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Vascular phenotype at 35–37 weeks' gestation in women with gestational diabetes mellitus

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KEYWORDS: aortic stiffness; cardiovascular function; gestational diabetes; ophthalmic artery PSV ratio; third trimester

CONTRIBUTION

What are the novel findings of this work?
At 35–37 weeks' gestation, women with gestational diabetes mellitus (GDM), compared to those without GDM, have increased ophthalmic artery peak systolic velocity ratio, central systolic blood pressure and aortic stiffness. In women with GDM, those treated with metformin or insulin have a higher ophthalmic artery PSV ratio compared to those treated with diet alone. Additionally, compared to those treated with diet alone, women treated with metformin have higher central systolic blood pressure and those treated with insulin have a higher carotid–femoral pulse-wave velocity.

What are the clinical implications of this work?
Women with GDM have evidence of early vascular disease, and this may contribute to their long-term cardiovascular risk.

ABSTRACT

Objectives *To examine the vascular phenotype at 35–37 weeks' gestation of women with gestational diabetes mellitus (GDM) and compare it to that in women without GDM, using ophthalmic artery Doppler and carotid–femoral pulse-wave velocity.*

Methods *This was a prospective observational study of women attending for a routine hospital visit at 35 + 0 to 37 + 6 weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, ophthalmic artery Doppler for calculation of the peak systolic velocity (PSV) ratio and assessment of cardiac output, stroke volume, total peripheral resistance, central systolic and diastolic blood pressure, carotid–femoral pulse-wave velocity and augmentation index. All measurements were standardized to remove the effects of maternal characteristics and elements from the medical history, and the adjusted values in the GDM group were compared with those in the non-GDM group.*

Results *The study population of 2018 pregnancies contained 218 (10.8%) that developed GDM, including 78 (35.8%) that were treated with diet alone, 81 (37.2%) treated with metformin and 59 (27.1%) treated with insulin with or without metformin. In the GDM group, compared with the non-GDM group, there were significantly higher ophthalmic artery PSV ratio, carotid–femoral pulse-wave velocity and central systolic blood pressure, but there was no significant difference in cardiac output, stroke volume, total peripheral resistance, central diastolic blood pressure or augmentation index. In the GDM group, women treated with metformin or insulin had a higher ophthalmic artery PSV ratio compared with those treated with diet alone. Additionally, compared with the diet group, the metformin group had higher central systolic blood pressure and the insulin group had a higher carotid–femoral pulse-wave velocity.*

Conclusion *Women with GDM have evidence of early vascular disease, and this may contribute to their long-term cardiovascular risk.* © *2022 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Epidemiological studies have consistently demonstrated that women with gestational diabetes mellitus (GDM), compared to those without GDM, have a 2-fold higher risk of developing premature cardiovascular disease, such as myocardial infarction and stroke, within the first

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decade after pregnancy, and this association could not be explained by the development of Type-II diabetes mellitus[1,2]. Our group has also reported that, in women with GDM, compared to those without GDM, there is increased aortic stiffness, augmentation index and central blood pressure[3]. These arterial changes appear to precede the development of GDM and suggest accelerated vascular aging, which may also contribute to the long-term increased cardiovascular risk of these women[4]. However, it remains to be established whether GDM development accentuates vascular changes and whether diabetic treatment can modify arterial disease progression.

Assessment of vascular disease can be performed using a variety of techniques for characterization of functional and structural changes in central and peripheral arteries[5]. Among various methodologies, aortic stiffness has gained considerable scientific interest, as its measurements can be performed easily, are accurate and reproducible, demonstrate little change during pregnancy and relate to cardiovascular outcome[6]. More recently, ophthalmic artery Doppler assessment has emerged as an easily performed technique that provides information about impedance to peripheral blood flow and potentially can identify women with more extensive vascular disease[7–9].

The objectives of this study were to perform detailed assessment of the vascular phenotype in an unselected population undergoing routine clinic assessment at 36 weeks' gestation, compare central and peripheral arterial changes in women with and those without GDM, and assess the effect of diabetic treatment on the vascular phenotype in women with GDM.

METHODS

Study design and participants

This was a prospective observational study of women attending for a routine hospital visit at 35 + 0 to 37 + 6 weeks' gestation at King's College Hospital, London, UK, between December 2021 and April 2022. This visit included recording of maternal demographic characteristics and medical history, ophthalmic artery Doppler assessment for calculation of the peak systolic velocity (PSV) ratio, and assessment of cardiac output, stroke volume, total peripheral resistance, central systolic and diastolic blood pressure, carotid–femoral pulse-wave velocity and augmentation index. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks' gestation or fetal head circumference at 19–24 weeks[10,11]. The women gave written informed consent to participate in the Advanced Cardiovascular Assessment in Pregnancy (REC: 18/NI/0013, IRAS ID:237936), which was approved by the NHS research ethics committee.

Patient characteristics included maternal age, weight, height (which were measured at the time of screening), race (white, black, South Asian, East Asian or mixed), method of conception (natural or assisted conception, requiring *in-vitro* fertilization or use of ovulation drugs), history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of GDM (first- or second-degree relative) and obstetric history, including parity (parous or nulliparous if no previous pregnancy at $\geq$ 24 weeks), previous pregnancy with GDM, gestational age at delivery and birth weight of the neonate in the last pregnancy.

The inclusion criteria for this study were singleton pregnancy delivering a non-malformed liveborn or stillborn fetus. Pregnancies with aneuploidy or major fetal abnormality were excluded.

Assessment of maternal vascular phenotype

Assessment of the ophthalmic arteries was carried out using a 7.5-MHz linear transducer (Canon Aplio i900 PLT-704SBT Linear Probe, Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) placed transversely and gently over the closed upper eyelid of the woman. Color flow was used to identify the ophthalmic artery, which is found superior and medial to the hypoechoic band representing the optic nerve[12]. Pulsed-wave Doppler was then used to record three to five similar waveforms; the angle of insonation was kept at $< 20°$, the sample gate was 2 mm, the depth was 3.0–4.5 cm, the high-pass filter was 50 Hz and the pulse repetition frequency was set at 3–6 kHz[13]. In order to minimize any potential adverse effects on the eyes, the duration of the examination was always less than 1 min, a special preset was used with significant reduction in output power and the maximum mechanical index was 0.4. Waveforms were obtained in sequence from the right eye, left eye and again from the right and then left eye. The first and second PSV were measured and the ratio of the second to the first PSV was calculated.

Aortic stiffness was assessed by measuring carotid–femoral pulse-wave velocity. Measurements were performed using the Vicorder device (Skidmore Medical Ltd., Bristol, UK). The device measures simultaneous pressure waveforms by a volume displacement technique using blood-pressure cuffs placed around the sites of interest in real time over at least 10 heartbeats. To calculate transit time, the Vicorder software automatically marks the steepest ascending part of the pulse wave (maximum systolic upstroke) and uses a definite timeframe to detect the nadir of the wave. The shift in time between the marked areas on the carotid and femoral pulse waves, which is the transit time, is detected by cross-correlation. The distance between the carotid and femoral pressure cuffs was measured using a tape. To account for differences in abdominal circumference associated with pregnancy and reduce variability and error in distance assessment, all measurements were performed from the suprasternal notch to the right shoulder and from there to the midpoint of the blood-pressure cuff on the thigh. Carotid–femoral pulse-wave velocity was

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expressed in m/s. The Vicorder device also allows assessment of augmentation index and central blood pressure by applying brachial-to-aortic transfer function, as described previously[14]. Augmentation index measures augmentation pressure as a proportion of central pulse pressure and is expressed as %. From this assessment, additional measurements were derived, including cardiac output, stroke volume and peripheral vascular resistance.

Screening, diagnosis and management of gestational diabetes mellitus

The diagnosis of GDM in our hospital is based on the results of the oral glucose tolerance test (OGTT) with administration of 75-g glucose; the diagnosis is made if the fasting plasma glucose level is ≥ 5.6 mmol/L and/or 2-h plasma glucose level is ≥ 7.8 mmol/L[15]. The OGTT was carried out in three groups of women. First, women with at least one risk factor (body mass index > 30 kg/m^2, previous birth of a macrosomic baby weighing > 4.5 kg, previous GDM, first-degree relative with diabetes or persistent glycosuria) were offered measurement of glycosylated hemoglobin at first visit and, if the value was $\geq 5.7\%$, they underwent OGTT, usually at 12 weeks' gestation. Second, in all women at 26–28 weeks' gestation, plasma glucose level was measured 1–2 h after eating ≥ 50 g of carbohydrate and, if the concentration was ≥ 6.7 mmol/L, OGTT was carried out. Third, after 28 weeks' gestation, OGTT was performed if there was polyhydramnios or the fetus became macrosomic.

Women with the diagnosis of GDM were given dietary and exercise advice and were 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-h post-meal blood glucose level was ≥ 5.5 and > 7 mmol/L, respectively, women were treated with metformin and/or insulin.

Statistical analysis

Data were expressed as median (interquartile range (IQR)) for continuous variables and *n* (%) for categorical variables. Student's *t*-test and chi-square test or Fisher's exact test were used to compare continuous and categorical data between outcome groups, respectively.

The measurements of the ophthalmic artery PSV ratio, carotid–femoral pulse-wave velocity and other cardiovascular parameters were standardized to remove the effects of maternal characteristics and elements from medical history by converting them into multiples of the median (MoM) or difference from the median (delta), as appropriate. The median MoM or delta values in the GDM and non-GDM groups were compared. Comparisons within the GDM group were made according to treatment (diet, metformin or insulin). The statistical software package R was used for data analysis[16].

RESULTS

Study participants

The study population of 2018 pregnancies contained 218 (10.8%) that developed GDM, including 78 (35.8%) that were treated with diet alone, 81 (37.2%) treated with metformin and 59 (27.1%) treated with insulin with or without metformin. Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the GDM group, compared with the non-GDM group, there were higher median maternal weight, body mass index and maternal age, and higher incidence of women of black, South Asian and East Asian race, family history of first-degree relative with diabetes mellitus, and previous pregnancy complicated by GDM.

Table 1 Maternal and pregnancy characteristics of study population

Characteristic	*No GDM (n = 1800)*	*GDM (n = 218)*	P
Maternal age (years)	33.8 (30.2–36.8)	33.9 (30.5–38.2)	0.003
Maternal weight (kg)	78.0 (70.0–87.9)	82.3 (74.1–96.2)	< 0.0001
Maternal height (cm)	166.0 (161.0–170.0)	163.0 (159.0–169.0)	0.0009
BMI (kg/m^2)	28.4 (25.7–31.8)	31.3 (27.4–35.4)	< 0.0001
Gestational age (days)	249 (248–251)	249 (248–252)	0.101
Race			< 0.0001
White	1310 (72.8)	118 (54.1)	
Black	274 (15.2)	45 (20.6)	
South Asian	104 (5.8)	36 (16.5)	
East Asian	39 (2.2)	10 (4.6)	
Mixed	73 (4.1)	9 (4.1)	
Medical history			
CH	6 (0.3)	2 (0.9)	0.468
Type-I DM	3 (0.2)	0 (0.0)	0.615
Type-II DM	5 (0.3)	0 (0.0)	0.615
SLE/APS	4 (0.2)	1 (0.5)	1
Smoker	28 (1.6)	1 (0.5)	0.345
Family history of DM			
First degree	176 (9.8)	48 (22.0)	< 0.0001
Second degree	160 (8.9)	18 (8.3)	< 0.0001
Method of conception			0.92
Natural	1652 (91.8)	201 (92.2)	
In-vitro fertilization	142 (7.9)	16 (7.3)	
Ovulation drugs	6 (0.3)	1 (0.5)	
Parity			< 0.0001
Parous			
Previous GDM	21 (1.2)	16 (7.3)	
No previous GDM	900 (50.0)	111 (50.9)	
Nulliparous	879 (48.8)	91 (41.7)	

Data are given as median (interquartile range) or *n* (%). Outcome groups were compared using chi-square or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. APS, antiphospholipid syndrome; BMI, body mass index; CH, chronic hypertension; DM, diabetes mellitus; GDM, gestational diabetes mellitus; SLE, systemic lupus erythematosus.

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Maternal vascular phenotype

The effects of maternal characteristics and medical history elements significantly associated with the measurements obtained from ophthalmic artery Doppler and carotid–femoral pulse-wave velocity assessment are shown in Table S1. These variables were used for standardization into MoM or delta values.

The distributions of MoM or delta values of the maternal vascular indices in the GDM and non-GDM groups are shown in Figure 1 and Table 2. In the GDM group, compared with the non-GDM group, there were significantly higher central systolic blood pressure, ophthalmic artery PSV ratio and carotid–femoral pulse-wave velocity, but there was no significant difference in cardiac output, stroke volume, total peripheral resistance, central diastolic blood pressure or augmentation index. In the GDM group, women treated with metformin or insulin had a higher ophthalmic artery PSV ratio compared to those

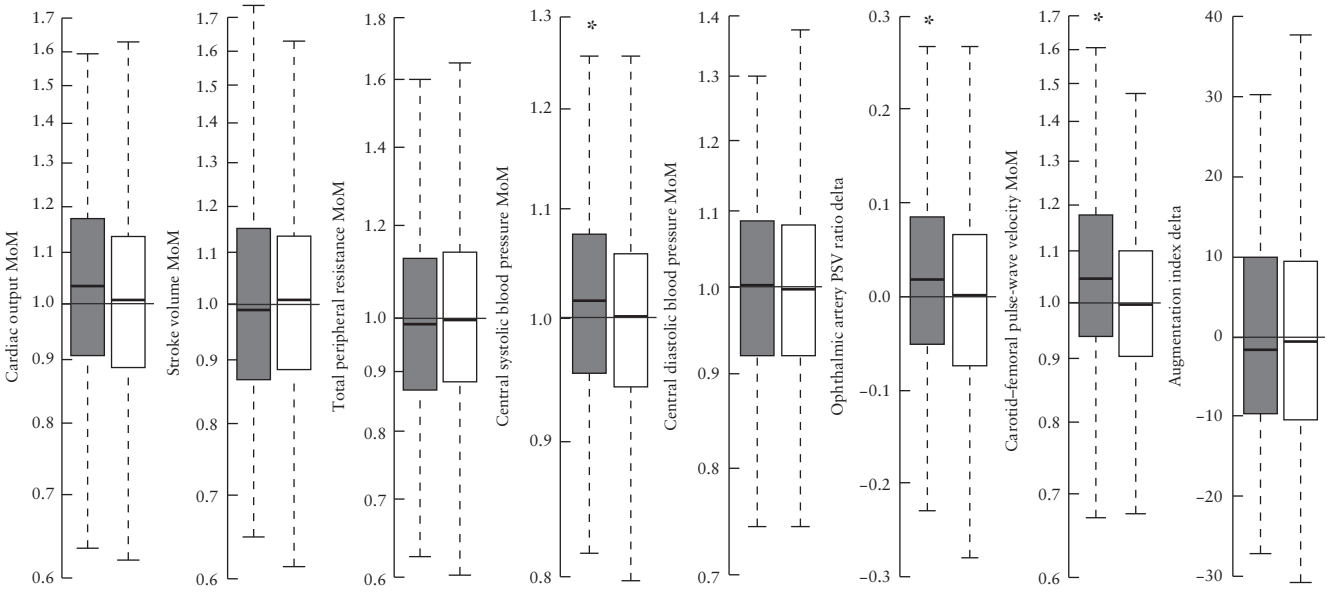

Figure 1 Box-and-whiskers plots showing quartiles, minimum and maximum for cardiovascular indices adjusted for maternal characteristics and medical history, expressed as multiples of the median (MoM) or difference from the median (delta), in pregnancies that developed gestational diabetes mellitus (■), compared with those that did not (□). *Significant difference between groups. PSV, peak systolic velocity.

Table 2 Cardiovascular indices, expressed as multiples of the median (MoM) or delta values, in pregnancies with and those without gestational diabetes mellitus (GDM), overall and according to treatment arm

		GDM			
Hemodynamic index	*No GDM (n = 1800)*	*All GDM (n = 218)*	*Diet (n = 78)*	*Metformin (n = 81)*	*Insulin (n = 59)*
Cardiac output MoM	0.998 (0.990–1.006)	1.017 (0.992–1.043)	0.990 (0.952–1.030)	1.037 (0.994–1.069)	1.033 (0.981–1.088)
Stroke volume MoM	1.002 (0.994–1.010)	0.985 (0.959–1.011)	0.976 (0.937–1.017)	0.983 (0.938–1.031)	0.999 (0.950–1.052)
Total peripheral resistance MoM	1.000 (0.992–1.009)	0.998 (0.973–1.023)	1.018 (0.971–1.067)	0.980 (0.943–1.018)	0.996 (0.945–1.049)
Central systolic blood pressure MoM	1.000 (0.996–1.004)	1.016 (1.004–1.027)*	1.009 (0.989–1.029)	1.023 (1.006–1.041)†	1.015 (0.988–1.042)
Central diastolic blood pressure MoM	1.000 (0.994–1.006)	1.000 (0.984–1.016)	1.001 (0.980–1.022)	0.997 (0.970–1.024)	1.004 (0.973–1.036)
Ophthalmic artery PSV ratio delta	0.000 (−0.005 to 0.005)	0.022 (0.008–0.035)*	0.006 (−0.017 to 0.028)	0.033 (0.011–0.055)†	0.027 (0.001–0.053)†
Carotid–femoral pulse-wave velocity MoM	1.000 (0.993–1.007)	1.037 (1.014–1.060)*	1.047 (1.006–1.091)	1.015 (0.978–1.054)	1.053 (1.016–1.091)†
Augmentation index delta	0.019 (−0.664 to 0.702)	−0.157 (−2.024 to 1.711)	−2.529 (−5.688 to 0.630)	1.523 (−1.195 to 4.241)	0.674 (−3.067 to 4.414)

Data are given as median (95% CI). Values were estimated using geometric mean, assuming Gaussian distribution. *Significantly different from no GDM. †Significantly different from GDM on diet. PSV, peak systolic velocity.

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treated with diet alone. Additionally, compared with the diet group, the metformin group had higher central systolic blood pressure and the insulin group had a higher carotid–femoral pulse-wave velocity.

DISCUSSION

Principal findings of this study

In this prospective screening study of an unselected population, we used established techniques to assess arterial structure and hemodynamic changes in women with and those without GDM. We showed that women in the GDM group, compared to those without GDM, have increased central systolic blood pressure, aortic stiffness and ophthalmic artery PSV ratio but show no significant difference in hemodynamic indices such as peripheral vascular resistance and augmentation index. The vascular changes in the GDM group were accentuated in women who received medical treatment for glycemic control. These findings suggest that GDM is associated with central and peripheral arterial changes, which may contribute to the increased cardiovascular risk reported in these women.

Comparison with findings of previous studies

Previous studies have assessed vascular changes in women with GDM in different trimesters. In a first-trimester screening study, we found that, in 105 women who subsequently developed GDM, compared with 6736 who did not develop GDM, there were increased carotid–femoral pulse-wave velocity and central systolic blood pressure[4]. In a second-trimester screening study involving 5214 women, we found that, in 509 women who subsequently developed GDM, maternal hemodynamics, including cardiac output, peripheral vascular resistance and ophthalmic artery PSV ratio, were not significantly different from those in the non-GDM group[17]. In a cross-sectional third-trimester study, we used a handheld pressure tonometer in the radial artery and found that, in 34 women with GDM, compared with 34 non-diabetic controls, aortic stiffness and augmentation index were marginally increased[3].

The findings of the current study complement the previous observations. Consistent with earlier reports, we found that, in women with GDM, aortic stiffness, assessed by measuring carotid–femoral pulse-wave velocity, was increased and central systolic blood pressure was also raised. In contrast, augmentation index was unaffected. Various reasons related to the measurement of augmentation index can explain the discrepancy. In our previous third-trimester study, augmentation index was calculated by using transfer function from the radial artery[3], whereas in the current study, the brachial artery was used. Although both methodologies have been introduced as non-invasive methods to estimate central hemodynamics, there is variability in such estimation. Peripheral waveforms are typically calibrated to brachial systolic and diastolic cuff pressures; thus, using brachial measurements for transfer function may be preferable, as it reduces any brachial-to-radial amplification error introduced in the radial pressure waveforms[18]. In addition, the use of an automated device, as in our current study, offers potential advantages by being less operator-dependent compared with handheld tonometry methods, and such device may be well-suited to use in the primary-care setting[19].

In this study, we have demonstrated for the first time an increase in ophthalmic artery PSV ratio in women with GDM. In our previous second-trimester study, before diagnosis of GDM, there was no increase in the ophthalmic artery PSV ratio[17]. These findings suggest progressive or more advanced vascular disease with development of GDM. For instance, in diabetic patients, an increase in ophthalmic artery Doppler has been associated with the extent of systemic atherosclerosis and reduced arterial compliance[20].

The mechanism linking abnormal vascular markers and GDM remains to be established. It is well-known that hyperglycemia is associated with increased production of advanced glycation end products, which can promote collagen deposition, tissue inflammation and fibrosis, alter the matrix of molecules in the vessel wall and contribute to increased arterial stiffening[21]. However, considering that previous studies have reported increased aortic stiffness prior to GDM development, it is possible that other mechanisms, such as hyperinsulinemia, hypertension, oxidative stress, chronic low-grade inflammation and endothelial dysfunction, may have a role in the development of vascular disease[22–26]. In the current study, women with GDM, compared to those without GDM, had increased body mass index, increased central blood pressure and higher incidence of first-degree relatives with diabetes. These risk factors are commonly associated with metabolic abnormalities, which might contribute to arterial disease progression.

Apart from the effect of GDM on the vasculature, we also had the opportunity to assess whether diabetic treatment can modify arterial disease. Women receiving metformin or insulin in our study had worse vascular indices compared with those treated with diet only. Previous studies have provided contradictory results regarding the effect of metformin on arterial stiffness in Type-II diabetic patients. Most of the studies have reported a beneficial effect of the medication, whereas few reported no improvement in arterial stiffness[27–29]. The deterioration of vascular indices in our study may simply suggest the presence of a more severe disease in women receiving medical treatment rather than a deleterious effect of medication on the vasculature, but this requires further exploration.

Strengths and limitations

The main strengths of the study are, first, detailed vascular phenotyping of a large unselected population of pregnant women attending for a routine ultrasound examination at 35–37 weeks' gestation, second, use of validated

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automated techniques to assess aortic stiffness and central hemodynamics to minimize variability of measurements, third, adherence to a strict protocol for the assessment of peripheral blood pressure and the distance between carotid and femoral sites for the calculation of pulse-wave velocity and, fourth, trained research fellows with high reproducibility figures who performed the ophthalmic artery Doppler assessment.

A limitation of the study is that OGTT was not carried out in all pregnancies, but only in a subgroup thought to be at high risk of GDM. Therefore, underdiagnosis of GDM may have occurred, but this would have misclassified women in the control group and likely would have attenuated the noted associations. In addition, analysis of the metabolic profile or glucose levels of the women at the time of the vascular assessment has not been performed; thus, no insights regarding the underlying mechanisms could be provided.

Conclusions

Our study provides evidence that women with GDM have accelerated vascular aging, with an increase in central hemodynamics, aortic stiffness and ophthalmic artery PSV ratio. Vascular indices were marginally worse in women with GDM who received medication; however, further studies are needed to clarify whether this reflects increased severity of disease or a deleterious effect of medication on vascular physiology.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Effects of maternal characteristics and medical history elements with significant influence on measurements obtained from ophthalmic artery Doppler and carotid–femoral pulse-wave velocity assessments

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