OBSTETRICS

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

Karin B. Grossman, MD; Roopen Arya, BMBCh, MA, PhD, FRCP, FRCPath; Alberto B. Peixoto, MD; Ranjit Akolekar, MD; Ismini Staboulidou, MD; Kypros H. Nicolaides, MD

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 venous thromboembolism in pregnancy due to their different behavior.

OBJECTIVE: We sought to establish normal values of fibrin monomer complexes and D-dimer as a diagnostic tool for the exclusion of venous thromboembolism 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 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.

CONCLUSION: 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: D-dimer, fibrin monomer complex, pregnancy, screening, venous thromboembolism

Introduction

Pregnancy is a hypercoagulable state exemplifying Virchow triad of altered coagulation, stasis, and vascular damage.[1] Venous thromboembolism (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, 5-fold higher than in nonpregnant women.[4] The antenatal risk for VTE is highest in the first and third trimester[5] and in the United Kingdom the majority of antenatal deaths occurred in the first trimester.[6]

Outside of pregnancy, diagnostic pathways for deep vein thrombosis (DVT) and pulmonary embolism are based on a combination of clinical scoring systems, blood tests, and imaging using compression ultrasound, ventilation-perfusion scans, or computed tomography pulmonary angiography.[7] Both ventilation-perfusion scans and computed tomography pulmonary angiography 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 such as disseminated intravascular coagulation syndrome soluble complexes may be formed when FM join with fibrinogen and fibrin degradation products.[11]

DD 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 hemostatic 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 utilize 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

Cite this article as: Grossman KB, Arya R, Peixoto AB, et al. Maternal and pregnancy characteristics affect plasma fibrin monomer complexes and D-dimer reference ranges for venous thromboembolism in pregnancy. Am J Obstet Gynecol 2016;volume:x.ex-x.ex.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2016.05.013

FLA 5.4.0 DTD ■ YMOB11102_proof ■ 31 May 2016 ■ 3:41 pm ■ ce

as well as the pregnancy might also affect hemostatic 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 their routine hospital visit in the first-trimester of pregnancy at King's College Hospital, London, from October 2011 through 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, 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 0.109 mol/L trisodium citrate (BD Medical Systems, Franklin Lakes, NJ).

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 1 hour after collection. After centrifugation at 2200*g* for 15 minutes at 20°C the undiluted plasma was analyzed immediately in the STA-Compact coagulation analyzer (Diagnostica Stago, Asnières-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 nonpregnant population of <6 μg/mL for FM and <0.5 μg/mL (expressed in FEU) for DD. The intraassay and interassay coefficients of variation were 5.55% and 5.7% for FM and 8.4% and 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 birthweight 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 gestational diabetes mellitus 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. A statistical software package (SPSS 21; IBM Corp, Armonk, NY) was used for data analyses.

Results

Study population

During the study period we examined 2870 singleton pregnancies with a live fetus at 11-13 weeks, but 256 were excluded: 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 2614 pregnancies are shown in Table 1. In keeping with the South East London population, 61.7% women were Caucasian, 27.9% Afro-Caribbean, and 10.5% of other ethnic origins. DD was measured in all cases but FM was measured in only 1286 of the cases due to reagent availability.

FM complex

The median and 5th and 95th percentiles of the measured FM concentration were 4.3, 2.16, and 8.84 mg/L, respectively. In 282 (21.9%) of the 1286 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 (0.96−1.00), 0.50 (0.45−0.53), 0.61 (0.57−0.64), 1.65 (1.58−1.74), and 2.01 (1.88−2.17), respectively (Figure 2).

FLA 5.4.0 DTD ■ YMOB11102_proof ■ 31 May 2016 ■ 3:41 pm ■ ce

D-dimer

The median and 5th and 95th percentiles of the measured DD concentration were 0.31, 0.11, and 1.16 mg/L, respectively. In 736 (28.2%) of the 2614 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 (0.96–1.00), 0.37 (0.34–0.39), 0.47 (0.46–0.49), 2.23 (2.09–2.34), and 2.93 (2.73–3.18), 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 nonpregnant 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. DD 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 11-13 weeks' gestation were not

TABLE 1
Maternal and pregnancy characteristics in study population

Maternal and pregnancy characteristics	Study population, n = 2614
Maternal characteristics	
Maternal age, y, median (IQR)	32.0 (28.1–35.5)
Maternal weight, kg, median (IQR)	66.5 (59.3–77.0)
Maternal height, m, median (IQR)	1.65 (1.60–1.69)
Gestational age, wk, median (IQR)	12.7 (12.3–13.0)
Cigarette smoker, n (%)	197 (7.5)
Cocaine use, n (%)	15 (0.6)
Racial origin, n (%)	
Caucasian	1612 (61.7)
Afro-Caribbean	728 (27.9)
South Asian	121 (4.6)
East Asian	72 (2.8)
Mixed	81 (3.1)
Conception, n (%)	
Spontaneous	2518 (96.3)
Assisted	96 (3.7)
Medical disorder, n (%)	
Sickle cell trait	90 (3.4)
Thyroid disorders	47 (1.8)
Chronic hypertension	54 (2.1)
Autoimmune disease	4 (0.2)
Diabetes mellitus	25 (1.0)
Family history	
History of preeclampsia in mother	94 (3.6)
Diabetes mellitus	371 (14.2)
Obstetric history, n (%)	
Nulliparous	1223 (46.8)
Parous—previous preeclampsia	102 (3.9)
Parous—previous gestational diabetes	21 (0.8)
Current pregnancy complication, n (%)	
Preeclampsia	62 (2.4)
Gestational diabetes	82 (3.1)
Fetal growth restriction	281 (10.7)
Pregnancy outcome, median (IQR)	
Gestation at delivery, wk	40.0 (39.0–40.9)
Birthweight, g	3390 (3080–3696)
Birthweight percentile	40.0 (39.0–40.9)

IQR, interquartile range.

Grossman et al. Characterizing plasma fibrin monomer complexes and D-dimer in pregnancy. Am J Obstet Gynecol 2016.

FLA 5.4.0 DTD ■ YMOB11102_proof ■ 31 May 2016 ■ 3:41 pm ■ ce

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

	Univariable analysis		Multivariable analysis	
Variable	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Maternal characteristics				
Maternal age, y, 32	−0.001 (−0.003 to 0.001)	.303		
Maternal weight, kg, 69	0.002 (0.002 to 0.003)	<.0001	0.001 (0.001 to 0.002)	<.0001
Maternal height, m, 1.64	0.029 (−0.134 to 0.192)	.727		
Gestational age, wk, 11	0.061 (0.043 to 0.079)	<.0001	0.054 (0.036 to 0.071)	<.0001
Cigarette smoker	−0.072 (−0.113 to −0.030)	.001	−0.057 (−0.096 to −0.017)	.005
Cocaine use	−0.108 (−0.251 to 0.036)	.142		
Racial origin				
Caucasian (reference)	1.000			
Afro-Caribbean	0.157 (0.132 to 0.181)	<.0001	0.124 (0.099 to 0.148)	<.0001
South Asian	0.052 (0.001 to 0.103)	.045	0.057 (0.007 to 0.107)	.027
East Asian	0.042 (−0.024 to 0.109)	.210		
Mixed	0.018 (−0.044 to 0.079)	.575		
Conception				
Spontaneous (reference)	1.000			
Assisted conception	0.008 (−0.050 to 0.065)	.796		
Medical disorders				
Sickle cell trait	0.243 (0.183 to 0.302)	<.0001	0.187 (0.129 to 0.245)	<.0001
Thyroid disorders	$8.9e^{-05}$ (−0.083 to 0.084)	.998		
Chronic hypertension	0.085 (0.008 to 0.162)	.030		
Autoimmune disease	0.271 (−0.050 to 0.591)	.098		
Diabetes mellitus	−0.007 (−0.119 to 0.105)	.902		
Family history				
History of preeclampsia in mother	−0.002 (−0.061 to 0.057)	.944		
Diabetes mellitus	−0.003 (−0.027 to 0.022)	.829		
Obstetric history				
Nulliparous	1.00			
Parous—previous preeclampsia	0.040 (−0.016 to 0.096)	.165		
Parous—previous gestational diabetes	0.154 (0.032 to 0.275)	.013		
Current pregnancy complication				
Preeclampsia	0.027 (−0.045 to 0.098)	.466		
Gestational diabetes	0.024 (−0.038 to 0.087)	.447		
Fetal growth restriction	−0.002 (−0.038 to 0.033)	.899		

CI, confidence interval.

Grossman et al. Characterizing plasma fibrin monomer complexes and D-dimer in pregnancy. Am J Obstet Gynecol 2016.

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 that is widely used for screening for pregnancy complications; secondly, measurement of maternal

FLA 5.4.0 DTD ■ YMOB11102_proof ■ 31 May 2016 ■ 3:41 pm ■ ce

TABLE 3
Univariable and multivariable regression analysis to examine factors from maternal and pregnancy characteristics affecting concentration of log_{10}-transformed fibrin monomer complex

	Univariable analysis		Multivariable analysis	
Variable	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Maternal characteristics				
Maternal age, y, 32	−0.001 (−0.003 to 0.001)	.339		
Maternal weight, kg, 69	0.001 (7.8e^{-05} to 0.002)	.031	0.001 (2.3e−04 to 0.002)	.012
Maternal height, m, 1.64	0.099 (−0.076 to 0.274)	.266		
Gestational age, wk, 11	0.007 (−0.013 to 0.027)	.468		
Cigarette smoker	−0.023 (−0.066 to 0.020)	.296		
Cocaine use	−0.145 (−0.279 to −0.011)	.034	−0.147 (−0.280 to −0.014)	.030
Racial origin				
Caucasian (reference)	1.000			
Afro-Caribbean	0.019 (−0.007 to 0.044)	.149		
South Asian	0.011 (−0.042 to 0.064)	.680		
East Asian	−0.010 (−0.081 to 0.061)	.780		
Mixed	0.054 (−0.015 to 0.124)	.124		
Conception				
Spontaneous (reference)	1.000			
Assisted conception	−0.030 (−0.086 to 0.026)	.295		
Medical disorders				
Sickle cell trait	−0.026 (−0.088 to 0.035)	.405		
Thyroid disorders	−0.036 (−0.127 to 0.054)	.432		
Chronic hypertension	−0.136 (−0.224 to −0.048)	.002	−0.150 (−0.238 to −0.062)	.001
Autoimmune disease	−0.312 (−0.712 to 0.089)	.127		
Diabetes mellitus	−0.136 (−0.288 to 0.016)	.079		
Family history				
History of preeclampsia in mother	0.010 (−0.050 to 0.070)	.740		
Diabetes mellitus	−0.005 (−0.036 to 0.027)	.776		
Obstetric history				
Nulliparous	1.000			
Parous—previous preeclampsia	0.017 (−0.037 to 0.071)	.540		
Parous—previous gestational diabetes	0.032 (−0.066 to 0.130)	.519		
Current pregnancy complication				
Preeclampsia	−0.018 (−0.089 to 0.053)	.616		
Gestational diabetes	0.022 (−0.043 to 0.087)	.503		
Fetal growth restriction	−0.014 (−0.049 to 0.022)	.447		

CI, confidence interval.

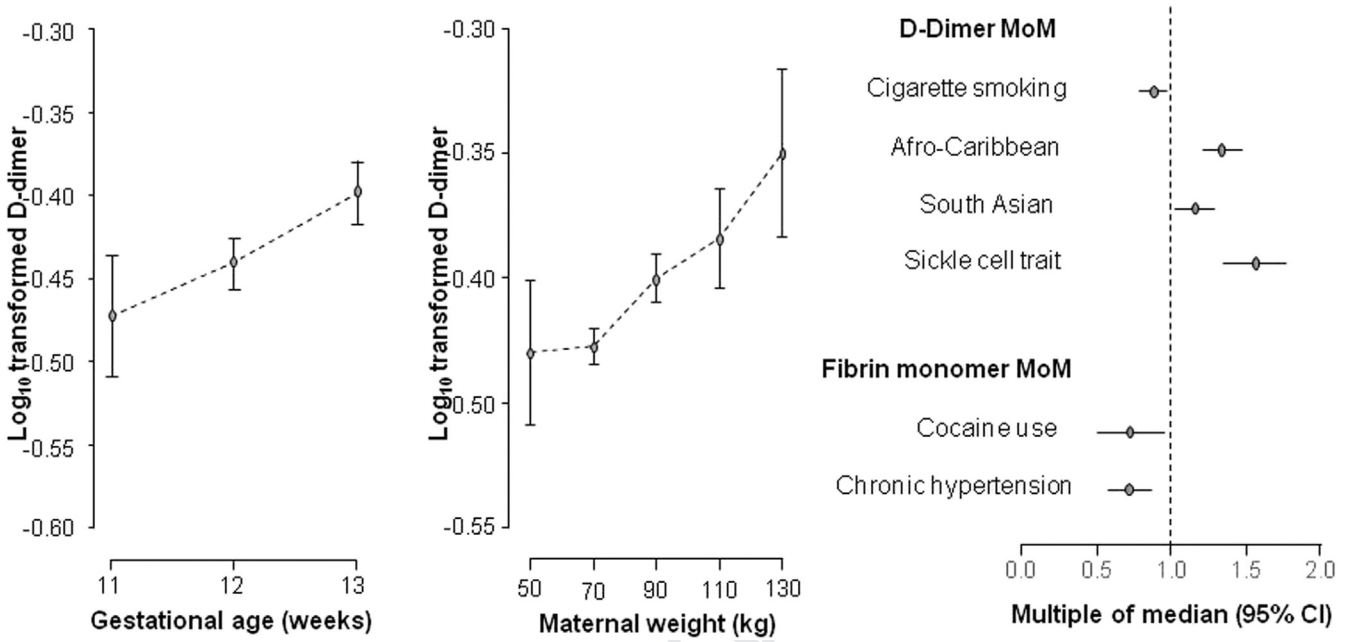
Grossman et al. Characterizing plasma fibrin monomer complexes and D-dimer in pregnancy. Am J Obstet Gynecol 2016.

serum concentration of fibrin-linked markers that have been shown to be altered in VTE; and thirdly, expression of the values as MoM 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

FLA 5.4.0 DTD ■ YMOB11102_proof ■ 31 May 2016 ■ 3:41 pm ■ ce

FIGURE 1



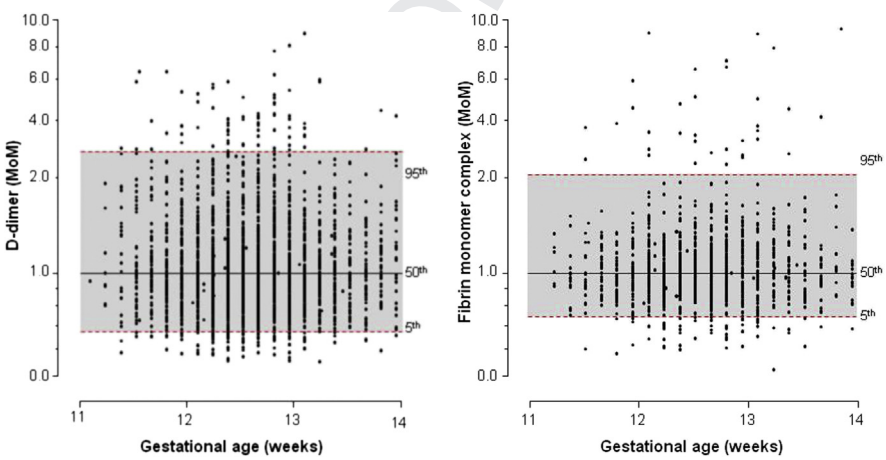
Association between $\log_{10}$ D-dimer with gestational age (left); maternal weight (middle); and smoking, racial origin, and medical history of sickle cell trait (right). Association between $\log_{10}$ fibrin monomer complexes with cocaine use and medical history of chronic hypertension (right).

CI, confidence interval; *MoM*, multiple of median.

Grossman et al. Characterizing plasma fibrin monomer complexes and D-dimer in pregnancy. Am J Obstet Gynecol 2016.

have been avoided by conducting compression ultrasound 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 depend on the instrument type; this article only describes the relevant values and ranges pertaining to the STA-Liatest FM and DD (Diagnostica Stago) as performed by our laboratory.

FIGURE 2



Distribution of D-dimer (left) and fibrin monomer (right) multiple of median values (MoM) with median, and 5th and 95th percentiles.

Grossman et al. Characterizing plasma fibrin monomer complexes and D-dimer in pregnancy. Am J Obstet Gynecol 2016.

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 et al[13] and Joly et al[22] also used the STA-Liatest FM (Diagnostica Stago) and the FM concentrations were comparable to our data.

FLA 5.4.0 DTD ■ YMOB11102_proof ■ 31 May 2016 ■ 3:41 pm ■ ce

In our study using the STA-Liatest assays (Diagnostica Stago), the median DD at 11-13 weeks' gestation was 0.31 mg/L. Several previous studies in small numbers of cases ranging from 5-350 normal pregnancies at <16 weeks' gestation reported that the median DD varied between 0.1-0.8 mg/L.[12,13,22-34] For the STA-Liatest assay (Diagnostica Stago) we found in the literature first-trimester concentrations of 0.3,[21] 0.49,[28] and 0.2 mg/L in a Chinese population[26]; 0.48 mg/L in women without DVT; and 5.4 mg/L in women 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 4364 mainly nonpregnant 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 healthy 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 body mass index, sickle cell carriers, and those of African and South Asian origin have elevated DD MoM and smokers have decreased DD MoM. The utility of this finding in improving diagnostic performance of DD has to be evaluated in future studies including pregnant women with confirmed VTE.

Currently, 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 >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 analyzed 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.[42-44] 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 1 study showed elevated DD in women with a history of preeclampsia outside of pregnancy[47-49]; hypercoagulability and increased fibrin deposition were proposed as an underlying mechanism. Our finding that DD were not significantly altered at 11-13 weeks in women who 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 (Diagnostica Stago) 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 body mass index, assisted conception, and preeclampsia.[2,50] An integrated first hospital visit at 11-13 weeks during which data from maternal characteristics and history are 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. Future studies might investigate how risk scoring and prevention of VTE might be improved by this new approach to pregnancy care. ■

References

1. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol 2008;143:180-90.

2. The American College of Obstetricians and Gynecologists. Thromboembolism in pregnancy. Practice bulletin no. 123. Obstet Gynecol 2011;118:718-29.

3. Schutte JM, Steegers EA, Schuitemaker NWE, et al; Netherlands Maternal Mortality Committee. Rise in maternal mortality in The Netherlands. BJOG 2010;117:399-406.

4. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ III. Trends in the incidence of venous thromboembolism during. Ann Intern Med 2005;143:697-706.

5. Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium—a register-based case-control study. Am J Obstet Gynecol 2008;198:1-7.

6. Centre for Maternal and Child Enquiries (CMACE). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG 2011;118(Suppl):1-203.

7. Arya R. How I manage venous thromboembolism in pregnancy. Br J Haematol 2011;153:698-708.

8. Cutts BA, Dasgupta D, Hunt BJ. New directions in the diagnosis and treatment of pulmonary embolism in pregnancy. Am J Obstet Gynecol 2013;208:102-8.

9. Guimicheva B, Czuprynska J, Arya R. The prevention of pregnancy-related venous thromboembolism. Br J Haematol 2015;2008:163-74.

10. Kearon C, Ginsberg JS, Douketis J, et al. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. Ann Intern Med 2005;142:490-6.

11. Nakahara K, Kazahaya Y, Shintani Y, Yamazumi K, Eguchi Y. Measurement of soluble fibrin monomer-fibrinogen complex in plasmas derived from patients with various underlying clinical situations. Thromb Haemost 2003;89:832-6.

12. Murphy N, Broadhurst DI, Khashan AS, Gilligan O, Kenny LC, O'Donoghue K. Gestation-specific D-dimer reference ranges: a cross-sectional study. BJOG 2015;122:395-400.

13. Onishi H, Kaniyu K, Iwashita M, Tanaka A, Watanabe T. Fibrin monomer complex in normal pregnant women: a potential thrombotic marker in pregnancy. Ann Clin Biochem 2007;44:449.

14. Kawamura M, Fukuda N, Suzuki A, et al. Use of fibrin monomer complex for screening for venous thromboembolism in the late pregnancy and post-partum period. J Obstet Gynaecol Res 2014;40:700-4.

15. Schutgens REG, Haas FJLM, Agterof MJ, Vos M, Biesma DH. The role of fibrin monomers in optimizing the diagnostic work-up of deep vein thrombosis. Thromb Haemost 2007;97:807-13.

16. Szecsi PB, Jørgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Hemostatic reference intervals in pregnancy. Thromb Haemost 2010;103:718-27.

17. Nicolaides KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. Prenat Diagn 2011;31:3-6.

18. Poon LCY, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. Fetal Diagn Ther 2012;32:156-65.

19. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX-XIV.

20. WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Available at: http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf↘nhttp://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Definition+and+diagnosis+of+diabetes+mellitus+and+intermediate+hyperglycemia:+report+of+a+WHO/IDF+consultation#0. Q7

21. Karlsson O, Sporrong T, Hillarp A, Jeppsson A, Hellgren M. Prospective longitudinal study of thromboelastography and standard hemostatic laboratory tests in healthy women during normal pregnancy. Anesth Analg 2012;115:890-8.

22. Joly B, Barbay V, Borg J-Y, Le Cam-Duchez V. Comparison of markers of coagulation activation and thrombin generation test in uncomplicated pregnancies. Thromb Res 2013;132:386-91.

23. Bergmann F, Pingel N, Czwalinna A, Koch M. D-dimer in normal pregnancy: determination of reference values for three commercially available assays. Clin Chem Lab Med 2014;52:257-9.

24. Kawaguchi S, Yamada T, Takeda M, et al. Changes in D-dimer levels in pregnant women according to gestational week. Pregnancy Hypertens 2013;3:172-7.

25. Yang J-I, Kim H-S, Chang K-H, et al. Difference in the D-dimer rise between women with singleton and multifetal pregnancies. Thromb Res 2013;131:493-6.

26. Wang M, Lu S, Li S, Shen F. Reference intervals of D-dimer during the pregnancy and puerperium period on the STA-R evolution coagulation analyzer. Clin Chim Acta 2013;425:176-80.

27. Jeremiah ZA, Adias TC, Opiah M, George SP, Mgbere O, Essien EJ. Elevation in D-dimer concentrations is positively correlated with gestation in normal uncomplicated pregnancy. Int J Womens Health 2012;4:437-43.

28. Hale SA, Sobel B, Benvenuto A, Schonberg A, Badger GJ, Bernstein IM. Coagulation and fibrinolytic system protein profiles in women with normal pregnancies and pregnancies complicated by hypertension. Pregnancy Hypertens 2012;2:152-7.

29. Kovac M, Mikovic Z, Rakicevic L, Srzentic S, Mandic V. The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol 2010;148:27-30.

30. Chan W-S, Lee AY, Spencer FA, et al. D-dimer testing in pregnant patients: towards determining the next "level" in the diagnosis of deep vein thrombosis. J Thromb Haemost 2010;8:1004-11.

31. Nishii A, Noda Y, Nemoto R, et al. Evaluation of D-dimer during pregnancy. J Obstet Gynaecol Res 2009;35:689-93.

32. Kline JA, Williams GW, Hernandez-Nino J. D-dimer concentrations in normal pregnancy: new diagnostic thresholds are needed. Clin Chem 2005;51:825-9.

33. Kjellberg U, van Rooijen M, Bremme K, Hellgren M. Increased activation of blood coagulation in pregnant women with the factor V Leiden mutation. Thromb Res 2014;134:837-45.

34. Uchikova EH, Ledjev II, Szecsi PB, et al. Hemostatic changes in pregnancy. Thromb Res 2004;114:409-14.

35. Kabrhel C, Courtney DM, Camargo CA, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. Acad Emerg Med 2010;17:589-97.

36. Larsen TB, Sørensen HT, Gislum M, Johnsen SP. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. Thromb Res 2007;120:505-9.

37. Leon-Garcia SM, Roeder HA, Nelson KK, et al. Maternal obesity and sex-specific differences in placental pathology. Placenta 2016;38:33-40.

38. Roberts LN, Patel RK, Chitongo P, Bonner L, Arya R. African-Caribbean ethnicity is associated with a hypercoagulable state as measured by thrombin generation. Blood Coagul Fibrinolysis 2013;24:40-9.

39. Patel R, Ford E, Thumpston J, Arya R. Risk factors for venous thrombosis in the black population. Thromb Haemost 2003;90:835-8.

40. Westerman MP, Green D, Beaman K, et al. Coagulation changes in individuals with sickle cell trait. Am J Hematol 2002;69:89-94.

41. Ortigosa S, Friguls B, Joya X, et al. Feto-placental morphological effects of prenatal exposure to drugs of abuse. Reprod Toxicol 2012;34:73-9.

42. Watts SW. 5-HT in systemic hypertension: foe, friend or fantasy? Clin Sci (Lond) 2005;108:399-412.

43. Ziu E, Hadden C, Li Y, et al. Effect of serotonin on platelet function in cocaine exposed blood. Sci Rep 2014;4:5945.

44. Ganapathy V. Drugs of abuse and human placenta. Life Sci 2011;88:926-30.

45. Iwaki T, Sandoval-Cooper MJ, Paiva M, Kobayashi T, Ploplis VA, Castellino FJ. Fibrinogen stabilizes placental-maternal attachment during embryonic development in the mouse. Am J Pathol 2002;160:1021-34.

46. Wang L, Matsunaga S, Mikami Y, Takai Y, Terui K, Seki H. Pre-delivery fibrinogen predicts adverse maternal or neonatal outcomes in patients with placental abruption. J Obstet Gynaecol Res 2016. Q8

47. Portelinha A, So A, Belo L, et al. Hemostatic factors in women with history of preeclampsia. Thromb Res 2009;124:52-6.

48. Pinheiro Mde B, Junqueira DRG, Coelho FF, et al. D-dimer in preeclampsia: systematic review and meta-analysis. Clin Chim Acta 2012;414:166-70.

49. Pinheiro MB, Carvalho MG, Martins-Filho OA, et al. Severe preeclampsia: are hemostatic and inflammatory parameters associated? Clin Chim Acta 2014;427:65-70.

50. Royal College of Obstetricians and Gynecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green-top Guide I 2015;(37a). Q9

51. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Am J Obstet Gynecol 2015.

Author and article information

From Harris Birthright Research Center for Fetal Medicine (Drs Grossman, Peixoto, Akolekar, and Nicolaides) and King's Thrombosis Center, Department of Hematological Medicine (Dr Arya), King's College Hospital Foundation Trust, London, United Kingdom; and Department of Obstetrics and Gynecology, Medical School of Hanover, Hannover, Germany (Dr Staboulidou).

Received Jan. 26, 2016; revised April 28, 2016; accepted May 4, 2016.

This study was supported by a grant from the Fetal Medicine Foundation (charity no. 1037116).

The authors report no conflict of interest.

Presented at the International Society on Thrombosis and Hemostasis 2015 Congress, Toronto, Ontario, Canada, June 20-25, 2015.

Corresponding author: Roopen Arya, BMBCh, MA, PhD, FRCP, FRCPath. roopen.arya@nhs.net