in whom glycemic control is poor, labor should be induced at 38 weeks and even prior to this gestational age if there are associated conditions such as severe preeclampsia, for example, or if fetal well-being is compromised. There is no need for amniocentesis to evaluate fetal lung maturity in patients after 38 weeks of pregnancy when gestational age is well documented (Conway et al., 2007; Nicholson et al., 2008).

## 6. Conclusions

The most recent evidence suggests that screening for gestational diabetes is beneficial; however, the best screening strategy remains to be defined. Clinical trials also need to be conducted to compare various diagnostic tests and glucose levels; however, until these studies are performed, clinicians and societies have to define their own protocols for screening and diagnosis taking the characteristics of the population to be screened into consideration. In populations with a high risk for diabetes and consequently for macrosomia, a universal screening policy leads to a significant reduction in perinatal morbidity.

With respect to treatment, although the Cochrane systematic review found only modest benefits with treatment, more recent randomized clinical trials suggest an improvement in perinatal outcome. Based on specialist opinion, initial dietetic therapy is recommended, with pharmacological treatment indicated when diet alone fails to control glucose levels. Despite recent evidence that treatment with antihyperglycemic drugs may represent a safe, reliable alternative for the pharmacological treatment of diabetes in pregnancy, the ADA and other guidelines continue recommending insulin therapy as standard treatment. There is insufficient evidence either to indicate or contraindicate exercise in women with gestational diabetes.

The types of tests and the ideal frequency at which fetal well-being should be monitored are factors that are yet to be determined; however, they are unnecessary in cases in which glucose levels are controlled by diet. In addition, there is insufficient evidence to recommend ultrasonography for the prediction of macrosomia and scans should not be performed routinely for this purpose in pregnant women on dietetic therapy in whom glucose levels are under control.

With respect to delivery, elective Cesarean sections are recommended by ACOG in the case of fetuses over 4,500 grams. In cases of gestational diabetes controlled by diet, it is possible to wait for spontaneous labor to occur up to a limit of 40/41 weeks. In patients in use of insulin or oral hypoglycemic drugs, labor should be induced at 39 weeks. In cases in which glucose control is poor, delivery should be anticipated at 38 weeks or earlier if fetal well-being is compromised or there are other associated morbid conditions.

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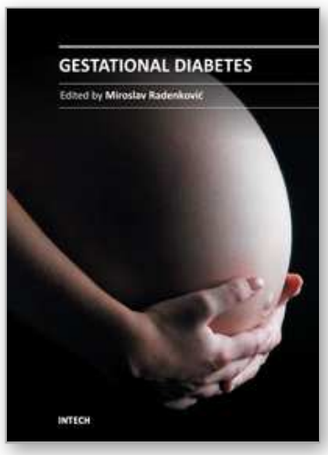


**Gestational Diabetes**

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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.



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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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