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Maternal Hemodynamics at 11–13 Weeks' Gestation in Gestational Diabetes Mellitus

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Key Words
Pregnancy · Gestational diabetes · Arterial stiffness · Pulse wave velocity · Central systolic blood pressure

Abstract
Objective: Women who develop gestational diabetes mellitus (GDM) are at increased risk of type 2 diabetes and subsequent cardiovascular mortality and morbidity. Individuals with cardiovascular disorders have increased central aortic systolic blood pressure (SBP_{Ao}) and arterial stiffness. The hypothesis of this study is that increased SBP_{Ao} and arterial stiffness are apparent before the development of GDM. ***Methods:*** In this screening study, SBP_{Ao}, pulse wave velocity (PWV) and augmentation index (AIx) were measured in women with singleton pregnancies attending for routine antenatal care at 11–13 weeks' gestation. We compared SBP_{Ao}, PWV and AIx, expressed as multiples of the median (MoM), after adjustment for maternal characteristics affecting these measurements, in women who subsequently developed GDM (n = 105) with the values in non-GDM controls (n = 6,736). ***Results:*** In the GDM group, compared to non-GDM controls, there was an increase in PWV [1.04 MoM, interquartile range (IQR) 0.93–1.15 vs. 1.00 MoM, IQR 0.90–1.12; p = 0.013] and SBP_{Ao} (1.03 MoM, IQR 0.98–1.14 vs. 1.00 MoM, IQR 0.94–1.08; $p < 0.0001$) but no significant difference in the AIx (1.02 MoM, IQR 0.89–1.22 vs. 1.00 MoM, IQR 0.87–1.17; p = 0.118). ***Conclusion:*** Women who develop GDM have increased SBP_{Ao} and arterial stiffness from the first trimester of pregnancy before the clinical onset of GDM.

Introduction

Diabetes mellitus is associated with an increased risk of cardiovascular mortality and morbidity [1–3]. In patients with and without diabetes mellitus, the development of cardiovascular disease is associated with increased central aortic systolic blood pressure (SBP_{Ao}) and arterial stiffness [4–8].

Pregnancy can be considered a stress test for the subsequent development of diabetes mellitus because more than 60% of women with gestational diabetes mellitus (GDM) develop type 2 diabetes within the following 15 years [9, 10]. We have previously examined SBP_{Ao} and arterial stiffness in women with established GDM and reported that they were both higher than in non-GDM controls [11].

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The hypothesis of this study is that susceptibility to cardiovascular disease is not the consequence of GDM and type 2 diabetes mellitus but rather of the increased SBP_{Ao} and arterial stiffness that may precede the development of diabetes itself.

Methods

This was a screening study for adverse obstetric outcomes in women attending for their routine first-trimester ultrasound scan in pregnancy at the University College Hospital and King's College Hospital, London, UK, between December 2009 and February 2011. At this visit, which was held between 11+0 and 13+6 weeks of gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies by measurement of the fetal crown-rump length and nuchal translucency thickness and maternal serum pregnancy-associated plasma protein A and free β-human chorionic gonadotropin [12, 13]. We also measured SBP_{Ao}, pulse wave velocity (PWV) and augmentation index (AIx) noninvasively (Arteriograph, TensioMed Ltd., Budapest, Hungary). Written informed consent was obtained from all women who agreed to participate in the study, which was approved by the London-Surrey Borders Research Ethics Committee.

Details of maternal characteristics and the findings of the assessment at 11–13 weeks were recorded in our database. Data on pregnancy outcome were obtained from the computerised maternity records or the general medical practitioners of the women and were also recorded in our database. The birth weight percentile for gestation at delivery was calculated using a reference range derived from our population [14].

The inclusion criteria for this study were as follows: singleton pregnancy delivering a phenotypically normal neonate at or after 30 weeks of gestation. We excluded pregnancies with pre-pregnancy diabetes mellitus, those in which preeclampsia (PE) developed and those ending in termination, miscarriage or delivery before 30 weeks' gestation because they may not have had screening and diagnosis of GDM before this gestation.

Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), medical history including pre-pregnancy diabetes mellitus type 1 or 2 and obstetric history including parity (parous or nulliparous if no previous pregnancies delivering at or after 24 weeks). The questionnaire was then reviewed by a doctor together with each woman. The maternal weight and height were measured and the body mass index was calculated in kilograms per meter squared.

Screening and Diagnosis of GDM

Screening for GDM in our hospital is based on a two-step approach. In all women, a random plasma glucose measurement is performed at 24–28 weeks' gestation, and if the concentration is more than 6.7 mmol/l, an oral glucose tolerance test is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is at least 6 mmol/l or the plasma glucose level 2 h after the oral administration of 75 g of glucose is 7.8 mmol/l or more [15]. In women with normal random blood sugar, an oral glucose tolerance test is performed if they have persistent glucosuria, they develop polyhydramnios or the fetus becomes macrosomic. Women with a diagnosis of GDM are given dietary and exercise advice and are encouraged to test capillary blood glucose before and 1 h after each meal. If during a period of 1–2 weeks the pre-meal or 1-hour post-meal blood glucose level is higher than 5.5 and 7 mmol/l, respectively, the women are treated with insulin.

Arteriograph Measurements

All the measurements were performed in a temperature-controlled room (22°C) with participants in the supine position. The arteriograph (TensioMed) cuff was then applied on the left arm over the brachial artery for estimation of SBP_{Ao} (millimetres of mercury), PWV (metres per second) and AIx (percentage) as previously described [16]. All recordings were made by doctors who had received appropriate training on the use of the arteriograph. The results of PWV, AIx and SBP_{Ao} were not given to the women or their doctors and did not influence the subsequent management of the pregnancies.

Statistical Analysis

Comparison between the outcome groups was made by χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Data are presented as medians and interquartile ranges (IQRs) for continuous data and as numbers and percentages for categorical variables.

The distributions of AIx, PWV and SBP_{Ao} were made Gaussian after logarithmic transformation. The normality of distributions was tested using histograms and probability plots after excluding outliers outside 3 standard deviations. Each value in the GDM and non-GDM groups was expressed as a multiple of the median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the log transformed value in the multiple regression analysis as previously described [16]. Pearson correlation analysis was used to examine the association between $\log_{10}$PWV MoM, $\log_{10}SBP_{Ao}$ MoM and $\log_{10}$AIx-75 MoM.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

Maternal PWV, AIx and SBP_{Ao} were successfully recorded in 7,653 singleton pregnancies. We excluded 569 women (7.4%) because they had missing outcome data (n = 449), the pregnancies resulted in fetal death or miscarriage before 24 weeks' gestation (n = 60) or the pregnancies were terminated for fetal abnormalities or social reasons (n = 60). In addition, we excluded 27 women who delivered before 30 weeks, 35 cases with pre-existing hypertension and 181 women who subsequently developed PE. Of the remaining 6,841 cases, 105 (1.5%) subsequently developed GDM and 6,736 (98.5%) did not.

Table 1. Maternal characteristics in the outcome groups

Maternal characteristics	Non-GDM (n = 6,736)	GDM (n = 105)
Age, years	31.9 (28.0–35.4)	32.9 (28.9–36.2)
Weight, kg	64.0 (57.6–72.0)	72.0 (64.8–84.7)*
Height, m	1.65 (1.60–1.69)	1.63 (1.58–1.69)
Body mass index	23.5 (21.3–26.4)	26.7 (23.9–31.4)*
Fetal crown-rump length, mm	62.3 (57.5–67.7)	63.2 (56.2–68.5)
Gestational age at recruitment, weeks	12.7 (12.1–13.1)	12.7 (12.1–13.1)
Ethnicity		
Caucasian, n	4,898 (72.7)	49 (46.7)*
African, n	994 (14.8)	30 (28.6)*
South Asian, n	408 (6.1)	14 (13.3)*
East Asian, n	267 (4.0)	6 (5.7)
Mixed, n	169 (2.5)	6 (5.7)
Parity		
Nulliparous, n	3,662 (54.4)	54 (51.4)
Parous, n	3,074 (45.6)	51 (48.6)*
Cigarette smoker, n	410 (6.1)	5 (4.8)
Conception		
Spontaneous, n	6,457 (95.9)	100 (95.2)
Ovulation drugs, n	279 (4.1)	5 (4.8)
Gestational age at delivery, weeks	40.0 (39.1–40.9)	38.6 (38.2–39.2)*
Birth weight percentile	46.8 (26.3–67.6)	57.2 (33.7–80.4)*

Values are shown as medians (IQR) or numbers (percentage), as appropriate. * $p < 0.05$, comparing the outcome group and unaffected controls (χ^2 test and Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables).

The maternal characteristics of the outcome groups are given in table 1. In the GDM group, compared to the non-GDM group, women had a higher median maternal weight, more women were of African or South Asian racial origin and there were more parous women who delivered a neonate in a higher birth weight percentile at an earlier gestational age.

In the pregnancies that developed GDM, compared to the non-GDM group, the PWV was increased (1.04 MoM, IQR 0.93–1.15 vs. 1.00 MoM, IQR 0.90–1.12; $p = 0.013$) and the SBP_{Ao} was increased (1.03 MoM, IQR 0.98–1.14 vs. 1.00 MoM, IQR 0.94–1.08; $p < 0.0001$), but there was no significant difference in the AIx-75 (1.02 MoM, IQR 0.89–1.22 vs. 1.00 MoM, IQR 0.87–1.17; $p = 0.118$; table 2).

Discussion

The findings of this study suggest that women who develop GDM have increased SBP_{Ao} and arterial stiffness, which are evident from the first trimester of pregnancy.

In this study, we prospectively examined a large number of pregnancies within a narrow window in the first trimester, which is emerging as a first hospital-based assessment for fetal aneuploidies and a wide range of pregnancy complications [17]. The major limitation of the study is the method of screening for GDM, which was based on a random blood glucose level at 24–28 weeks' gestation rather than the recent recommendation of the International Association of Diabetes and Pregnancy Study Groups Consensus Panel that all women should have a 75-gram glucose challenge test at 24–28 weeks [18]. It is therefore possible that some of the women included in our non-GDM group actually had GDM, but the small number of such cases is unlikely to have had a significant effect on the results given the many thousands of women included in the study.

In our normal pregnancies, PWV, AIx-75 and SBP_{Ao} were related to certain maternal characteristics, including an increase with maternal age for AIx-75 and PWV, a decrease for AIx-75 and an increase for PWV with maternal height and an increase with maternal weight for SBP_{Ao}

Table 2. AIx, PWV and SBP_{Ao} in pregnancies that developed GDM and those that did not

Variable	Non-GDM (n = 6,736)	GDM (n = 105)	p value
AIx			
%	10.7 (5.5–16.8)	9.3 (5.4–16.6)	
MoM	1.00 (0.87–1.17)	1.02 (0.89–1.22)	0.118
PWV			
m/s	6.54 (5.82–7.41)	7.14 (6.39–8.00)	
MoM	1.00 (0.90–1.12)	1.04 (0.93–1.15)*	0.013
SBP_{Ao}			
mm Hg	108 (101–117)	117 (107–125)	
MoM	1.00 (0.94–1.08)	1.03 (0.98–1.14)*	<0.0001

Values are shown as medians (IQR). * $p < 0.05$, comparing the outcome group and unaffected controls (Mann-Whitney U test).

[16]. AIx was inversely related to heart rate, and therefore each measured value was standardized to a heart rate of 75 bpm as previously suggested. The multiple regression models of the association of each parameter with maternal characteristics were used to derive MoM values before valid comparisons could be made between the GDM and non-GDM pregnancies.

Possible mechanisms for increased SBP_{Ao} and arterial stiffness in patients with established diabetes, which could also apply to GDM, include alterations in the composition of the extracellular matrix and arterial remodelling due to hyperglycaemia, advanced glycation end products, hyperinsulinaemia, oxidative stress, chronic low-grade inflammation and endothelial dysfunction [19–21]. Additionally, diabetes is associated with reduced nitric oxide production and increased homocysteine levels, which are strongly associated with increased arterial stiffness [22–25].

Previous studies reported increased SBP_{Ao} and arterial stiffness in women with established GDM and in those with pre-existing type 2 but not type 1 diabetes mellitus [11, 26]. Similarly, studies in non-pregnant individuals reported increased SBP_{Ao} and arterial stiffness in subjects with impaired glucose tolerance and type 2 diabetes [27–29]. Our results demonstrate that these cardiovascular alterations are likely to precede rather than accompany the clinical onset of the disease and provide further support to the proposal that pregnancy could be viewed as a stress test which unmasks diabetes and other medical conditions, such as hypertension, in women who are predisposed and have pre-clinical risk factors for these conditions. The mechanism linking abnormal vascular markers and GDM may be analogous to hypertensive disorders, in which women destined to develop cardiovascular disease in their 40s or 50s often present with PE in their 20s or 30s [30]. As in the case of GDM, there is increased SBP_{Ao} and arterial stiffness in women with clinically established PE, but this is also apparent at 11–13 weeks' gestation several months before the clinical onset of the disease [16, 31–34].

In conclusion, the increased SBP_{Ao} and arterial stiffness which have previously been reported in women with type 2 diabetes and GDM and which are thought to predispose to cardiovascular disease in such patients may be apparent from the first trimester of pregnancy. Consequently, predisposition to cardiovascular disease may actually precede conception but is manifested as GDM or PE in response to the stress imposed by the cardiovascular and metabolic changes of pregnancy.

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