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Blood pressure augmentation and maternal circulating concentrations of angiogenic factors at delivery in preeclamptic and uncomplicated pregnancies

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Abstract

Objective—The objective of the study was to determine whether blood pressure increases are associated with maternal angiogenic factors in uncomplicated and preeclamptic pregnancies.

Study Design—Associations of blood pressure increases from mid- to late pregnancy with maternal serum concentrations of soluble fms-like tyrosine kinase receptor (sFlt1), soluble endoglin (sEng), and placental growth factor (PIGF) at delivery were analyzed in 43 uncomplicated and 44 preeclamptic pregnancies.

Results—In uncomplicated pregnancies, increases in diastolic and mean arterial pressure were inversely associated with PIGF at delivery and positively associated with sEng and sFlt1/PIGF ratio. There were no significant associations between blood pressure increases and angiogenic factor concentrations in preeclampsia.

Conclusion—These data suggest that angiogenic factors are involved in blood pressure modulation in normotensive pregnancy and are consistent with the hypothesis that angiogenic balance plays a role in maternal breast cancer risk reduction associated with mid- to late blood pressure increases in uncomplicated pregnancies.

Keywords

angiogenic factors; blood pressure; breast cancer; preeclampsia; pregnancy

Preeclampsia is a pregnancy complication characterized by the development of hypertension and proteinuria in the latter half of pregnancy.¹ Central to its pathogenesis is shallow placentation with abnormal maternal-placental vascular development.² Placental release of endothelial deranging factors to the maternal circulation ensues.

Among these placenta-derived factors are the antiangiogenic proteins soluble fms-like tyrosine kinase receptor (sFlt1)^{3,4} and soluble endoglin (sEng).^{5,6} sFlt1 binds and reduces free circulating levels of the proangiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). sFlt thereby blunts the beneficial effects of these proangiogenic factors on maternal endothelium, with consequent maternal hypertension and proteinuria.⁷

Excess sEng blocks proangiogenic effects of transforming growth factor- β . In vitro studies indicate that the soluble receptors sFlt1 and sEng may act in concert to disrupt endothelial integrity, probably by opposing nitric oxide-dependent vasodilation and vasomotor effects.⁵

Alterations in circulating maternal angiogenic factors (sFlt1, PlGF, and sEng but not VEGF) precede clinical presentation of preeclampsia^{4,6,8} and are associated with disease severity and onset of symptoms.^{4,6,8-10} Concentrations of circulating maternal antiangiogenic factors are clearly lower in uncomplicated pregnancy, but it is unknown whether they correlate with blood pressure increases that are below the diagnostic criteria for pregnancy induced hypertension or preeclampsia. The angiogenic profile could be important for understanding blood pressure increases in pregnancy and the development of preeclampsia.

In addition, the angiogenic profile of preeclamptic and uncomplicated pregnancies may provide insight into the underlying mechanisms involved in the association of preeclampsia with subsequent risk of chronic diseases. For example, long-term risk of cardiovascular disease is elevated^{11,12} among women with a history of pregnancy hypertension and breast cancer risk is reduced in the women¹³⁻¹⁵ and in their female offspring.^{16,17} Furthermore, a breast cancer risk reduction has also been observed with elevated mean arterial pressure¹⁸ and systolic blood pressure increases from mid to late pregnancy in otherwise normotensive pregnancies.¹⁵

The biological mechanisms explaining these associations are unknown but could involve the relatively antiangiogenic profile found in preeclampsia. Angiogenesis, defined as formation of new vessels from preexisting ones, is critical for tumor growth and metastasis.¹⁹ It is not known whether blood pressure augmentation in otherwise normotensive pregnancy is associated with alterations in circulating angiogenic profile. We therefore assessed the association of serum concentrations at delivery of antiangiogenic-associated factors sFlt1 and sEng as well as the proangiogenic factor, PlGF, with blood pressure augmentations in uncomplicated and preeclamptic pregnancies to determine whether the findings were consistent with our hypothesis.

Materials and Methods

The data derive from an ongoing biobank collection of patient samples from preeclamptic and uncomplicated pregnancies at Ullevål University Hospital, Oslo, Norway. All women with singleton pregnancies who were scheduled for cesarean section during the study physicians' usual work schedule were recruited. Cesarean section was indicated in the patients with preeclampsia because of disease progression and/or unfavorable cervical ripening. The main indications for cesarean section in the uncomplicated pregnancies were breech presentation (55%), patient's preference/no medical indication (38%), and previous cesarean and mechanical disproportion (7%). Women with preexisting chronic hypertension, renal disease or diabetes were excluded.

All patients were fasting and none were in active labor or had ruptured membranes or clinical signs of infection at the time of delivery and blood sampling. A total of 43 women with uncomplicated pregnancies (in whom blood pressure never reached 140/90 mm Hg and proteinuria did not develop) and 44 women with preeclamptic pregnancies were included in the present analysis. Preeclampsia was defined as an increase in blood pressure after 20 weeks' gestation to 140/90 mm Hg or greater on 2 or more occasions 6 hours apart in a previously normotensive woman, combined with proteinuria. Proteinuria was defined as protein dip stick of 1 + or greater on 2 or more midstream urine samples 6 hours apart or a 24-hour urine excretion of protein of 0.3 g or more, in the absence of urinary infection.

The study protocol was approved by the Regional Committee of Medical Research Ethics in Eastern Norway, and informed, written consent was obtained from each participant.

Maternal fasting blood samples were obtained before cesarean section, and processed as described previously.⁹ Serum concentrations of sEng, sFlt1, and PlGF were determined by enzyme-linked immunosorbent assay, performed in duplicates according to the manufacturer's instructions (R&D Systems, Minneapolis, MN). Median concentrations of sEng, sFlt1, VEGF, and PlGF in maternal and umbilical cord serum and amniotic fluid have been published previously from this cohort.^{9,10} The PlGF assay detects free, not bound, forms of the growth factor. The lowest standard concentrations of the PlGF, sEng, and sFlt1 kits are 15.6 pg/mL, 0.156 ng/mL, and 31.2 pg/mL, respectively. The inter- and intraassay coefficients of variation were 11.2% and 5.4% for the PlGF assay, 7.4% and 3.2% for the sFlt1 assay, and 6.7% and 3.2% for the sEng assay.

Systolic (SBP) and diastolic blood pressure (DBP) were available from individual national pregnancy charts, which are standardized and completed at each visit to the general practitioner, midwife, and/or gynecologist during pregnancy in Norway. The number of blood pressure measurements during the pregnancy ranged from 4 to 13 (median 9) for women with uncomplicated pregnancies, and from 2 to 12 (median 6) for those with preeclamptic pregnancies.

Detailed clinical data were abstracted from hospital charts and by interviewing each patient prior to cesarean delivery. Mean arterial pressure (MAP) was calculated as $DBP + 1/3 (SBP - DBP)$. Mean SBP, DBP, and MAP were calculated for the first (week 4^o days through week 11⁶ days), second (weeks 12^o to 27⁶) and third (28^o to 42⁶) trimesters. We determined blood pressure change by subtracting mean DBP (or SBP or MAP) in the second trimester from the corresponding mean blood pressure value in the third trimester.

The derived blood pressure variables for change between trimesters 2 and 3 were categorized by dichotomizing at the median using the individual distributions in the uncomplicated and preeclamptic pregnancies. Ten women with preeclampsia were delivered in the second trimester; therefore, 77 of the 87 pregnancies had clinical data available for both trimesters 2 and 3. To include the participants who delivered in the second trimester in the analysis of second- to third-trimester blood pressure change, we created another variable by subtracting mean blood pressure up to gestational week 20 from the highest recorded blood pressure value after 20 weeks.

Spearman rank correlations were calculated among continuous values for angiogenic factors and blood pressure measurements. Linear regression models with the logarithm-transformed angiogenic factors as dependent variables included gestational length (continuous variable) and blood pressure categories as independent variables. Geometric means based on these models (exponent of the logarithmic means) are presented by dichotomous blood pressure categories. We presented the angiogenic factor concentration data by categories because this type of analysis uses fewer assumptions. Because the results could be sensitive to the choice of cut point, we repeated the analyses using blood pressure as a continuous, independent variable in the linear regression models. Our interpretation of the data was unchanged. Statistical significance was defined as $P < .05$.

Results

Clinical characteristics of the uncomplicated and preeclamptic pregnancies are shown in Table 1. All 3 blood pressure measurements (DBP, SBP, and MAP) increased from mid to late pregnancy in the majority of the pregnancies (57 of 77). In uncomplicated pregnancies, blood pressure changes from mid to late pregnancy, in particular for DBP and MAP, were inversely correlated with maternal PlGF concentrations at delivery and positively correlated with sEng and the ratios of sFlt1/PlGF and (sFlt1 plus sEng)/PlGF. Positive correlations between blood

pressure changes and sFlt1 in these pregnancies did not reach statistical significance (Table 2). In preeclamptic pregnancies, mean second-trimester blood pressure measurements were inversely correlated with PlGF and positively correlated with the 2 ratios (sFlt1/PlGF and [sFlt1 plus sEng]/PlGF).

A similar pattern of correlations with third-trimester blood pressure measures in preeclamptic pregnancies was not statistically significant. Consistent with findings in the uncomplicated pregnancies, MAP increase in preeclamptic pregnancies was inversely correlated with PlGF and positively correlated with both ratios and sEng, although the correlations were weaker and none reached statistical significance. Scatter plots of second- to third-trimester increase in MAP and serum concentrations of angiogenic factors are presented for uncomplicated and preeclamptic pregnancies in the Figure.

Table 3 presents geometric means for the angiogenic factor concentrations by category of blood pressure change with adjustment for gestational length among uncomplicated and preeclamptic pregnancies, respectively. In uncomplicated pregnancies (Table 3, A), the inverse associations between DBP and MAP increases between the second and third trimesters and PlGF remained significant. The positive associations of DBP and MAP increases with sEng and the ratios of sFlt1/PlGF and (sFlt1 plus sEng)/PlGF also remained significant, whereas the positive associations of DBP ($P = .05$) and MAP ($P = .06$) with sFlt1 were of borderline significance. In addition, second-trimester mean DBP was inversely associated with sFlt1 and the 2 antiangiogenic ratios (sFlt1/PlGF and [sFlt1 plus sEng]/PlGF) and positively associated with PlGF. There were no statistically significant associations between any of the blood pressure measurements and angiogenic factors in the preeclampsia group (Table 3, B).

Compared with those based on blood pressure increases from the second to the third trimester, the pattern of results was similar but attenuated when assessed in relation to increase in blood pressure from the first half of pregnancy to the highest recorded blood pressure after that time in uncomplicated pregnancies (Table 4). Only the inverse association between DBP increases and PlGF concentrations at term, the positive associations between DBP increases and the angiogenic ratios (sFlt1/PlGF and [sFlt1 plus sEng]/PlGF), and the positive association of MAP increases and sEng were statistically significant.

Whereas there were no statistically significant associations between the angiogenic factors and blood pressure increases from the second to the third trimester in the preeclamptic pregnancies (Table 3, B), several associations became stronger when assessed in relation to blood pressure increase from up to 20 weeks' gestation to the highest recorded blood pressure after 20 weeks (Table 4). However, only the inverse associations between DBP and MAP increases and PlGF concentrations became statistically significant.

Among the preeclamptic women, 12 were taking antihypertensive medication following hospital admission. Because this could obscure an association between blood pressure change and the angiogenic factors, we repeated the analyses excluding these individuals. The results showed stronger associations between DBP and MAP increases from the second to third trimesters and angiogenic factors in the same pattern demonstrated in the uncomplicated pregnancies, but none of the associations reached statistical significance. The inverse associations of increases in DBP and MAP from up to 20 weeks' gestation to the highest value after 20 weeks with PlGF also became stronger (data not shown).

Comment

Our findings show that maternal circulating angiogenic factors measured at delivery reflect maternal blood pressure increases from mid- to late pregnancy in uncomplicated pregnancies. We observed a statistically significant positive association of second- to third-trimester blood

pressure increases with maternal serum concentrations of the antiangiogenic factor sEng and an inverse association with the proangiogenic factor PlGF in otherwise healthy pregnancies. Furthermore, the antiangiogenic ratio (ie, relative proportion of concentrations of maternal anti- to proangiogenic factors) at delivery (sFlt1/PlGF and [sFlt1 + sEng]/PlGF) was significantly elevated in uncomplicated pregnancies among women with the greatest blood pressure increases from mid- to late pregnancy.

Our study had a few limitations. The small sample size limited the extent we could explore the associations of blood pressure change and angiogenic balance in subgroups, and random measurement error in the blood pressure values may have attenuated the magnitude of our findings. The patients recruited for the biobank collection were only those scheduled for cesarean section when the study physicians were in the clinic. Thus, some women with preeclamptic and normal pregnancies who delivered at the hospital were not included in the present study. We are not aware, however, of any systematic bias that the exclusion of these patients would have introduced into the study. The subgroup of patients with preeclampsia included in this study tended to have more severe disease than the overall group of preeclamptics delivered at this hospital because they were included only if a cesarean section was clinically indicated.

Second-trimester DBP was inversely associated with sFlt1 and positively associated with PlGF in uncomplicated pregnancies in our data. This result would appear contrary to the findings for change in second- to third-trimester DBP, which showed a positive association with sFlt1 and an inverse association with PlGF. The likely explanation for this is a strong inverse correlation between second-trimester DBP and change in DBP from second to third trimester ($r = -0.57$) because of the limitation on possible increases in DBP, given that these are normotensive pregnancies (ie, DBP can only increase so much before the individual is diagnosed with preeclampsia). Because second-trimester blood pressure and blood pressure increase from trimester 2 to 3 were highly correlated, it would be difficult to sort out which variable is more important in regard to associations with angiogenic profile. It seems likely, however, that blood pressure augmentation from mid to late pregnancy is biologically significant because this is what occurs in preeclampsia, albeit at a lower overall level.

There is unlikely to be significant pathology among normotensive women whose blood pressure may be relatively high in the second trimester but does not increase further. A previous study in normotensive women showed no association of sFlt1 concentrations with blood pressure levels in the second trimester.²⁰ This study, however, did not address, as we did, blood pressure change from mid- to late pregnancy in women who remained normotensive throughout the pregnancy.

Previous studies show that compared with uncomplicated pregnancy, sFlt1 and sEng are elevated and PlGF is reduced in clinically evident preeclampsia.³⁻⁸ This shift toward an antiangiogenic profile is also observed in the second trimester preclinically in women destined to develop preeclampsia.³⁻⁸ In our data, the pattern of associations of angiogenic factors measured at delivery with blood pressure increases between the second and third trimesters in the preeclampsia group was similar to those observed among the uncomplicated pregnancies. However, the associations were much weaker and not statistically significant. There were significant inverse associations, however, between DBP and MAP increases from up to 20 weeks' gestation to the highest recorded value after 20 weeks and PlGF in preeclampsia.

Power was more limited in the preeclampsia group to detect differences in angiogenic factors on the order of those observed in the uncomplicated pregnancies. In addition, excluding the preeclamptic women who were taking antihypertensive medication from the analysis strengthened the associations. This suggests that blood pressure increase from mid to late

pregnancy may be related to maternal angiogenic factors also in preeclamptic pregnancies, albeit more weakly than among the normotensive pregnancies, perhaps because of their higher baseline blood pressure values. Larger sample sizes may be required to investigate this further as well as longitudinal data in which blood is sampled before administration of antihypertensive medication.

Preeclampsia is defined by the American College of Obstetricians and Gynecologists²¹ as augmented blood pressure ($\geq 140/90$ mm Hg) and proteinuria (≥ 0.3 g per 24-h) developing de novo in pregnancy after week 20. The association we observed between antiangiogenic profile in the maternal circulation and blood pressure augmentation in normal pregnancies (in which blood pressure levels did not reach the clinical definition of preeclampsia and proteinuria was absent) may not be surprising in light of the similarly antiangiogenic profile demonstrated in established preeclampsia.

Our previous work demonstrated maternal sFlt1 was significantly higher in severe preeclampsia, compared with mild disease, as well as with uncomplicated pregnancies.¹⁰ Both balance in circulating angiogenic factors and blood pressure modulations in pregnancy may be a continuum with the diagnosis of preeclampsia at the extreme. Most studies indicate that preeclamptic features are not unique to preeclampsia, existing in normal pregnancies as well, albeit at a lower level. Evidence of endothelial activation and low grade maternal inflammation in preeclampsia, known as the final common pathway,²² is present in all pregnancies and is merely more pronounced in preeclampsia, with an excessive inflammatory response.²³

Our findings may have implications with regard to subsequent cancer and cardiovascular disease risk in the mother and offspring. Women with a history of preeclampsia or pregnancy-induced hypertension have approximately 20% lower breast cancer risk, compared with women who have had only uncomplicated pregnancies.^{13,14} A more marked reduction in breast cancer risk, up to 50%, has also been observed with elevated mean arterial pressure¹⁸ as well as with systolic blood pressure increases from mid to late pregnancy below the diagnostic criteria for preeclampsia.¹⁵ Furthermore, daughters of mothers with preeclampsia, compared with daughters of uncomplicated pregnancies appear to be similarly protected against breast cancer.^{16,17}

The biological mechanisms involved in subsequent breast cancer protection after pregnancy blood pressure augmentation, either in preeclamptic or normotensive pregnancies, is unknown but could involve differences in angiogenic profile. Angiogenesis is a critical component of tumor development¹⁹ and studies show a more proangiogenic profile in breast cancer cases than controls as well as positive associations with tumor size and metastasis.²⁴⁻²⁷ The relatively antiangiogenic profile revealed in preeclampsia and following the highest blood pressure augmentation in otherwise normotensive pregnancies may be a marker for persistent difference, prepregnancy and/or postpregnancy, in angiogenic response among these women. Although antiangiogenic factors decline rapidly after delivery,⁴⁻⁶ persistent differences in circulating proteins could be involved in the subsequent breast cancer risk reduction observed in women with development of hypertension or preeclampsia during pregnancy.

Longitudinal data on circulating angiogenic factors from prior to pregnancy, during pregnancy, and between pregnancy and the development of breast cancer have not been reported. Serum sFlt1 concentrations have been shown to be elevated an average of 18 months postpartum in women with a history of preeclampsia compared with those with prior normotensive pregnancies only,²⁸ providing some evidence that these women may tend toward a persistent antiangiogenic state.

In summary, among uncomplicated pregnancies, there was a positive association of second- to third-trimester blood pressure increases with maternal circulating concentrations at delivery

of sFlt1, sEng, and with the ratios of anti- to proangiogenic factors (sFlt1/PlGF and [sFlt1 plus sEng/PlGF]) and an inverse association with PlGF concentrations. Confirmation of these findings and further investigation of their clinical implications for maternal and neonatal health in a larger study are warranted. In addition, these data may have relevance for the long-term health of the mother and offspring.

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Figure. Maternal serum concentrations

The maternal serum concentrations of sFlt1 (picograms per milliliter), PIGF (picograms per milliliter), sFlt1/PIGF ratio, sEng (nanograms per milliliter), and (sFlt1 plus sEng)/PIGF ratio by categories of MAP change between the second and third trimesters for **A**, uncomplicated pregnancies and **B**, preeclamptic pregnancies.

Table 1

Medians (ranges: minimum, maximum values) and frequencies (percent) for selected clinical characteristics, blood pressure measurements, and maternal serum angiogenic factors in preeclamptic and uncomplicated pregnancies

	Uncomplicated (n = 43)	Preeclampsia (n = 44)
Age at delivery (y)	30 (21-40)	31 (18-42)
Parity (number of previous deliveries)		
0	30 (70%)	23 (52%)
≥ 1	13 (30%)	21 (48%)
Body mass index before pregnancy (kg/m ²)	22.5 (17.4-29.4)	23.7 (18.9-41.1)
Length of gestation at delivery (wks)	38.7 (34.4-41.7)	32.9 (24.9-38.7)
Second-trimester SBP	111 (86-138)	118 (93-151)
Second-trimester DBP	65 (50-77)	74 (58-96)
Second-trimester MAP	80 (68-97)	88 (73-114)
Third-trimester SBP	114 (90-136)	133 (115-175)
Third-trimester DBP	69 (55-78)	88 (71-105)
Third-trimester MAP	84 (71-96)	103 (86-128)
Δ SBP trimester 2-3	3.5 (-11 to 12)	20 (-2 to 42)
Δ DBP trimester 2-3	3.9 (-9 to 19)	16 (1-33)
Δ MAP trimester 2-3	3.1 (-8 to 15)	16 (3-34)
sFlt1 (pg/mL)	3417 (1134-9235)	9932 (6045-28540)
PlGF (pg/mL)	169 (73.0-995)	82.0 (12.0-269)
sFlt1/PlGF	18.6 (1.7-78.8)	124 (36.0-953)
sEng (ng/mL)	15.1 (6.2-71.5)	66.9 (16.1-216)
(sFlt1 + sEng)/PlGF	123 (8.2-602)	1077 (201-7733)

Δ, change.

Table 2
Spearman rank correlations between blood pressure measures and angiogenic factors in uncomplicated and preeclamptic pregnancies

	sFlt1	PlGF	sFlt1/PlGF	sEng	(sFlt1 + sEng)/PlGF
Uncomplicated					
SBP trimester 2	-0.00	0.17	-0.13	0.10	-0.08
DBP trimester 2	-0.04	0.26	-0.19	-0.10	-0.21
MAP trimester 2	-0.06	0.27	-0.22	-0.06	-0.21
SBP trimester 3	0.21	0.06	0.08	0.32 ^a	0.08
DBP trimester 3	0.08	-0.01	0.06	0.14	0.09
MAP trimester 3	0.09	0.10	0.00	0.19	0.04
Δ SBP trimester 2-3	0.26	-0.16	0.27	0.41 ^b	0.35 ^a
Δ DBP trimester 2-3	0.29	-0.39 ^a	0.42 ^b	0.32 ^a	0.46 ^b
Δ MAP trimester 2-3	0.28	-0.37 ^a	0.41 ^a	0.40 ^b	0.47 ^b
Preeclampsia					
SBP trimester 2	0.16	-0.35	0.37 ^a	0.19	0.33
DBP trimester 2	0.27	-0.43 ^a	0.49 ^b	0.21	0.41 ^a
MAP trimester 2	0.25	-0.41 ^a	0.45 ^a	0.20	0.38 ^a
SBP trimester 3	0.26	-0.15	0.31	-0.05	0.16
DBP trimester 3	0.31	-0.30	0.41	0.13	0.32
MAP trimester 3	0.31	-0.21	0.37	0.05	0.22
Δ SBP trimester 2-3	0.21	-0.12	0.26	0.07	0.10
Δ DBP trimester 2-3	0.02	-0.13	0.13	0.23	0.19
Δ MAP trimester 2-3	0.14	-0.20	0.27	0.15	0.17

Δ, change.

^a $P < .05$.

^b $P < .01$.

Table 3

Mean maternal serum concentrations of angiogenic factors adjusted for gestational length by category of second- and third-trimester blood pressure measures and by change between trimesters in uncomplicated (A) and preeclamptic (B) pregnancies^a

A. Uncomplicated pregnancies						
	sFlt1 (pg/mL)	PlGF (pg/mL)	sFlt1/PlGF	sEng (ng/mL)	(sFlt1 + sEng)/PlGF	
SBP trimester 2 (mm Hg)						
< 111	3137	172	18.3	15.0	96.7	
≥ 111	3439	185	18.5	17.9	114	
<i>P</i>	.58	.67	.97	.32	.53	
DBP trimester 2 (mm Hg)						
< 65	4141	138	30.1	18.9	153	
≥ 65	2787	213	13.2	14.6	83.5	
<i>P</i>	.02	.01	.003	.19	.03	
MAP trimester 2 (mm Hg)						
< 80	3388	174	19.6	17.2	106	
≥ 80	3217	183	17.5	15.8	105	
<i>P</i>	.76	.75	.68	.65	.96	
SBP trimester 3 (mm Hg)						
< 114	2917	173	17.0	15.1	97.5	
≥ 114	3672	184	19.9	18.0	115	
<i>P</i>	.16	.70	.57	.34	.55	
DBP trimester 3 (mm Hg)						
< 69	3588	181	19.8	14.4	92.3	
≥ 69	3048	177	17.4	18.6	118	
<i>P</i>	.35	.89	.66	.18	.39	
MAP trimester 3 (mm Hg)						
< 84	3357	174	19.4	15.2	105	
≥ 84	3236	183	17.6	17.8	106	
<i>P</i>	.82	.79	.73	.38	.96	
Δ SBP trimester 2-3 (mm Hg)						
< 3.5	2918	188	15.6	13.8	90.1	
≥ 3.5	3671	170	21.5	19.6	124	
<i>P</i>	.16	.57	.25	.05	.23	

A. Uncomplicated pregnancies					
	sFit1 (pg/mL)	PIGF (pg/mL)	sFit1/PIGF	sEng (ng/mL)	(sFit1 + sEng)/PIGF
Δ DBP trimester 2-3 (mm Hg)					
< 3.9	2775	217	12.8	13.0	73.4
≥ 3.9	3840	148	25.9	20.7	152
<i>P</i>	.05	.02	.009	.009	.005
Δ MAP trimester 2-3 (mm Hg)					
< 3.1	2822	223	12.8	12.7	72.8
≥ 3.1	3842	142	27.2	21.2	160
<i>P</i>	.06	.005	.005	.003	.002
B. Preeclamptic pregnancies					
	sFit1 (pg/mL)	PIGF (pg/mL)	sFit1/PIGF	sEng (ng/mL)	(sFit1 + sEng)/PIGF
SBP trimester 2 (mm Hg)					
< 118	10,608	69.2	149	61.9	1147
≥ 118	10,451	76.2	132	58.9	913
<i>P</i>	.93	.62	.57	.80	.51
DBP trimester 2 (mm Hg)					
< 74	10,884	69.5	152	61.6	1140
≥ 74	10,202	75.9	129	59.3	918
<i>P</i>	.71	.68	.49	.85	.56
MAP trimester 2 (mm Hg)					
< 88	11,518	71.9	156	62.1	1127
≥ 88	9674	73.4	126	58.8	927
<i>P</i>	.28	.92	.34	.78	.58
SBP trimester 3 (mm Hg)					
< 133	11,095	94.0	118	57.7	725
≥ 133	9172	99.7	92.0	49.9	682
<i>P</i>	.12	.72	.19	.50	.86
DBP trimester 3 (mm Hg)					
< 88	9502	94.5	100.5	54.7	696
≥ 88	10,768	98.4	109.5	52.9	716
<i>P</i>	.28	.80	.64	.88	.93
MAP trimester 3 (mm Hg)					

A. Uncomplicated pregnancies

	sFit1 (pg/mL)	PIGF (pg/mL)	sFit1/PIGF	sEng (ng/mL)	(sFit1 + sEng)/PIGF
< 103	9983	96.1	104	54.0	696
≥ 103	10,327	97.0	107	53.5	716
<i>P</i>	.79	.96	.90	.97	.93
Δ SBP trimester 2-3 (mm Hg)					
< 20	9793	94.5	104	54.8	727
≥ 20	10,630	99.2	107	52.8	681
<i>P</i>	.42	.72	.84	.86	.82
Δ DBP trimester 2-3 (mm Hg)					
< 16	10,056	95.5	105	50.4	669
≥ 16	10,264	97.5	105	57.2	743
<i>P</i>	.84	.88	.99	.55	.70
Δ MAP trimester 2-3 (mm Hg)					
< 16	10,229	95.7	107	55.6	723
≥ 16	10,083	97.9	103	51.9	681
<i>P</i>	.89	.87	.82	.73	.83

^aExcludes 10 women with preeclampsia who delivered before the third trimester. Linear regression models with the logarithm-transformed angiogenic factors as dependent variables included gestational length (continuous variable) and blood pressure categories as independent variables. Geometric means based on these models (exponent of the logarithmic means) are presented.

Table 4

Mean maternal serum concentrations of angiogenic factors adjusted for gestational length by category of change between mean blood pressure up to 20 weeks' gestation and highest recorded blood pressure after 20 weeks in uncomplicated and preeclamptic pregnancies^a

	sFlt1 (pg/mL)	PlGF (pg/mL)	sFlt1/PlGF	sEng (ng/mL)	(sFlt1 + sEng)/PlGF
Uncomplicated					
Δ SBP (mm Hg)					
< 10	2934	209	14.1	13.6	78.9
≥ 10	3473	166	20.9	17.9	122
P	.35	.20	.19	.19	.13
Δ DBP (mm Hg)					
< 10	2886	230	12.6	14.4	73.9
≥ 10	3556	153	23.2	18.0	133
P	.22	.02	.03	.22	.03
Δ MAP (mm Hg)					
< 10	3142	200	15.8	13.2	81.9
≥ 10	3420	162	21.0	20.1	133
P	.61	.21	.32	.02	.07
Preeclampsia					
Δ SBP (mm Hg)					
< 50	9184	77.4	118	62.7	986
≥ 50	11357	68.7	157	59.2	1067
P	.06	.40	.07	.73	.76
Δ DBP (mm Hg)					
< 35	11003	89.2	116	56.0	830
≥ 35	10036	63.2	157	64.8	1174
P	.46	.02	.07	.39	.21
Δ MAP (mm Hg)					
< 41	10224	87.0	118	57.8	837
≥ 41	10572	61.9	160	63.3	1214
P	.78	.01	.06	.59	.15

Δ, change.

^dLinear regression models with the logarithm-transformed angiogenic factors as dependent variables included gestational length (continuous variable) and blood pressure categories as independent variables. Geometric means based on these models (exponent of the logarithmic means) are presented.