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The role of first trimester fetal heart rate in the prediction of gestational diabetes: A multicenter study

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ABSTRACT

Objective: Early pregnancy models for prediction of GDM have been proposed, mostly using anamnestic and biochemical parameters. The aim of our study was to evaluate the strength of association of first trimester fetal heart rate (FHR) in predicting the development of gestational diabetes (GDM).
Study design: We considered in our analysis singleton non-diabetic pregnant women who underwent a first trimester screening at 11–14 weeks. Data on maternal age, BMI, cigarette smoking, NT, FHR, CRL, DV-PVI, β-hCG and PAPP-A were included in the analysis. Multivariate logistic regression analysis was used to estimate the association between maternal characteristics and first-trimester ultrasound measurements and GDM. We evaluated the efficacy of different models for the prediction of GDM.
Results: We considered 603 women, of whom 199 (33%) were subsequently diagnosed with GDM. ROC analysis showed that first trimester FHR was highly predictive of GDM (AUC 0.809, 95% CI 0.769–0.849, $p < 0.001$). At FPR of 20%, first trimester FHR had a detection rate of 65.2% for GDM (positive likelihood ratio: 3.26; negative likelihood ratio: 0.43), which increased to 89.5% at FPR of 40% (positive likelihood ratio: 2.24; negative likelihood ratio: 0.17). When considering as threshold 162 bpm, FHR showed detection rate of 76.9%, specificity of 67.1% and negative predictive value of 85.5% for GDM.
Conclusion: This is the first study to highlight the potential role of first trimester FHR as early predictor of GDM. In our cohort, a threshold of 162 bpm has shown high detection rate and NPV for GDM.

Introduction

Diabetes represents a clinical challenge especially in pregnant women, where it is crucial to monitor and assess both the maternal and the fetal wellbeing. Apart from women with pregestational diabetes (type 1 or type 2 diabetes mellitus (DM)), a growing rate of women develops gestational DM (GDM), considered as a glucose intolerance diagnosed for the first time in non-diabetic pregnant women and that typically resolves after delivery [1,2].

The HAPO study showed that the association of macrosomia and birth complications with oral glucose tolerance test (OGTT) results is continuous with no clear inflection points [3]. According to the American Diabetes Association, screening for GDM can be performed at 24–28 gestation weeks with either of two strategies: "One-step" 75-g OGTT or "Two-step" approach, with a 50-g (non-fasting) screen followed by a 100-g OGTT for those who screen positive [1]. However, it could be crucial to identify earlier pregnancies at risk for GDM and to correct lifestyle and dietary intake from the beginning of the pregnancy, in order to reduce the percentage of patients that will need insulin therapy and will develop complications related to GDM [4].

A recent FIGO analysis of research priorities in hyperglycaemia in pregnancy (HIP) stated that pressing research issues requiring priority in early pregnancy include the development, testing and implementation of risk engines to identify women who require earlier testing for HIP and the development and evaluation of alternative convenient, reliable, quick, low cost, non-fasting testing strategies to detect GDM at the point of care or close to home [5].

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Therefore, early pregnancy models for prediction of GDM have been proposed, mostly using anamnestic and biochemical parameters, but they showed a quite low sensitivity and specificity. In a recent study has been demonstrated that in pregnancies complicated by pregestational diabetes first trimester fetal heart rate (FHR) is higher than in controls [6]. No data are up to now available on first trimester FHR in women who will develop GDM. Therefore, we designed a study to evaluate the predictive role of first trimester FHR for the development of GDM.

Materials and methods

We included in our analysis patients examined between 2016 and 2018 at three referral centres for High-Risk Pregnancies in Central and Southern Italy: University Federico II, Naples, Italy; University Tor Vergata, Rome, Italy and Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. After a retrospective electronic database research, we included in our analysis singleton non-diabetic pregnant women who underwent a first trimester screening for chromosomal abnormalities at 11–14 weeks. Exclusion criteria were: presence of chromosomal or congenital anomalies, abnormal combined screening (risk for trisomy 21 > 1:250), nuchal translucency (NT) >95th centile, one or more abnormal markers for aneuploidies (ductus venosus, nasal bone and tricuspid regurgitation). 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 collected the following data: maternal age, body mass index (BMI), cigarette smoking, NT, FHR, CRL, ductus venosus (DV)-PVI, β-hCG and PAPP-A. We grouped patients according to the presence (cases) or absence (controls) of GDM after a one step 75 g OGTT at 24–28 weeks in a ratio of 1:2. During the ultrasound examination FHR was recorded using a transverse section of fetal thorax at level of the tricuspid valve. Using Doppler and real-time B mode imaging recordings of 6–10 cardiac cycles were obtained, the interval between cardiac cycles was measured with electronic calipers and the FHR was calculated using the ultrasound machine software.

Maternal and ultrasound parameters were compared between cases and controls. 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 compared by Chi-squared test. Multivariate logistic regression analysis was used to estimate the association between maternal characteristics and first-trimester ultrasound measurements and GDM and to determine the independence and relative contribution of variables. The risk for each of the pregnancy outcomes was then calculated from the formula: odds/(1 + odds), where odds = e^Y and Y was derived from the multivariate logistic regression analysis. The performance of screening was determined by receiver operating characteristic (ROC) curve analysis. We evaluated the efficacy of different models for the prediction of GDM according to the Nagelkerke's R^2. AUCs of different models for GDM were compared with DeLong test for paired samples. 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).

Results

We included in our analysis 603 patients matching the inclusion criteria (325 from University Tor Vergata, Rome; 175 from University Federico II, Naples; 103 from Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome. We included women 199 (33%) women who were diagnosed with GDM after a 75 g OGTT at 24–28 gestation weeks and 404 (67%) controls. Maternal and ultrasound characteristics are summarized in Table 1.

Table 1
Maternal, biochemical and ultrasound characteristics of the study population.

	GDM n = 199	Controls n = 404	χ^2	p*
Age (years)	29; 7	32; 8	17.16	<0.001
BMI (kg/m$^{2)}$	24.8; 4.6	23.6; 5.3	14.64	<0.001
CRL (mm)	64; 18.3	64; 13.6	0.21	0.648
NT (mm)	1.9; 0.7	1.76; 0.7	3.62	0.057
FHR (bpm)	165; 5	160; 7	125.28	<0.001
DV-PVI	1; 0.30	1; 0.31	0.34	0.561
β-hCG (mU/mL)	27.8; 8.5	36.1; 11.4	3.62	0.143
PAPP-A (mU/mL)	2.93; 1.8	2.86; 1.58	0.10	0.748
Smoke	27 (13.6 %)	32 (7.9%)	3.68	0.055

Data given as median; interquartile range (IQR). *Kruskal-Wallis test. BMI, body mass index; CRL, crown-rump length; NT, nuchal translucency; FHR, fetal heart rate; DV-PVI, ductus venosus peak velocity index.

Kolgomorov-Smirnov test showed that included variables (maternal age, BMI, NT, FHR, CRL, DV-PVI, β-hCG, PAPP-A) were not normally distributed. Compared to controls, women who were diagnosed GDM at 24–28 weeks showed lower median age (29, IQR 7 vs 32, IQR 8; $\chi^2 = 17.16$; $p < 0.001$), higher BMI (24.8, IQR 4.6 vs 23.6, IQR 5.3; $\chi^2 = 14.64$; $p < 0.001$) and FHR (165, IQR 5 vs 160, IQR 7; $\chi^2 = 125.28$; $p < 0.001$) at 11–14 weeks Fig. 1.

Logistic regression analysis showed that maternal age, FHR and maternal cigarette smoking were independently associated with GDM Table 2. ROC analysis showed that first trimester FHR was highly predictive of GDM (AUC 0.809, 95% CI 0.769–0.849, $p < 0.001$). In particular, first trimester FHR had an aOR of 1.358 (95% CI 1.270–1.453, $p < 0.001$) for GDM. When adding other parameters to FHR, we did not find any significant difference in the prediction of GDM Fig. 2.

A model including FHR, maternal age, maternal BMI and DV-PVI showed an AUC of 0.813 (95% CI 0.773–0.853, $p < 0.001$), while a model including FHR, maternal age, maternal BMI, DV-PVI, NT, CRL, maternal cigarette smoking showed an AUC of 0.825 (95% CI 0.786–0.863, $p < 0.001$). At FPR of 20%, first trimester FHR had a detection rate of 65.2% for GDM (positive likelihood ratio: 3.26; negative likelihood ratio: 0.43), which increased to 89.5% at FPR of 40% (positive likelihood ratio: 2.24; negative likelihood ratio: 0.17), not significantly different from the other two models Table 3.

When considering a threshold of 162 bpm, FHR showed a detection rate of 76.9%, specificity of 67.1% and negative predictive value (NPV) of 85.5% for GDM. Among women with GDM, 153 had first trimester FHR $\geq$ 162 bpm, compared to 133 women in the control group (OR 6.77 95% CI 4.59–10).

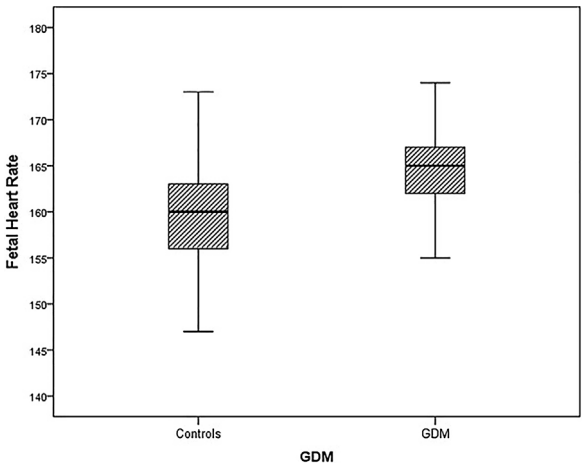

Fig. 1. Box and whisker plots of fetal heart rate (FHR) in diabetic pregnancies and controls. Medians, interquartile boxes and ranges (whiskers).

Table 2
Logistic regression analysis: unadjusted and adjusted odds ratios of variables associated with GDM.

	Estimate	Wald	OR	p	95% CI	aOR	p	95% CI
Age (years)	−0.059	6.338	0.938	<0.001	0.909-0.969	0.943	0.012	0.901-0.987
BMI (kg/m$^{2)}$	0.034	1.293	1.056	0.004	1.017-1.097	1.035	0.256	0.976-1.098
CRL (mm)	0.013	0.876	1.001	0.850	0.986-1.017	1.013	0.349	0.986-1041
NT (mm)	−0.013	0.002	1.204	0.214	0.898-1.614	0.987	0.966	0.552-1.767
FHR (bpm)	0.306	79.598	1.207	<0.001	1.159-1.258	1.358	<0.001	1.270-1.453
DV-PVI	0.886	2.032	1.334	0.506	0.571-3.116	2.425	0.154	0.717-8.196
Smoke								
No (RC)			1.00	–	–	1.00	–	–
Yes	0.849	4.089	1.812	0.58	0.981-3.347	2.338	0.043	1.026-5.328
Constant	−50.807	75.791					<0.001	

GDM: gestational diabetes; OR: Odds Ratio; aOR: adjusted Odds Ratio; 95th CI: 95th confidence interval; RC: reference category; BMI, body mass index; CRL, crown-rump length; NT, nuchal translucency; FHR, fetal heart rate; DV-PVI, ductus venosus peak velocity index.

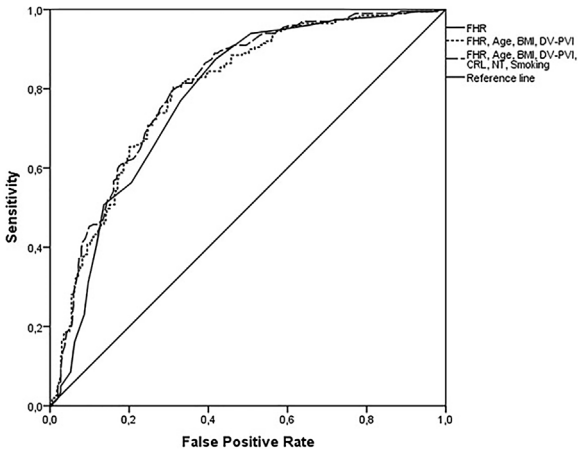

Fig. 2. Receiver-operating characteristics curves for prediction of GDM by first trimester ultrasound and maternal characteristics.

Comment

In this study we demonstrate that, in pregnant women at 11–14 gestation weeks, FHR is independently correlated to the risk of developing GDM and a threshold of 162 bpm has high detection rate and NPV for GDM.

First trimester FHR is a parameter of early pregnancy cardiac function and has been shown to predict cases of early pregnancy loss [7,8]. To the best of our knowledge, this is the first study to evaluate first trimester fetal cardiac function in women who subsequently developed GDM. Our theory is that, at 11–14 weeks, women who develop glucose intolerance later in pregnancy present already fluctuating mild hyperglycaemias, which are yet not diagnostic of GDM but may impair fetal cardiac function, resulting in higher FHR. Even if the biological association between hyperglycaemia and higher FHR has not been established yet, accumulating evidence has revealed that defects in calcium homeostasis are related to impaired mechanical performance of the diabetic heart leading to the prevalence of contractile dysfunction [9].

Up-to-date literature does not provide an established predictive model for GDM in early pregnancy. In the pre-HAPO era, Naylor et al. proposed a prediction model for GDM based on maternal age, race and BMI. This model provided 65.9% detection rate at FPR 16% [10]. In 2014 Syngelaki et al. developed a multivariate prediction model on a large population at 11–13 weeks' gestation based on maternal characteristics and history (previous GDM, parity, age, weight, height, race, birth weight z-score of previous pregnancies, use of ovulation drugs, relatives with DM) [11]. This model provided an AUC of 0.823 (0.820-0.826) for GDM with a detection rate of 68% and 84% at FPR of 20% and 40%, respectively. More recently, Sweeting et al. evaluated a prediction model including both anamnestic and first trimester biochemical parameters (maternal BMI, parity, race, previous GDM, PAPP-A, triglycerides and Lipocalin-2) in a case-control study of 980 women [12]. This model provided an AUC of 0.91 (0.89–0.94) for GDM with a detection rate of 85.9% and 93% at FPR of 20% and 40%, respectively.

Our data investigated for the first time the predictive role of first trimester FHR in women who develop GDM. The main strengths of our study are the large cohort of included women and the exclusion of possible biases that could affect our analysis through a logistic regression analysis. The main limitations of the study are its retrospective design, the lack of information on first trimester maternal fasting glucose and the perinatal outcomes of included pregnancies. Further research is needed to validate these findings in a prospective cohort study.

In conclusion, first trimester FHR may represent a novel, simple, reliable and cheap tool to predict women who have higher risk to develop GDM. First trimester FHR may be useful especially in low-resource settings, where there is no general screening for GDM or the chance to evaluate women using complex algorithms or expensive biochemical analyses.

A simple validated model for early prediction of GDM could be useful to select women who may benefit from an OGTT screening, avoiding the economic burden of a general screening for national

Table 3
ROC analysis: screening for GDM by different models including first trimester variables.

Model	AUC	SE	95% CI	20% FPR			40% FPR		
				DR %	LH^+	LH^-	DR %	LH^+	LH^-
FHR	0.809	0.020	0.769 – 0.849	65.2	3.26	0.43	89.5	2.24	0.17
FHR, Age, BMI, DV-PVI	0.813	0.020	0.773 – 0.853	69.1	3.45	0.39	86.2	2.15	0.23
FHR, Age, BMI, DV-PVI, NT, CRL, Smoke	0.825	0.020	0.786 – 0.863	66.3	3.31	0.42	87.8	2.19	0.20

ROC, receiver operative curve; GDM, gestational diabetes; AUC, area under the curve; SE, standard error; CI, confidence interval; FPR, false positive rate; DR: detection rate; LH^+, positive likelihood ratio; LH-, negative likelihood ratio; FHR, fetal heart rate; BMI, body mass index; DV-PVI, ductus venosus peak velocity index; NT, nuchal translucency; CRL, crown-rump length.

health systems. Furthermore, a first trimester predictor of GDM may be also of worth to validate an early screening for GDM in high-risk women, in order to improve the antenatal management of these pregnancies and reduce the risk of adverse pregnancy outcomes.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

References

[1] Diabetes Care 2019 Jan; 42(Supplement 1): S1-S2.
[2] Gortazar L, Flores-Le Roux JA, Benaiges D, Sarsanedas E, Payà A, Mañé L, et al. DIAGESTCAT STUDY: trends in prevalence of gestational diabetes and perinatal outcomes in Catalonia, Spain, 2006–2015. Diabetes Metab Res Rev 2019;13 (March):e3151.
[3] Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. HAPO study cooperative research group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002.
[4] Fan ZT, Yang HX, Gao XL, Lintu H, Sun WJ. Pregnancy outcome in gestational diabetes. Int J Gynaecol Obstet 2006;94(July (1)):12–6.
[5] McIntyre D, Desoye G, Dunne F, Simeoni U, Visser GHA, Kapur A, et al. FIGO analysis of research priorities in hyperglycemia in pregnancy. Diabetes Res Clin Pract 2018;145(November):5–14.
[6] Sirico A, Sarno L, Zullo F, Martinelli P, Maruotti GM. Pregestational diabetes and fetal heart rate in the first trimester of pregnancy. Eur J Obstet Gynecol Reprod Biol 2019;232(January):30–2.
[7] Rozmus-Warcholinska W, Wloch A, Acharya G, Cnota W, Czuba B, Sodowski K, et al. Reference values for variables of fetal cardiocirculatory dynamics at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 2010;35(May (5)):540–7.
[8] Yi Y, Lu G, Ouyang Y, lin G, Gong F, Li X. A logistic model to predict early pregnancy loss following in vitro fertilization based on 2601 infertility patients. Reprod Biol Endocrinol 2016;31(March 14):15.
[9] Singh RM, Waqar T, Howarth FC, Adeghate E, Bidasee K, Singh J. Hyperglycemia-induced cardiac contractile dysfunction in the diabetic heart. Heart Fail Rev 2018;23(January (1)):37–54.
[10] Naylor CD, Sermer M, Chen E, Farine D. Selective screening for gestational diabetes mellitus. Toronto Trihospital Gestational Diabetes Project Investigators. N Engl J Med 1997;337:1591–6.
[11] Syngelaki A, Pastides A, Kotecha R, Wright A, Akolekar R, Nicolaides KH. First-trimester screening for gestational diabetes mellitus based on maternal characteristics and history. Fetal Diagn Ther 2015;38(1):14–21.
[12] Sweeting AN, Wong J, Appelblom H, Ross GP, Kouru H, Williams PF, et al. A novel early pregnancy risk prediction model for gestational diabetes mellitus. Fetal Diagn Ther 2019;45(2):76–84.