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Pregestational diabetes and fetal heart rate in the first trimester of pregnancy

Angelo Sirico, Laura Sarno, Fulvio Zullo, Pasquale Martinelli, Giuseppe M. Maruotti*

Department of Neurosciences, Reproductive and Dentistry Sciences, University Federico II, Naples, Italy

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ABSTRACT

Objective: The aim of our study is to evaluate if pregestational diabetes affects fetal heart rate (FHR) readings at 11–14 weeks of pregnancy.
Study design: For each patient, we recorded age, body mass index (BMI), presence of pregestational diabetes, nuchal translucency (NT), FHR, crown-rump length (CRL), biparietal diameter (BPD) and gestational age. Pregnancies were grouped according to the presence or absence of pregestational diabetes and maternal and fetal variables were compared. Ordinal regression analysis was performed to assess the influence of maternal and fetal variables on the FHR.
Results: We included 994 pregnancies from 2009 to 2016. Kruskal-Wallis test showed that median FHR was higher in women with pregestational diabetes than in controls (161; IQR 11 vs. 158; IQR 10, $\chi 2 = 5.13$, $p = 0.02$). Ordinal regression analysis showed that differences in FHR were significantly correlated with the presence of pregestational diabetes ($p = 0.007$) and the CRL ($p = 0.042$) but not with the maternal BMI, maternal age, gestational age, BPD and NT.
Conclusions: First trimester FHR is higher in diabetic pregnancies than in non-diabetic pregnancies. Therefore, further research is needed to assess whether these pregnancies may benefit from a correction of FHR for a better estimation of the chromosomal abnormalities risk.

Introduction

Fetal heart rate is one of the variables necessary to calculate the risk for chromosomal abnormality in the first trimester [1]. During the first trimester, insulin dependent diabetes mellitus (IDDM) has shown to be associated to a reduction of the maternal serum pregnancy-associated plasma protein-A (PAPP-A) levels, but not to changes in fetal nuchal translucency (NT) or maternal serum free β-hCG levels [2,3]. Little is known on how pregestational diabetes influences FHR, despite it has been shown to be associated with peculiar umbilical artery blood flow features [4], higher incidence of congenital cardiac and neural tube defects and hypertrophic septal cardiomyopathy [5–8]. The aim of our study is to evaluate if pregestational diabetes influences FHR in the first trimester.

Material and methods

In this retrospective study, we included singleton pregnant women who underwent first trimester screening for chromosomal abnormalities between 11^{+0} and 13^{+6} weeks of pregnancy at the Maternal-Fetal Unit of the University Federico II, Naples, Italy, from January 2009 to April 2017. Authors followed STROBE guidelines for observational studies [9]. Cases were identified by searching the electronic database (ViewPoint 5.6, ViewPoint Bildverarbeitung GmbH, Wessling, Germany). We included pregnancies with absence of chromosomal or congenital anomalies, positive ductus venosus a-wave, presence of the nasal bone, crown-rump length (CRL) of 45–84 mm and NT < 2.5 mm. Gestational age was assessed by last menstrual period, if in agreement of 7 days with CRL dating using Robinson formula, or by CRL if there was more than 7 days discrepancy. For each patient, we recorded age, body mass index (BMI), presence of pregestational diabetes mellitus (DM), type of DM, DM therapy, HbA1c, NT, FHR, CRL, biparietal diameter (BPD) and gestational age. Ultrasound scans were performed using Voluson E8 Expert ultrasound equipment (GE Medical Systems, Milwaukee, WI, USA) equipped with 2–5 MHz transabdominal probes and using colour and pulsed wave Doppler functions.

Pregnancies were grouped according to the presence (cases) or absence (controls) of pregestational diabetes. The Kolmogorov-Smirnov test was performed to test for normality. When normally distributed, continuous variables were compared by Student's *t*-test, otherwise by Kruskal-Wallis test; categorical variables were

* Corresponding author at: Via Sergio Pansini 5, 80131, Naples, Italy.
E-mail address: gm.mar@tiscali.it (G.M. Maruotti).

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compared by Chi-squared test. Ordinal regression analysis was performed to assess the influence of maternal and fetal variables on the FHR. A p value <0.05 was considered as significant. Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) Statistics v. 19 (IBM Inc., Armonk, New York, USA). The study was approved by the local Ethics Committee.

Results

1366 women underwent first trimester screening during the observed period. After exclusion of pregnancies complicated by: chromosomal anomalies (95, 6.9%), congenital anomalies (28, 2%), absent ductus venosus a-wave (23, 1.7%), absent nasal bone (26, 1.9%), CRL < 45 or >84 mm (72, 5.3% %) and NT > 2.5 mm (128, 9.4%), 994 (72.8%) women were included in the final analysis. There were n = 45 (4.5%) pregnancies of women with pregestational diabetes and n = 949 (95.5%) controls matching inclusion criteria. Among the 45 cases, 28 women were diagnosed with type I DM and 17 with type II DM. All the 45 diabetic pregnancies were on insulin treatment prior to pregnancy. Kolmogorov-Smirnov test showed that FHR, NT, gestational age, maternal BMI and maternal age had not a normal distribution, whereas CRL had a normal distribution. Maternal characteristics and fetal ultrasound variables are summarized in Table 1.

We found no difference in mean CRL, median NT, gestational age and maternal age between cases and controls. Median maternal BMI was significantly higher in women with pregestational diabetes than in controls (29.6; IQR 6.02 vs. 24.95; IQR 7.05, $\chi^2 = 11.48$, $p < 0.001$).

Kruskal-Wallis test showed that median FHR was higher in women with pregestational diabetes than in controls (161; IQR 11 vs. 158; IQR 10, $\chi^2 = 5.13$, $p = 0.02$) Fig. 1. Linear regression analysis showed that there was no linear relationship between FHR and maternal BMI (constant = 157.93, slope = 0.18, r = 0.13, p = 0.791). Ordinal multiple regression analysis showed that differences in FHR were significantly correlated with the presence of pregestational diabetes (p = 0.007) and the CRL (p = 0.042) but not with the maternal BMI, maternal age, gestational age, BPD and NT Table 2.

Comment

In this study we demonstrate that first trimester FHR is higher in pregnancies complicated by pregestational diabetes than in non-diabetic pregnancies. We also demonstrate that this relationship is independent from any other variables (maternal age, maternal BMI, gestational age, NT, CRL, BPD). Our data show that there is no influence of maternal BMI on first trimester FHR. Furthermore, we confirm the results of other studies showing that there is an independent negative correlation between FHR and CRL [10].

Our results are in accordance with recent studies, which demonstrated that third trimester FHR is higher in pregnancies complicated by diabetes than in controls. Tincello et al. showed

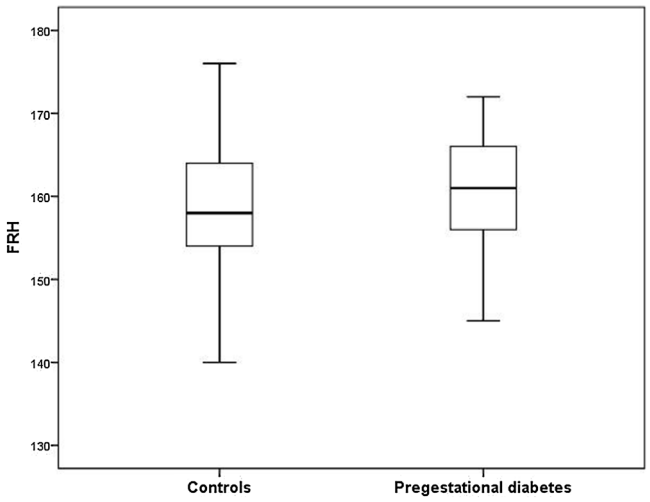

Fig. 1. Box and whisker plots of fetal heart rate (FHR) in diabetic pregnancies and controls. Medians, interquartile boxes and ranges (whiskers).

Table 2
Ordinal logistic regression analysis of factors associated with FHR in first trimester pregnancies.

	Estimate	SE	Wald test	p	95% confidence interval	
BMI	−0.002	0.016	0.022	0.882	−0.034	0.030
Maternal age	0.009	0.015	0.387	0.534	−0.020	0.038
Gestational age	−0.271	0.241	1.265	0.261	−0.742	0.201
CRL	−0.037	0.018	4.135	0.042	−0.072	−0.001
BPD	−0.051	0.038	1.818	0.178	−0.125	0.023
NT	−0.079	0.275	0.082	0.775	−0.618	0.461
[Diabetes = no]	−1.020	0.375	7.384	0.007	−1.755	−0.284
[Diabetes = yes]	0					

SE, standard error; BMI, body mass index; CRL, crown-rump length; BPD, biparietal diameter; NT, nuchal translucency.

that basal heart rate at third trimester cardiotocography (CTG) analysis was significantly higher in the diabetic population than the published parameters for non-diabetic pregnancies [11]. Analysis on CTG traces in third trimester of diabetic pregnancies showed also that there is a direct correlation between maternal glycaemia and FHR, since fetuses from mothers with poor glycaemic control showed also higher mean FHR than fetuses from mothers with good glycaemic control [12].

Other studies have shown that diabetes influences fetal cardiac function as soon as in the first trimester [13]. These differences were prevalent for pregnancies with poor glycaemic control. These results were confirmed also by Russell et al., who showed that, when compared with controls, first trimester diabetic pregnancies are characterized by lower left E/A ratio, longer isovolumetric relaxation time and higher myocardial performance index [14]. Furthermore, Turan et al. observed also a

Table 1
Maternal characteristics and fetal ultrasound variables.

	Women with pregestational diabetes (n = 45)	Controls (n = 949)	p value*
Maternal age (years) median; IQR	31.82; 11	31.35; 7	0.068
Maternal BMI (kg/m^2) median; IQR	29.6; 6.02	24.95, 7.05	0.001
Hba1c (%) mean, SD	6.7; 0.83	6.3; 1.56	0.088
NT (mm) median; IQR	1.6; 0.73	1.8; 0.5	0.256
Gestational age (weeks) median; IQR	12.61; 2	12.57; 1	0.116
CRL (mm) mean; SD	62.0; 9.24	62.37; 7.26	0.752
BPD (mm) median; IQR	21.3; 2.97	20.45; 3.5	0.868

* Kruskal-Wallis test for non-normal data and Student's *t*-test for normal data distribution. IQR, interquartile range; BMI, body mass index; NT, nuchal translucency; CRL, crown-rump length; BPD, biparietal diameter.

shorter isovolumetric contraction time for the left ventricle in the diabetic pregnancies [15].

To the best of our knowledge, this is the first study to evaluate FHR in first trimester pregnancies complicated by pregestational diabetes. Hyperglycaemia can influence proliferation and migration of neural crest cells which are involved in the fetal cardiac function adaptation to the advancing gestation. Hyperglycaemia can delay FHR reduction as the pregnancy progresses [16] and the disruption of these mechanisms may affect the autonomic nervous control of the FHR even in the early stages of pregnancy.

The lack of differences in HbA1c levels between cases and controls could be explained since the fetus may only be vulnerable to effect of hyperglycaemia during a short time window, and HbA1c may not reflect actual excursions in blood glucose at that specific time.

The main limitations of our study are its retrospective design and the sample size of pregnant women with pregestational diabetes. Furthermore, our dataset lacks information on the biochemical markers, which were not part of the routine screening for chromosomal abnormalities in our clinic during the study period, and information about the neonatal outcome.

In conclusion, the correlation between pregestational diabetes and FHR may be worth of consideration during the first trimester screening. A prospective cohort study would be useful to assess the role of a coefficient of correction for FHR in diabetic women as improving tool of the standard first trimester screening of chromosomal abnormalities.

Conflict of interest

Authors declare no conflict of interest.

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