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Maternal and pregnancy characteristics affect plasma fibrin monomer complexes and D-Dimer reference ranges for venous thromboembolism in pregnancy

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Condensation:

The utility of fibrin linked markers as a tool for exclusion of venous thromboembolism in pregnancy might be improved by adjusting for patient specific characteristics

Short version of title:

Characterising plasma fibrin monomer complexes and D-Dimer in pregnancy

Abstract

Background:

D-dimers have a high negative predictive value for excluding venous thromboembolism outside of pregnancy but the use in pregnancy remains controversial. A higher cut-off value has been proposed in pregnancy due to a continuous increase across gestation. Fibrin monomer complexes have been considered as an alternative diagnostic tool for exclusion of VTE in pregnancy due to their different behaviour.

Objective: To establish normal values of Fibrin monomer complexes and D-dimer as a diagnostic tool for the exclusion of VTE in pregnancy and examine the effect of maternal and obstetric factors on these markers.

Study Design: Plasma D-dimer and fibrin monomer complexes were measured by quantitative immunoturbidimetry in 2870 women with singleton pregnancies attending for their routine first trimester hospital visit in a prospective screening study for adverse obstetric outcome. Multiple regression analysis was used to determine maternal characteristics and obstetric factors affecting the plasma concentrations and converting these into multiple of the median values after adjusting for significant maternal and obstetric characteristics.

Results: Plasma fibrin monomer complexes increased with maternal weight and were lower in women with a history of cocaine abuse and chronic hypertension.D-dimers increased with gestational age and maternal weight and were higher in sickle cell carriers and in women of African and South Asian racial origin compared to Caucasians.

Conclusions: Fibrin monomer complexes and D-dimers are affected by maternal and obstetric characteristics rather than only gestational age. The utility of these fibrin-linked markers as a tool for exclusion of venous thromboembolism in pregnancy might be improved by adjusting for patient specific characteristics.

Key words: Fibrin monomer complex, D-dimer, Pregnancy, Screening ,venous thromboembolism

Introduction

Pregnancy is a hypercoagulable state exemplifying Virchow's triad of altered coagulation, stasis and vascular damage [1]. VTE is one of the leading causes of maternal death in developed countries with about 1-2 deaths per 100 000 maternities or 9% of all maternal deaths in the United States[2,3]. The incidence of VTE in pregnancy is 1-2 per 1000, fivefold higher than in non–pregnant women [4]. The antenatal risk for VTE is highest in the first and third trimester[5] and in the UK the majority of antenatal deaths occurred in the first trimester [6].

Outside of pregnancy, diagnostic pathways for DVT and PE are based on a combination of clinical scoring systems, blood tests and imaging using compression ultrasound (CUS), ventilation-perfusion (V/Q) scans or computed tomography pulmonary angiography (CTPA) [7]. Both V/Q scans and CTPA are considered safe but concerns remain about fetal radiation and breast radiation exposure respectively with these modalities[8].

In pregnancy there are no clinically validated scoring systems and the clinical presentation can be confused with features of a healthy pregnancy[9].

D-dimer (DD) is integral to diagnostic pathways outside of pregnancy and in individuals with low clinical probability has a high negative predictive value for VTE [10]. Another marker of thrombin activation is the fibrin monomer (FM), an intermediate in cross-linked fibrin formation. FM are produced when thrombin proteolyses

fibrinogen into fibrinopeptides A and B and FM.In prothrombotic conditions like disseminated intravascular coagulation syndrome (DIC) soluble complexes may be formed when FM join with fibrinogen and fibrin degradation products[11]
D-dimers are produced by lysis of cross-linked fibrin and are therefore downstream from FM in this pathway. However DD levels normally rise in pregnancy and higher cut-off value have been proposed[12]There is evidence that DD and FM might behave differently in clinical scenarios, possibly reflecting the different stages of thrombin activation and fibrinolysis. For instance, there are small studies showing that changes in FM concentrations in uncomplicated pregnancy seem to be minimal compared to other haemostatic markers and FM are therefore considered an alternative tool for exclusion of VTE in pregnancy [13,14].

It would be desirable to be able to utilise fibrin-linked markers within pregnancy to help exclude the likelihood of VTE and reduce the requirement for imaging as shown for the use of FM outside pregnancy[15]. [16]. Further, it is likely that characteristics of the mother as well as the pregnancy might also affect haemostatic markers. The objectives of this screening study at 11-13 weeks' gestation are to establish a reference range for plasma FM and DD and examine the maternal and pregnancy characteristics that affect the measurements.

Materials and Methods

Study population

The data for the study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the first-trimester of pregnancy at King's College Hospital, London, between October 2011 and May 2012. This visit, which was held at 11^{+0}-13^{+6} weeks' gestation, included recording of maternal characteristics and medical history, ultrasound examination for measurement of fetal crown-rump length (CRL), diagnosis of fetal abnormalities and measurement of fetal nuchal translucency thickness as part of combined screening for fetal trisomies[17]. Venous blood (4 mL) was obtained from the antecubital vein and collected into tubes containing liquid 0.109M trisodium citrate (BD Medical Systems, Franklin Lakes, NJ, USA).

Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the Ethics Committee of the hospital. The pregnancies included in the study were those resulting in live birth or stillbirth of phenotypically normal babies at ≥24 weeks' gestation. Women on current anticoagulation were excluded.

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, sickle cell trait and autoimmune disease, including systemic lupus erythematosus or rheumatoid arthritis, family history of thromboembolic events and obstetric history including parity (parous or nulliparous if no previous pregnancies at ≥ 24 weeks' gestation). The maternal weight and height were measured.

Sample analysis

The blood samples were processed within one hour after collection. After centrifugation at 2200g for 15 minutes at 20ºC the undiluted plasma has been analysed immediately in the STA-Compact® coagulation analyser (Diagnostica Stago, Asnieres Sur Seine, France) by quantitative immunoturbidimetry following the manufacturer's instructions. We used STA®-Liatest® FM (Diagnostica Stago) and STA®-Liatest® DD (Diagnostica Stago) assays with respective working ranges of 5 - 150 µg/mL and 0.22- 4.0 µg /mL, and an expected normal threshold in the adult non-pregnant population of <6 µg/mL for fibrin monomers and <0.5 µg/mL (expressed in FEU) for D-dimer. The intra-assay coefficient of variation [CV] and inter-assay CV were 5.55 %, 5.7% for FM and 8.4%,10.3% for DD, respectively

Pregnancy outcome

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The birth weight percentile for gestational age at delivery was derived from a reference range for our population[18]. The definition of preeclampsia was that of the International Society for the Study of Hypertension in Pregnancy [19]. Diagnosis of GDM was based on a 75-g oral glucose tolerance test performed at 24-28 weeks' gestation[20].

Statistical analysis

Data for continuous variables are presented as median (interquartile range) and data for categorical variables are presented as n (%). The observed values of serum DD and FM concentrations were $\log_{10}$ transformed to make their distributions Gaussian.

Normality was assessed using histograms and probability plots. Univariable regression analysis was used to examine the individual variables contributing significantly to prediction of log_{10} transformed values of DD and FM. Multivariable regression analysis with backward stepwise regression analysis was used to determine the significance of contribution from maternal and pregnancy characteristics. The measured concentration of DD and FM were converted into multiple of the median (MoM) values after adjusting for maternal characteristics that significantly affected log_{10} transformed values in the multiple regression analysis. The statistical software package SPSS 21 (SPSS Inc., Chicago,Ill., USA) was used for data analyses.

Results

Study population

During the study period we examined 2,870 singleton pregnancies with a live fetus at 11-13 weeks, but 256 were excluded because of the pregnancy resulted in miscarriage or termination for fetal abnormalities and those with major fetal defects (n=107), anticoagulation therapy (n=28) or no pregnancy follow up (n=121). The characteristics of the study population of 2,614 pregnancies are shown in Table 1. In keeping with the South East London population, 61.7% women were of Caucasian origin, 27.9% Afro-Caribbean and 10.5% of other ethnic origins. D-dimers were measured in all cases but FM was measured in only 1286 of the cases due to reagent availability.

Fibrin-Monomer Complex

The median, 5th and 95th percentiles of the measured FM concentration was 4.3, 2.16 and 8.84 mg/L, respectively. In 282 (21.9%) of the 1,286 pregnancies the values were >6 mg/L.

Univariable regression analysis demonstrated that significant contributions to log_{10} FM were provided by several maternal and pregnancy characteristics (Table 3). Multivariable regression analysis demonstrated that significant contributions to log_{10} FM were provided by maternal weight, cocaine use and medical history of chronic hypertension (Figure 1).

The median and 5th, 10th, 90th and 95th percentiles, with 95% confidence intervals for FM MoM, were 0.99 (0.96 to 1.00) and 0.50 (0.45 to 0.53), 0.61 (0.57 to 0.64), 1.65 (1.58 to 1.74) and 2.01 (1.88 to 2.17), respectively (Figure 2).

D-Dimer

The median, 5th and 95th percentiles of the measured DD concentration was 0.31, 0.11 and 1.16 mg/L, respectively. In 736 (28.2%) of the 2,614 pregnancies the values were >0.5 mg/L.

Univariable regression analysis demonstrated that significant contributions to log_{10} DD were provided by several maternal and pregnancy characteristics (Table 2). Multivariable regression analysis demonstrated that significant contributions to log_{10} DD were provided by gestational age, maternal weight, smoking, maternal ethnic origin and medical history of sickle cell trait (Figure 1).

The median and 5th, 10th, 90th and 95th percentiles, with 95% confidence intervals for DD MoM, were 0.98 (0.96 to 1.00) and 0.37 (0.34 to 0.39), 0.47 (0.46 to 0.49), 2.23 (2.09 to 2.34) and 2.93 (2.73 to 3.18), respectively (Figure 2).

Comment

This study has established a reference range for serum FM and DD in singleton pregnancies at 11-13 weeks' gestation and reports the maternal and pregnancy characteristics that affect the measurements. The study also illustrates that the cut-offs of 6 mg/L for FM and 0.5 mg/L for DD used for exclusion of VTE in non-pregnant individuals are not applicable to pregnancy because these values were already exceeded by the end of the first trimester in 22% and 28% of cases, respectively.

Multivariable regression analysis demonstrated that the level of FM increased with maternal weight and was decreased in women with chronic hypertension and those reporting use of cocaine. The level of DD increases with gestational age and maternal weight and is higher in those with sickle cell trait. D-dimer is increased in women of Afro-Caribbean and South Asian racial origin relative to Caucasians, and it is decreased in cigarette smokers. We also examined the association with pregnancy outcomes: levels of DD and FM at 11 to 13 weeks gestation were not significantly altered in pregnancies that subsequently developed preeclampsia, fetal growth restriction or gestational diabetes mellitus.

Strengths and limitations:

The strengths of this first-trimester study are firstly, examination of a large population of pregnant women attending for routine care in a gestational age range which is widely used for screening for pregnancy complications; secondly, measurement of maternal serum concentration of fibrin-linked markers that have been shown to be altered in VTE and thirdly, expression of the values as MoMs after adjustment for factors that affect the measurements.

One limitation of the study is that despite the fact that all women were clinically free from signs or symptoms of VTE at the time of testing, we did not exclude the possibility of asymptomatic VTE. This potential complication could have been avoided by conducting CUS of the lower extremities in all women. However, this technique has been validated only for the diagnosis of DVT in symptomatic women, rather than for the diagnosis of VTE in asymptomatic women. Consequently, in selecting our study population we relied on clinical signs and symptoms at the time of recruitment and in obtaining postpartum data on all pregnancy complications. A further limitation is that absolute plasma values and cut-offs are not exactly comparable between different assay types and methodologies and also depend on the instrument type; this paper only describes the relevant values and ranges pertaining to the STA-Liatest FM and DD as performed by our laboratory.

Interpretation:

In our study the median FM at 11-13 weeks' gestation was 4.3 mg/L. Three previous studies examined FM levels in the first-trimester of normal pregnancy; the number of patients examined were 43[21],33[13] and 36[22] and the reported median FM was 2.3, 3.4

and 4.3 mg/L, respectively ’. Onishi and Joly also used the STA Liatest FM and the FM concentrations were comparable to our data.

In our study using the STA-Liatest assays, the median DD at 11-13 weeks' gestation was 0.31 mg/L. Several previous studies in small numbers of cases ranging from 5 to 350 normal pregnancies at <16 weeks' gestation, reported that the median DD varied between 0.1 and 0.8 mg/L[13,12,22,23,24,25,26,27,28,29,30,31,32,33,34,24]. For the STA-Liatest assay we found in the literature first trimester concentrations of 0.3mg/L[21], 0.49 mg/L [28],0.2 mg/L in a Chinese population [26] and 0.48 mg/L in women without DVT and 5.4mg/L with confirmed DVT [30].

None of the previous studies in pregnant women on either FM or DD examined the possible association of levels with maternal demographic characteristics. However, a study in 4,364 mainly non-pregnant individuals presenting to a medical emergency department examined the effect of patient characteristics on DD level and reported significant positive associations with several factors including black race, cocaine use, rheumatoid arthritis, SLE and sickle cell trait [35].

Our finding of increasing levels of both FM and DD with maternal weight might reflect the increased susceptibility of obese women to VTE [36]. Maternal obesity is also histopathologically associated with chronic villitis and fetal thrombosis. [37]

Similarly the association of increased levels of DD in women of Afro-Caribbean racial origin is compatible with the increased susceptibility of these women to VTE [38]. It is possible that there might be ethnic differences in the regulation of proteins in the coagulation cascade; a further example is the elevated levels of factor VIII in the black population, both in normal subjects and those with VTE, relative to those of Caucasian origin[39].

Individuals with sickle cell trait have an association with increased coagulation activity but the mechanism is not well understood[40].

Pregnant women with increased BMI, sickle cell carriers and African and South Asian origin have elevated and smokers decreased DD-MoMs.The utility of this finding in improving diagnostic performance of DD has to be evaluated in future studies including pregnant women with confirmed VTE.

At present we can only speculate why FM behave differently than DD and are negatively affected by chronic hypertension and cocaine use. A subanalysis of the women with FM concentrations above the 95th percentile showed that the median DD concentration in this group was 0,44 mg/L and therefore not similarly high.FM were not affected by the analysed pregnancy complications but lower in women with chronic hypertension and cocaine use,both conditions associated with vasoconstriction,smaller placental size and placental abruption[41].Platelet activation through the 5HT pathway independent of thrombin formation is an underlying mechanism linked to both conditions [42] [43] [44].Decreased FM may also reflect impaired maternal-placental attachment[45] and at term fibrinogen predicts adverse maternal or neonatal outcomes in patients with placental abruption[46]

Several previous studies have reported elevated DD levels in women with established preeclampsia and one study showed elevated DDs in women with a history of pre-eclampsia outside of pregnancy [47,48,49]; hypercoagulability and increased fibrin deposition has been proposed as an underlying mechanism. Our finding, that DDs were not significantly altered at 11-13 weeks in women that subsequently develop preeclampsia, suggests that such activity may not precede the clinical onset of the disease and is certainly not present from the first trimester.

Conclusion:

By contributing to the establishment of a reference range for STA-Liatest FM and DD and identifying the maternal characteristics that affect these markers at 11-13 weeks we open the possibility of using fibrin linked markers as a diagnostic screening tool for VTE in pregnancy. Further, the traditional approach to thromboprophylaxis in pregnancy is to identify the high-risk group for VTE from maternal characteristics and medical history, including previous VTE, increased maternal age and BMI, assisted conception and preeclampsia[50,2]. An integrated first hospital visit at 11 to 13 weeks during which data from maternal characteristics and history is combined with findings of biophysical and biochemical tests can already define the patient-specific risk for a wide spectrum of pregnancy complications, including fetuses with aneuploidy, miscarriage and fetal death, preterm delivery, preeclampsia, gestational diabetes, fetal growth restriction and macrosomia [17,51]. A similar approach of early pregnancy risk assessment might have the potential to be applied to VTE risk assessment too. Future studies might investigate how risk scoring and prevention of VTE might be improved by this new approach to pregnancy care.

Details of ethics approval: Ethical approval was granted by the King's College Hospital Ethics Committee (02-03-033).

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Table 1. Maternal and pregnancy characteristics in the study population

Maternal and pregnancy characteristics	**Study population (n=2,614)**
Maternal characteristics	
Maternal age in years, median (IQR)	32.0 (28.1 to 35.5)
Maternal weight in Kg, median (IQR)	66.5 (59.3 to 77.0)
Maternal height in meters, median (IQR)	1.65 (1.60 to 1.69)
Gestational age in weeks, median (IQR)	12.7 (12.3 to 13.0)
Cigarette smoker, n (%)	197 (7.5)
Cocaine use, n (%)	15 (0.6)
Racial origin	
Caucasian, n (%)	1,612 (61.7)
Afro-Caribbean, n (%)	728 (27.9)
South Asian, n (%)	121 (4.6)
East Asian, n (%)	72 (2.8)
Mixed, n (%)	81 (3.1)
Conception	
Spontaneous, n (%)	2,518 (96.3)
Assisted, n (%)	96 (3.7)
Medical disorder	
Sickle cell trait, n (%)	90 (3.4)
Thyroid disorders, n (%)	47 (1.8)
Chronic hypertension, n (%)	54 (2.1)
Autoimmune disease, n (%)	4 (0.2)
Diabetes mellitus, n (%)	25 (1.0)
Family history	
History of preeclampsia in mother	94 (3.6)
Diabetes mellitus	371 (14.2)
Obstetric history	
Nulliparous, n (%)	1,223 (46.8)
Parous – previous preeclampsia, n (%)	102 (3.9)
Parous – previous gestational diabetes, n (%)	21 (0.8)
Current pregnancy complication	
Preeclampsia, n (%)	62 (2.4)
Gestational diabetes, n (%)	82 (3.1)

Fetal growth restriction, n (%)	281 (10.7)
Pregnancy outcome	
Gestation at delivery in weeks, median (IQR)	40.0 (39.0 to 40.9)
Birth weight in grams, median (IQR)	3390 (3080 to 3696)
Birth weight in percentile, median (IQR)	40.0 (39.0 to 40.9)

IQR=interquartile range

Table 2. Univariable and multivariable regression analysis to examine factors from maternal and pregnancy characteristics affecting the concentration of $\log_{10}$ transformed D-dimer

Variable	Univariable analysis		Multivariable analysis	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Maternal characteristics				
Maternal age in years - 32	-0.001 (-0.003 to 0.001)	0.303		
Maternal weight in Kg - 69	0.002 (0.002 to 0.003)	<0.0001	0.001 (0.001 to 0.002)	<0.0001
Maternal height in meters -1.64	0.029 (-0.134 to 0.192)	0.727		
Gestational age in weeks - 11	0.061 (0.043 to 0.079)	<0.0001	0.054 (0.036 to 0.071)	<0.0001
Cigarette smoker	-0.072 (-0.113 to -0.030)	0.001	-0.057 (-0.096 to -0.017)	0.005
Cocaine use	-0.108 (-0.251 to 0.036)	0.142		
Racial origin				
Caucasian (reference)	1.000			
Afro-Caribbean	0.157 (0.132 to 0.181)	<0.0001	0.124 (0.099 to 0.148)	<0.0001
South Asian	0.052 (0.001 to 0.103)	0.045	0.057 (0.007 to 0.107)	0.027
East Asian	0.042 (-0.024 to 0.109)	0.210		
Mixed	0.018 (-0.044 to 0.079)	0.575		
Conception				
Spontaneous (reference)	1.000			
Assisted conception	0.008 (-0.050 to 0.065)	0.796		
Medical disorders				
Sickle cell trait	0.243 (0.183 to 0.302)	<0.0001	0.187 (0.129 to 0.245)	<0.0001
Thyroid disorders	$8.9e^{-05}$ (-0.083 to 0.084)	0.998		
Chronic hypertension	0.085 (0.008 to 0.162)	0.030		
Autoimmune disease	0.271 (-0.050 to 0.591)	0.098		
Diabetes mellitus	-0.007 (-0.119 to 0.105)	0.902		
Family history				
History of preeclampsia in mother	-0.002 (-0.061 to 0.057)	0.944		
Diabetes mellitus	-0.003 (-0.027 to 0.022)	0.829		
Obstetric history				
Nulliparous	1.00			
Parous – previous preeclampsia	0.040 (-0.016 to 0.096)	0.165		
Parous – previous gestational diabetes	0.154 (0.032 to 0.275)	0.013		
Current pregnancy complication				
Preeclampsia	0.027 (-0.045 to 0.098)	0.466		
Gestational diabetes	0.024 (-0.038 to 0.087)	0.447		
Fetal growth restriction	-0.002 (-0.038 to 0.033)	0.899		

CI=confidence interval

Table 3. Univariable and multivariable regression regression analysis to examine factors from maternal and pregnancy characteristics affecting the concentration of $\log_{10}$ transformed fibrin monomer complex

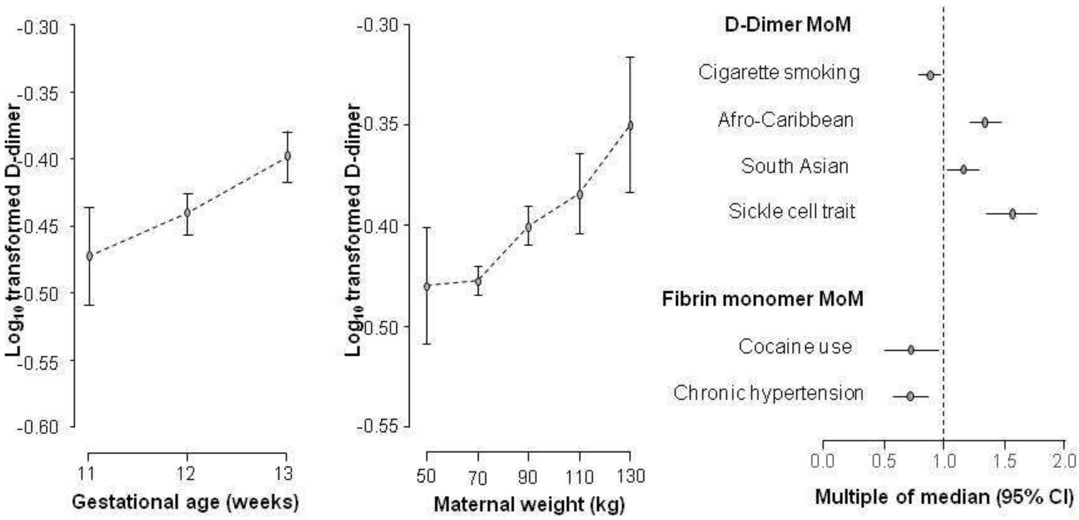
Variable	Univariable analysis		Multivariable analysis	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Maternal characteristics				
Maternal age in years - 32	-0.001 (-0.003 to 0.001)	0.339		
Maternal weight in Kg - 69	0.001 ($7.8e^{-05}$ to 0.002)	0.031	0.001 (2.3e-04 to 0.002)	0.012
Maternal height in meters -1.64	0.099 (-0.076 to 0.274)	0.266		
Gestational age in weeks - 11	0.007 (-0.013 to 0.027)	0.468		
Cigarette smoker	-0.023 (-0.066 to 0.020)	0.296		
Cocaine use	-0.145 (-0.279 to -0.011)	0.034	-0.147 (-0.280 to -0.014)	0.030
Racial origin				
Caucasian (reference)	1.000			
Afro-Caribbean	0.019 (-0.007 to 0.044)	0.149		
South Asian	0.011 (-0.042 to 0.064)	0.680		
East Asian	-0.010 (-0.081 to 0.061)	0.780		
Mixed	0.054 (-0.015 to 0.124)	0.124		
Conception				
Spontaneous (reference)	1.000			
Assisted conception	-0.030 (-0.086 to 0.026)	0.295		
Medical disorders				
Sickle cell trait	-0.026 (-0.088 to 0.035)	0.405		
Thyroid disorders	-0.036 (-0.127 to 0.054)	0.432		
Chronic hypertension	-0.136 (-0.224 to -0.048)	0.002	-0.150 (-0.238 to -0.062)	0.001
Autoimmune disease	-0.312 (-0.712 to 0.089)	0.127		
Diabetes mellitus	-0.136 (-0.288 to 0.016)	0.079		
Family history				
History of preeclampsia in mother	0.010 (-0.050 to 0.070)	0.740		
Diabetes mellitus	-0.005 (-0.036 to 0.027)	0.776		
Obstetric history				
Nulliparous	1.000			
Parous – previous preeclampsia	0.017 (-0.037 to 0.071)	0.540		
Parous – previous gestational diabetes	0.032 (-0.066 to 0.130)	0.519		
Current pregnancy complication				
Preeclampsia	-0.018 (-0.089 to 0.053)	0.616		
Gestational diabetes	0.022 (-0.043 to 0.087)	0.503		
Fetal growth restriction	-0.014 (-0.049 to 0.022)	0.447		

CI=confidence interval

Figure legends

Figure 1. Association between $\log_{10}$ D-dimer with gestational age (left), maternal weight (middle) and smoking, racial origin and medical history of sickle cell trait (right). Association between $\log_{10}$ fibrin monomer complexes with cocaine use and medical history of chronic hypertension (right).

Figure 2. Distribution of D-dimer (left) and fibrin monomer (right) multiple of the median values (MoM) with the median, 5^{th} and 95^{th} percentiles.



Log10 transformed D-dimer
-0.30
-0.35
-0.40
-0.45
-0.50
-0.55
-0.60
11
12
13
Gestational age (weeks)
Log10 transformed D-dimer
-0.30
-0.35
-0.40
-0.50
-0.55
50
70
90
110
130
Maternal weight (kg)
D-Dimer MoM
Cigarette smoking
Afro-Caribbean
South Asian
Sickle cell trait
Fibrin monomer MoM
Cocaine use
Chronic hypertension
0.0
0.5
1.0
1.5
2.0
Multiple of median (95% CI)

Figure 1

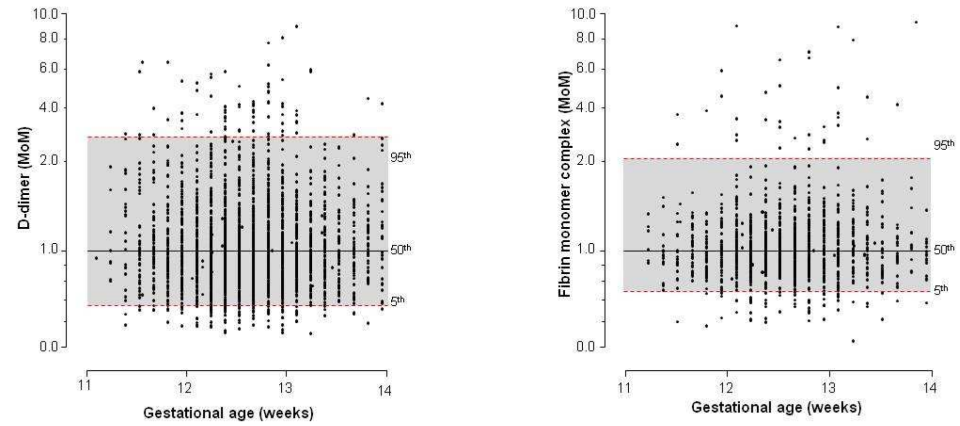

10.0
8.0
6.0
4.0
2.0
1.0
0.0
D-dimer (MoM)
95th
50th
5th
11
12
13
14
Gestational age (weeks)
10.0
8.0
6.0
4.0
2.0
1.0
0.0
Fibrin monomer complex (MoM)
95th
50th
5th
11
12
13
14
Gestational age (weeks)

Figure 2