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# Congenital Cardiopathies Screening Associated with Diabetes Mellitus Using Maternal Fructosamine Plasma Concentration

Zilma Silveira Nogueira Reis and Gabriel Costa Osanan  
*Obstetrics and Gynecology Department,  
Universidade Federal de Minas Gerais  
Brazil*

## 1. Introduction

The consequences of uncontrolled diabetes mellitus during pregnancy are severe for both mother and fetus. The risk of congenital malformations among infants of diabetic mothers is related to the quality of the diabetic control (Allen et al., 2007; American Diabetes Association [ADA], 2004). In diabetic pregnancy, unsatisfactory glycemic control at the moment of diagnosis or delivery of care was associated with an increased risk of anomalies (Allen et al., 2007; Schaefer-Graf et al., 2000). The most common anomalies involve the cardiac, musculoskeletal, and central nervous systems (Sheffield et al., 2002). Despite this knowledge, it has been disappointing that so few diabetic women receive preconception counseling, plan their pregnancies or are early referred to tertiary centers (American Diabetes Association [ADA], 2004; Reis et al., 2010a). Considering this reality, it is important to study second trimester markers of congenital cardiopathies, in order to decrease fetal morbidity and mortality, at birth.

## 2. Congenital cardiopathies and diabetes mellitus

If maternal hyperglycemia is present during organogenesis there is an increased risk of congenital anomalies and miscarriage (American Diabetes Association [ADA], 2004). Experimental studies suggest that hyperglycemia is the major teratogen in diabetic pregnancies, but other diabetes-related factors may also affect fetal outcomes (Aberg et al., 2001; Buchanan & Kjos, 1999; Leonard et al., 1989; Ren et al., 2011). It is a fact that an uncontrolled diabetes mellitus in early gestation is associated with a teratogenic effect, causing primary cardiogenesis defects. Most types of cardiac structural lesions have been associated with diabetes mellitus, ranging from small septal defects to major heart disease (Sekhavat et al., 2010; Abu-Sulaiman & Subaih, 2004).

The exact teratogenic mechanism of maternal diabetes is not fully defined and is likely multifactorial (Hornberger, 2006; Kumar et al., 2007). Diabetes mellitus affects the fetal heart both structurally and functionally. In late gestation, it causes a unique form of hypertrophic cardiomyopathy (Ren et al., 2011; Hornberger, 2006; Chaudhari et al., 2008; Russell et al., 2008), illustrated at Fig. 1. Cardiomegaly is a common finding in stillborn infants of mothers

with diabetes mellitus and may contribute to the risk of fetal death in these pregnancies (Russell et al., 2008). Hypertrophic cardiomyopathy observed in the infant of the diabetic mother is characterized by thickening of the interventricular septum, and to a lesser extent the ventricular free walls (Hornberger, 2006). The presence of this pathology whether is associated with fetal hyperinsulinaemia and general somatic growth in maternal diabetes (Buchanan & Kjos, 1999; Ren et al., 2011). But, the wide variety of cardiac abnormalities suggests a complex pathogenesis. Experimental study proposed that the down-regulation of genes involved in development of cardiac neural crest could contribute to the pathogenesis of maternal diabetes-induced congenital heart defects (Kumar et al., 2007).

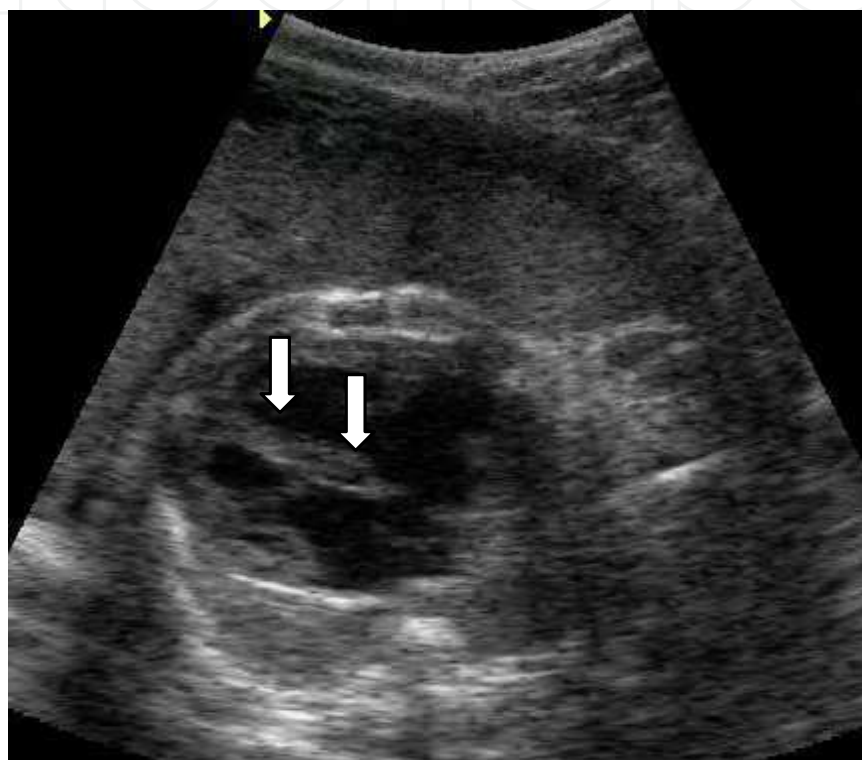


Fig. 1. Image of fetal ultrasonography: hypertrophic cardiomyopathy associated with Diabetes Mellitus

### 3. The strategies for prevention and management of the cardiac teratogenic effects in diabetes mellitus

The prevalence of pregestational diabetes among women early in their reproductive years is increasing. Thus, identifying women with diabetes is important because the diagnosis and appropriate therapy can decrease fetal and maternal morbidity (Crowther et al., 2005). Preconceptional evaluation and counseling of women with diabetes mellitus (type 1 or type 2) is fundamental point to minimize the risk to the fetus and mother. It is known that pregnancies in diabetes mellitus women should be planned, but that condition was not so frequent (American Diabetes Association [ADA], 2004; Reis et al., 2010a; Chaudhari et al., 2008). Unplanned pregnancy occurs in about two-thirds of women with diabetes leading to a persistent excess of malformations in their infants (American Diabetes Association [ADA], 2004).

Given the increased risk of congenital abnormalities among infants of diabetic mothers, an appropriate biochemical, ultrasonographic screening process and a detailed evaluation of fetal cardiac structure should be offered to all pregnant women with diabetes (Allen et al., 2007). A prenatal cardiac screening is purposed to identify defects that may require further evaluation and treatment, and to provide appropriate counselling to the family in a timely manner (American Diabetes Association [ADA], 2004; Sekhavat et al., 2010). Detailed fetal anatomic surveys in the early second trimester are common practice and typically include examination of both four-chamber and outflow tract views of the fetal heart.

The occurrence of congenital cardiopathies at echocardiography in fetuses whose mothers had preexisting diabetes mellitus was investigated in our tertiary university medical center (Reis et al., 2010a, 2010b). The most frequent conditions were hypertrophic cardiomyopathy (70%), pericardial effusion (15%), followed by intermittent or persistent bradycardia (15%). The most frequent structural congenital cardiopathies at echocardiography was interventricular communication (85.7%) associated or not to another heart malformations (Fig. 2). Functional findings at echocardiography were significantly more frequent among the poorly-controlled diabetic pregnancies.

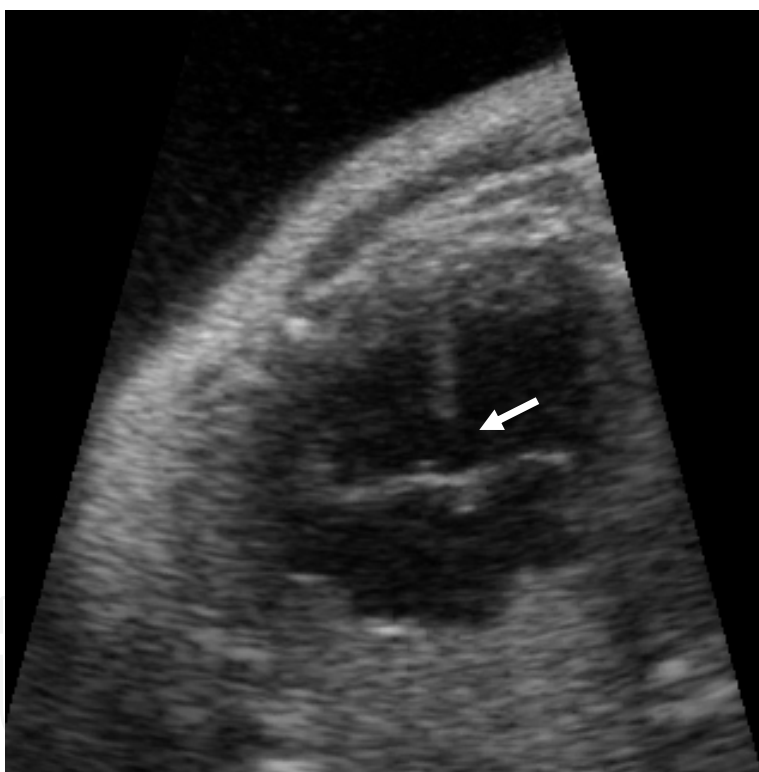


Fig. 2. Image of fetal ultrasonography: interventricular communication associated with Diabetes Mellitus

In other reports, the malformations found in neonates, born of insulin-dependent diabetes mellitus gestations, included endocardial cushion defects, persistent truncus arteriosus and ventricular septal defects which appear to result from aberrant cardiac neural crest development (Sekhavat et al., 2010; Abu-Sulaiman & Subaih, 2004; Hornberger, 2006; Kumar et al., 2007; Russell et al., 2008). Hypertrophic cardiomyopathy was observed in 38% of neonates from insulin-dependent diabetes mellitus pregnant women, mainly hypertrophy of the interventricular septum (Abu-Sulaiman & Subaih, 2004).

#### 4. The fructosamine level as a late marker (beyond the first trimester) for congenital cardiopathies

The measurement of glycated hemoglobin (HbA1c) and serum fructosamine in order to assess the recent glycemic control of diabetic patients has become well established. Maternal HbA1c at the beginning of pregnancy and maternal age at the onset of diabetes were associated with congenital malformations (Aberg et al., 2001).

Fructosamines are keto-amines formed by a non-enzymatic reaction between glucose and a protein (60-70% of which is glycosylated with albumin in serum), depending upon the severity and the duration of the hyperglycemia. Therefore, serum fructosamine directly reflects the dynamics of blood glucose concentration and correlates significantly with the mean plasma glucose levels from the preceding 1 to 3 weeks (Roberts et al., 1988; Weerasekera, 2000; Jenkins et al., 2007). Fructosamine testing has been available since the 1980s. Both fructosamine and HbA1c are used primarily as monitoring tools to help diabetics control their blood sugar, but the A1C test is much more popular and more widely accepted. However, the American Diabetes Association recognizes both tests and says that fructosamine may be useful in situations where the A1C cannot be reliably measured (Goldstein et al., 2004). In addition, the measurement of fructosamine can be a helpful adjunct to HbA1c glycaemic control monitoring during pregnancy (Chaudry et al., 2007). The role of fructosamine levels as a teratogenic marker is less studied.

Fetuses presenting a normal and abnormal echocardiography were compared using plasma fructosamine level means (Reis et al., 2010a). An association between congenital cardiopathies at echocardiography (functional and structural including isolated hypertrophic cardiomyopathy) and types of diabetes mellitus (insulin-dependent or not), was evaluated. An abnormal plasma fructosamine level at  $20.4 \pm 8.0$  weeks of gestation was associated with congenital cardiopathies at echocardiography, whether or not the cardiac embryogenesis happened in the first trimester. The congenital cardiopathies at echocardiography odds ratio was 9.6 (95% CI: 2.8 - 33.7) for abnormal plasma fructosamine ( $\geq 2.68$  mmol/L) and 10.9 (95% CI: 2.7 - 45.2) when adjusted for maternal age and insulin usage. There was also an increased chance (3.1, 95% CI: 1.1 - 8.8) of fetal heart anomaly with insulin usage, but only when evaluated individually by crude odds ratio.

In many underdeveloped countries, women do not have access or do not attend medical care early in pregnancy (Reis et al., 2010a, 2010b). Therefore, they are especially subject to the teratogenic effects of hyperglycemia. Analyzing results of our university referral center, it was disappointing that so few diabetic women receive preconception counseling and plan their pregnancies (Reis et al., 2010a). Therefore, considering this reality, without HbA1c early values, it was important to determine the correlation between fructosamine maternal levels and fetal malformations.

Based on our previous study, abnormal maternal fructosamine levels, even at the second trimester of pregnancy, predicts a high risk of fetal cardiac anomalies (Reis et al., 2010a). In this way, a fetal echocardiographic exam should be, routinely, performed in all diabetic mothers whose fructosamine levels are above 2.23 mmol/L (Reis et al., 2010b).

This recommendation was based on the significant capacity of maternal fructosamine levels to predict fetal heart anomaly in diabetic patients (Area Under Curve: 0.78 p-value  $< 0.0001$ ), as shown in Fig. 3. However, different cut-off values from which fructosamine could indicate these malformations and they should be cautiously defined and discussed as shown in Table 1.

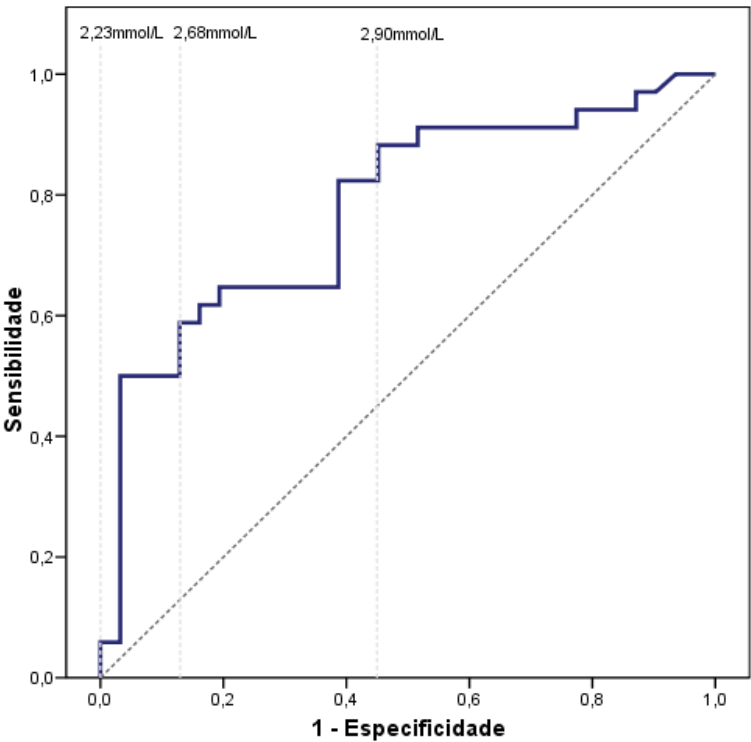


Fig. 3. Receiver–operating characteristics (ROC) curve for prediction of congenital cardiopathies at echocardiography for fetuses whose mothers had preexisting diabetes mellitus (n=65). AUC 0.78 (95% CI, 0.66–0.89), from: Reis et al., 2010

Cut-off points (maternal plasmatic levels of fructosamine )	Sensitivity	Specificity	False negative	Positive Likelihood ratio
2.23 mmol/L	88.2%	54.8%	11.8%	2.0
2.68 mmol/L	58.8%	87.1%	41.2%	4.6
2.90 mmol/L	44.1%	96.8%	55.9%	13.7

Table 1. Accuracy of the maternal fructosamine levels for the prediction of fetal cardiac anomalies in gestations complicated by diabetes mellitus. Reference: Reis et al., 2010b

If it is considered the cut-off value of fructosamine recommended for our local population (2.68mmol\L), this test will have a good specificity (87.1%) but a low sensitivity (58.8%), with a false negative rate of 41.2%. Even though, for an abnormal exam, the risk of fetal cardiac anomaly is increased 4.6-fold. If it is considered the cut-off value recommended by the manufacturer of the test (2.90mmol/L), the exam will have a high specificity (96.8%) but a low sensitivity (44.1%) with a false negative rate of 55.9%. In this case, for an abnormal test, the risk of fetal cardiac defects would be increased 13.7-fold. Finally considering the use of a cut-off point of 2.23mmol\L, the test will show a low specificity (54.8%) but a high sensitivity (88.2%), with a false negative rate of 11.8%. Thus, the cut-off point of 2.23 mmol/L is better than the other values tested, since it has the greatest sensitivity and lowest false negative rate among them.



## 5. Conclusions

Abnormal echocardiographic findings were associated with the first maternal plasma fructosamine levels in referral pregnancies complicated by diabetes mellitus. Hyperglycemia seems to be the most important determinant of these risks. Many pregnant diabetic women are referred at a late stage to a tertiary level of care. At this context, an abnormal plasma fructosamine level increases the chances of abnormalities at fetal echocardiography. It is possible to use a second trimester plasma fructosamine level to refer women with pregestational diabetes mellitus to a center of maternal-fetal medicine in order to offer them an appropriated assistance at birth. These findings are important for the management of women with diabetes mellitus and late prenatal care.

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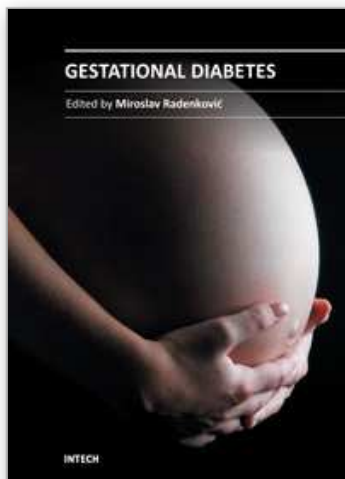
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## **Gestational Diabetes**

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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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