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Association of First-trimester Placental Thickness by Ultrasound and the Risk of Preeclampsia or Small Gestational Age

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ABSTRACT

Introduction and aim: Placenta play a crucial role in normal fetal development. Any deviation from normal could firstly affect placenta and subsequently represented on the fetus. Thus, different placental measurements could be used as predictors for complicated pregnancy. The current work was designed to examine the potential association between maximum placental thickness in the first-trimester and the subsequent risk of preeclampsia or the risk of the delivery of small for gestational age neonate

Methodology: This study included 150 pregnant women with singleton pregnancy. All women were assessed by full medical history and physical examination. Clinical examination preceded the routine laboratory investigations. Finally, an ultrasound was performed and repeated each weak from 11 to 14 gestational weeks to determine crown-lump length and measure maximum placental thickness. All females were followed till delivery, with documentation of preeclampsia development and/or delivered a small for gestational age (SGA) neonate.

Results: We excluded 4 women from the study due to abortion. Preeclampsia with preterm delivery recorded for 5 females, preeclampsia without preterm delivery developed in13 females, preeclampsia with SGA (5 females) and SGA among 7 females; and 116 non-complicated pregnancies. Cesarean delivery was performed for 80 females (54.8%). There was significant progressive increase of maximum placental thickness (MPT) from the 11th to the 14th weeks of gestation. Preeclampsia was associated with significant increase of MPT, while SGA was associated with significant reduction of it. The area under the curve was more than 0.7. For preeclampsia, the sensitivity was 88.89% at cutoff value > 1.0; while for SGA, the sensitivity was 100.0% at cutoff value ≤0.94.

Conclusion: Maximum placental thickness at 11 to 14 weeks provides a good predictive power for development of preeclampsia and delivery of small for gestational age. This permits early therapeutic intervention.

Keywords: **Preeclampsia; Small for Gestational Age; Preterm Delivery; Cesarean Section; Maximum Placental Thickness.**

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INTRODUCTION

The placenta principally provides the fetus by the oxygen and different nutrients [1]. The adequate function of the placenta is associated with fetal growth and subsequent neonatal normal birth weight. Fetal growth restriction (FGR) is associated with utero-placental abnormalities [2].

Preeclampsia is a serious complication of the pregnancy and in its most severe from, represents of the principle causes of maternal and associated perinatal morbidity and mortality. It is the best described as "a pregnancy–specifics syndrome includes the development of new –onset hypertension in the second half of pregnancy accompanied by new-onset proteinuria". Proteinuria is an objective marker and reflects the endothelial dysfunction of placenta [3].

Preeclampsia and fetal growth restriction (FGR) are associated two obstetric complications. Histopathological and gross placental abnormalities are common in both conditions [4]. Uterine artery Doppler is a marker of pathology of utero-placental vascular unit. Large cohort studies showed that, diverse placental pathologies are observed in both diseases [5]. Due to a broader spectrum of these pathologies especially disease related to placental, size and shape, several researchers have utilized ultrasound to assess the placental morphology in the first and second pregnancy trimesters as an independent predictors of preeclampsia and fetal growth restriction [6].

THE AIM OF THE WORK

The current work aimed to evaluate the possible association between maximum placental thickness in the first-trimester and the risk of preeclampsia and/or the delivery of small for gestational age neonates.

PATIENTS AND METHODS

This study had been conducted at Obstetrics and Gynecology Department, Al-Azhar University Hospital (New Damietta); from March to October 2021. This was a prospective study, which included 150 pregnant women with singleton pregnancy of gestational age (11-14) weeks of gestation at inclusion.

The inclusion criteria were primigravida with age from 18 to 40 years, singleton pregnancy, gestational age from 11 weeks to 13 weeks and 6 days, and regular menstruation. The exclusion criteria, on the other side, were maternal chronic medical disease (e.g., diabetes mellitus, hypertension (systemic hypertension), and/or anemia), low laying placenta, multiple pregnancies, and irregular menstrual cycle

Ethical considerations: After selection, counseling and explanation the study nature to all participants, an informed written consents were taken and approval of the study by the Institutional Review Board (IRB) of Damietta Faculty of Medicine Al-Azhar University were obtained.

All women were assessed by full medical history and physical examination with stress of the sure date of the last menstrual period to estimate the gestational age that was confirmed by ultrasound examination. The physical examination included measurement of hemodynamic vital signs, registration of pre-pregnancy maternal weight and height, then calculation of body mass index (BMI). Subsequently, abdominal examination was carried out in the standard manner, which followed by routine laboratory investigations (e.g., complete blood count, blood grouping, blood sugar, renal function tests, liver function tests and urine analysis).

Finally, an ultrasound was performed by Voluson 10 Expert ultrasound machines equipped with a 4-8 MHz transducer. An ultrasound was scheduled and performed between 11 weeks+0 day and 13 weeks +6 days to measure the following:

1-Crown-lump length (CRL) to determine the gestational age. Gestational age was determined based on last menstrual period unless the difference with first-trimester ultrasound was greater than 5 days.

2- Maximum placental thickness at its apparent center at the insertion of umbilical cord.

Follow up: Participants were followed up at 20, 28, 36 weeks and until delivery for detection of preeclampsia (defined according to the International Society as blood pressure ≥140/90 mmHg in previously normotensive women after the 20th week of pregnancy and proteinuria ≥300 mg/24hr urine collection) [7] and/or delivery of SGA neonate (defined as birth weight below 10th percentile according to gestational age and sex of a standard birthweight curve) [8]. The Maximum placental thickness (MPT) of each participant who developed preeclampsia and/or delivered SGA neonate were compared with those who did not develop both complications by using statistical analysis. The data for each patient was expressed in multiple of median (MoM) for gestational age.

Sample size calculation: The sample size was calculated using the following formula in figure (1) [9]. Based on the formula at least 145 patients were required to detect a significant incidence at α value of 0.05 and power of study 85%. Assumptions used in the formula were based on results of previous studies [10, 11]. Accordingly, we included a total of 150 participants

$$N = \frac{p_0 q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

$$N = \frac{0.075 * 0.925 \left\{ 1.96 + 1.04 \sqrt{\frac{0.02*0.98}{0.075*0.925}} \right\}^2}{(0.02 - 0.075)^2}$$

$$N = 145$$

p_0 = proportion (incidence) of population
p_1 = proportion (incidence) of study group
N = sample size for study group
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β

Figure (1): Sample size calculation formula for our study

Statistical analysis of the data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR) when appropriate. Significance of the obtained results was judged at the 5% level. The used tests were the Student *t*-test for normally distributed quantitative variables, to compare between two studied groups; One way analysis of variance (ANOVA) for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pairwise comparisons; while repeated ANOVA was used to measure effect over time (from the 11 to 14 weeks of gestation). The Receiver operating characteristic curve (ROC) was generated by plotting sensitivity (TP) on Y axis versus 1- specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 70% gives acceptable performance and area about 100% is the best performance for the test.

RESULTS

This study included 150 pregnant women with singleton pregnancy. They were recruited at gestational age of (11-14) gestation weeks who admitted to the antenatal care unit of Obstetrics and Gynecology Department at Al-Azhar University Hospital (New Damietta). We excluded 4 women from the study due to abortion, so the number of women in this study becomes 146 women.

The fetal sex represented 60.3%, the birth weight ranged between 2.98 to 3.2 kg, the mean birth weight was 2.973±0.4796 kg; the gestational age at delivery ranged between 35 to 40 weeks of gestation. The maternal age ranged between 19 to 33 years, the mean age was 26.84±4.66 years, while body mass index (kg/m^2) ranged between 25 to 31 kg/m^2 (Table 1).

In the current work, preeclampsia with preterm delivery was recorded among 5 females (3.4%), preeclampsia without preterm delivery among 13 females (8.9%), preeclampsia with small for gestation age among 5 females (3.4%) and small for gestational age among 7 females (4.8%); and non-complicated pregnancies (116; 79.5%). Cesarean delivery was performed for 80 females (54.8%) and normal vaginal delivery among 66 females (45.2%) (Table 2).

At the 11th week of gestation, maximum placental thickness ranged between 10 to 13.20; while at 12 weeks, it ranged between 13.50 to 17.10, and at 13 weeks, it ranged between 15.70 to 19.20. Finally, at 14 weeks of gestation, it ranged between 17.40 to 20.90. There was significant progressive increase of maximum placental thickness from the 11th to the 14th weeks of gestation (Table 3).

In the current work, patients with preeclampsia had significantly higher MOM than those without preeclampsia (1.16±0.11 vs 1.02±0.13, respectively). In addition, preeclampsia with preterm delivery had higher MOM than those without preeclampsia (1.18±0.12 vs 1.02±0.13, respectively). On the other side, females with SGA without preeclampsia had significantly lower MOM than those without (0.82±0.08 vs 1.05±0.13, respectively). However, the difference between preeclampsia with small for gestational age did not significantly differ than normal pregnancies, and between normal pregnancies and those with preeclampsia and/or SGA (Table 4).

For prediction of preeclampsia and SGA, the area under the curve was more than 0.7, indicating good predictive power. For preeclampsia, the sensitivity was 88.89% at cutoff value > 1.0; while for SGA, the sensitivity was 100.0% at cutoff value ≤0.94 (Table 5, figures 2 and 3).

Table (1): Maternal and Neonatal Characteristics of studied populations

Variable		Statistics
Fetal sex (n,%)	Male	88(60.3%)
	Female	58(39.7%)
Maternal age (years)	Mean±SD; min.-max; (median (IQR))	26.84±4.66; 19- 33; 27.0 (26.0-28.0)
BMI (kg/m^2)	Mean±SD; min.-max; (median (IQR))	27.44±1.73; 25.0-31.0; (26.0-28.0)
GA at delivery (weeks)	Mean±SD; min.-max; (median (IQR))	38.65±1.01; 35.0- 40.0; 39.0 (38.0-39.0)
Birthweight (kg)	Mean±SD; min.-max; (median (IQR))	2.973±0.4796; 1.9- 3.5 (3.1 (2.98-3.2)

BMI: Body mass index; SD: Standard deviation; IQR: Interquartile range.

Table (2): Fetal and maternal outcome among studied populations

	Outcome	Statistics
Fetal-maternal outcome	Preeclampsia with preterm delivery (<37 weeks)	5(3.4%)
	Preeclampsia without preterm delivery	13 (8.9%)
	Preeclampsia with small for gestational age	5(3.4%)
	Small for gestational age	7(4.8%)
	Normal pregnancies	116 (79.5%)
Mode of delivery	CS	80(54.8%)
	NVD	66(45.2%)

Table (3): Ultrasound maximum placental thickness at 11 – 14 weeks gestational age, among studied populations

Maximum placental thickness	Min.-Max.	Mean ± SD	Repeated ANOVA (F)	p
11 weeks	10-13.20	11.93±0.88	5271.0	<0.001*
12 weeks	13.50-17.10	14.99±1.03		
13 weeks	15.70-19.20	17.35±0.93		
14 weeks	17.40 -20.90	19.03±0.82		

Table (4): Relation between maximum placental thickness of first trimester and preeclampsia

		n.	Maximum placental thickness of first-trimester (MOM)		Test	p
			Min. – Max.	Mean±SD		
Preeclampsia	No	128	0.72- 1.24	1.02±0.13	***4.44***	***<0.001****
	Yes	18	0.94 -1.32	1.16±0.11		
Preeclampsia with preterm Delivery	No preeclampsia	128	0.72- 1.24	1.02±0.13#	***10.412***	***<0.001****
	Preterm	5	1.02 – 1.20	1.11±0.07		
	At term	13	0.94 – 1.32	1.18±0.12		
Preeclampsia with SGA	No	141	0.72 – 1.32	1.04±0.14	0.238	0.626
	Yes	5	0.97 – 1.17	1.07±0.08		
SGA without preeclampsia	No	139	0.84 – 1.32	1.05±0.13	***4.75***	***<0.001****
	Yes	7	0.72 – 0.94	0.82±0.08		
Normal pregnancies	No	30	0.72 – 1.32	1.07±0.18	1.27	0.20
	Yes	116	0.84 – 1.24	1.03±0.12		

#: significant difference between preeclampsia and those with preeclampsia at term. *: significant variance between groups.

Table (5): Validity of maximum placental thickness of first trimester in diagnosis of preeclampsia

	Maximum placental thickness of first-trimester (MOM)							
	AUC	p	95.0% CI	***Cut off***	***Sensitivity***	***Specificity***	***PPV***	***NPV***
Preeclampsia (yes/no) (18/128)	0.797	<0.001*	0.689-0.905	>1.0	88.89	60.94	24.2	97.5
SGA (yes/no) (7/139)	0.949	<0.001*	0.884-1.015	≤0.94	100.0	76.26	17.5	100.0

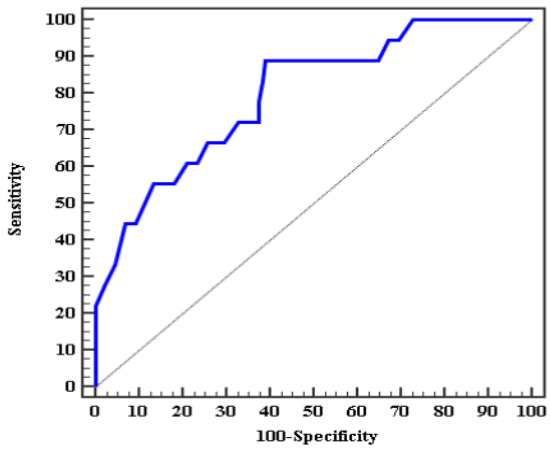

Figure (2): ROC curve for maximum placental thickness to predict preeclampsia (n=18) from none (n = 128)

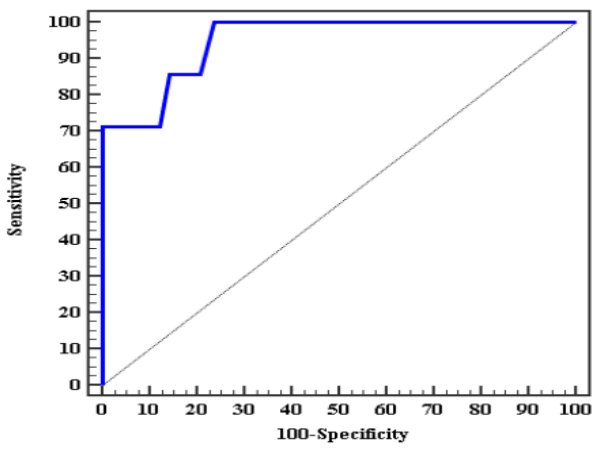

Figure (3): ROC curve for maximum placental thickness to predict small for gestational age (n=7) from none (n=139)

DISCUSSION

The present study aimed to assess the possible link between the maximum placental thickness (MPT) in the first-trimester and subsequent the risk of preeclampsia and/or FGR. The first-trimester MPT was decreased in the women who give a SGA neonate. Conversely, there was a positive association between MPT and the subsequent preeclampsia development. However, pregnancies complicated by both preeclampsia and/or SGA (5 cases) had non-significant differences than women with uncomplicated pregnancies.

These results agree with observations reported by

VachonMarceau *et al*. [11]. In addition, they provided important information on the correlation between first-trimester MPT and subsequent risk of preeclampsia and the delivery of small for gestational age neonate during the study period in Mount Sinai hospital in Canada. They recruited 991 women at a 12.7 ± 0.7 weeks of gestation. SGA (52 cases) had a significant reduction of the first MPT (median: 0.89 vs 0.98; $p < 0.01$). Pregnancies complicated by preeclampsia (20 cases) tended to have greater MPT (median: 1.10 vs 0.97). Pregnancies complicated by SGA and preeclampsia (5 cases) had similar MPT in the first-trimester when compared to uncomplicated pregnancies (median: 1.03 vs 0.98; $p = 0.33$).

By contrast, Vachon-Marceau *et al*. [11] observed when they made comparison between 16 women at term preeclampsia and 4 cases of preterm preeclampsia, they observed a trend towards thicker placentas in women developed the disease at preterm. In our study we found trend towards thicker placentas in women who developed preeclampsia at term.

Our observations are also in line with several studies that showed a relationship between placental thickness in the first-trimester and neonatal birth weight with small placentas being a risk factor for FGR or SGA. Plasencia *et al*. [12] studied the predictive value of placental volume at 11–13 weeks' gestation, different maternal characteristics and serum pregnancy-associated plasma protein-A (PAPP-A) in the prediction of delivery of SGA or large for gestational age (LGA) neonates. They found significant reduction of placental volume and PAPP-A in the SGA group (placental volume 0.88 vs. 1.00 in average for gestational age (AGA), PAPP-A 0.92 vs. 1.00 in AGA).

Effendi *et al*. [6] studied association between first-trimester placental volume and birth weight. They found that, first-trimester placental volume was smaller in women who delivered SGA neonates (0.79 vs 1.00; $p < 0.001$) and not associated with the risk of preeclampsia (AUC= 0.01; $p = 0.87$).

Schwartz *et al.* [13] studied first-trimester placental ultrasound and maternal serum markers as predictors of small-for-gestational-age and reported that, pregnancies complicated by SGA had a significantly smaller placental volume (PV), quotient (placental quotient [PQ]= PV/ gestational age), mean placental diameter (MPD) and higher placental morphology index (PMI=MPD/PQ) compared with normal pregnancies ($P < .001$ for each). These data reflected the importance of placental measurements in prediction of complicated pregnancies or pregnancies with unfavorable outcome. They also observed that first-trimester PlGF was lower in pregnancies complicated by SGA neonates but did not improve the predictive model using placental morphologic variables.

Our findings support the reported results in the previous literatures that the divergent placental morphologic findings at the end of the first trimester from normal in different ways, influencing the subsequent risk of developing preeclampsia or fetal growth restriction (FGR). The potential explanation for this association is the observed decreasing in elaboration of peripheral nutrient-and gas-exchanging terminal villi in placentas from severely growth-restricted placentas [14-16], a condition described by pathologists as distal villous hypoplasia. Such pregnancies may secrete less placental growth factor (PlGF) than normal, ultimately presenting with FGR [17,18].

By contrast, preeclampsia may increase placental weight and thickness via reactive changes in placental villi to ischemia [19] (driving up the production of several trophoblast-derived proteins in maternal blood (hCG, activin and inhibin) and ultimately producing an antiangiogenic state (due to excess synthesis and secretion of the VEGF antagonist Soluble fms-like tyrosine kinase-1 (sFlt1 or sVEGFR-1) from syncytial knots [20] triggering the disease in the third trimester [21-24].

Our study adds to other literatures by showing that a simple measure, placental thickness, performed at the time of the 11-13 weeks ultrasound, could help in the differentiation of women who are more or less likely to develop either FGR or preeclampsia. As the first trimester placenta may react to its maternal and/or local environment; such changes could be a physiologic compensation to several factors, such as high altitude or nutrient deprivation. We recommend future studies to add other factors to measurements of placental thickness, especially disease-specific biomarkers, to improve the prediction of FGR and preeclampsia.

Financial and Non-Financial Relationships and Activities, and Conflicts of Interest

None

REFERENCES

1. David AL, Jauniaux E. Ultrasound and endocrinological markers of first trimester placentation and subsequent fetal size. Placenta. 2016 Apr; 40:29-33. doi: 10.1016/j.placenta. 2016.02.005.

2. Kim YR, Jung I, Park G, Chang SW, Cho HY. First-trimester screening for early preeclampsia risk using maternal characteristics and estimated placental volume. J Matern Fetal Neonatal Med. 2021; 34(7):1155-1160. doi: 10.1080/ 14767058.2019.1628207.

3. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013 Sep; 170(1):1-7. doi: 10.1016/j.ejogrb.2013.05.005.

4. Chassen SS, Ferchaud-Roucher V, Gupta MB, Jansson T, Powell TL. Alterations in placental long chain poly-unsaturated fatty acid metabolism in human intrauterine growth restriction. Clin Sci (Lond). 2018 Mar 15; 132(5):595-607. doi: 10.1042/CS20171340.

5. van Westering-Kroon E, Huizing MJ, Villamor-Martínez E, Villamor E. Male Disadvantage in Oxidative Stress-Associated Complications of Prematurity: A Systematic

Review, Meta-Analysis and Meta-Regression. Antioxidants (Basel). 2021; 10(9):1490. doi: 10.3390/ antiox10091490.

6. Effendi M, Demers S, Giguère Y, Forest JC, Brassard N, Girard M, Gouin K, Bujold E. Association between first-trimester placental volume and birth weight. Placenta. 2014 Feb; 35(2):99-102. doi: 10.1016/j.placenta.2013.11.015.

7. Zhou X, Zhang GY, Wang J, Lu SL, Cao J, Sun LZ. A novel bridge between oxidative stress and immunity: the interaction between hydrogen peroxide and human leukocyte antigen G in placental trophoblasts during preeclampsia. Am J Obstet Gynecol. 2012 May; 206(5): 447.e7-16. doi: 10.1016/j.ajog.2012.03.013.

8. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, Blondel B, Bréart G; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 2001 Aug; 108(2): E35. doi: 10.1542/peds.108.2.e35.

9. Rosner B. Sample size determination. In: Fundamentals of biostatistics. Nelson Education. 8th edition, Copyright 2016 Cengage Learning pp 228-229.

10. Mayrink J, Souza RT, Feitosa FE, Rocha Filho EA, Leite DF, Vettorazzi J, *et al*.; Preterm SAMBA study group. Incidence and risk factors for Preeclampsia in a cohort of healthy nulliparous pregnant women: a nested case-control study. Sci Rep. 2019 Jul 2;9(1):9517. doi: 10.1038/s41598-019-46011-3.

11. Vachon-Marceau C, Demers S, Markey S, Okun N, Girard M, Kingdom J, Bujold E. First-trimester placental thickness and the risk of preeclampsia or SGA. Placenta. 2017 Sep; 57:123-128. doi: 10.1016/j.placenta.2017.06.016.

12. Plasencia W, Akolekar R, Dagklis T, Veduta A, Nicolaides KH. Placental volume at 11-13 weeks' gestation in the prediction of birth weight percentile. Fetal Diagn Ther. 2011; 30(1): 23-8. doi: 10.1159/000324318.

13. Schwartz N, Sammel MD, Leite R, Parry S. First-trimester placental ultrasound and maternal serum markers as predictors of small-for-gestational-age infants. Am J Obstet Gynecol. 2014 Sep; 211(3): 253.e1-8. doi: 10.1016/j.ajog. 2014. 02.033.

14. Kingdom JC, Audette MC, Hobson SR, Windrim RC, Morgen E. A placenta clinic approach to the diagnosis and management of fetal growth restriction. Am J Obstet Gynecol. 2018 Feb; 218(2S): S803-S817. doi: 10.1016/ j.ajog. 2017.11.575.

15. Burton GJ, Jauniaux E. Placentation in the Human and Higher Primates. Adv Anat Embryol Cell Biol. 2021; 234:223-254. doi: 10.1007/978-3-030-77360-1_11.

16. Brosens I, Puttemans P, Benagiano G. Placental bed research: I. The placental bed: from spiral arteries remodeling to the great obstetrical syndromes. Am J Obstet Gynecol. 2019 Nov; 221(5):437-456. doi: 10.1016/j.ajog.2019.05.044.

17. Nucci M, Poon LC, Demirdjian G, Darbouret B, Nicolaides KH. Maternal serum placental growth factor (PlGF) isoforms 1 and 2 at 11-13 weeks' gestation in normal and pathological pregnancies. Fetal Diagn Ther. 2014;36(2):106-16. doi: 10.1159/000357842.

18. Zhang J, Han L, Li W, Chen Q, Lei J, Long M, *et al*. Early prediction of preeclampsia and small-for-gestational-age via multi-marker model in Chinese pregnancies: a prospective screening study. BMC Pregnancy Childbirth. 2019 Aug 19;19(1):304. doi: 10.1186/ s12884-019-2455-8.

19. Eskild A, Romundstad PR, Vatten LJ. Placental weight and birth weight: does the association differ between pregnancies with and without preeclampsia? Am J Obstet Gynecol. 2009 Dec; 201(6): 595.e1-5. doi: 10.1016/j.ajog.2009.06.003.

20. Sasagawa T, Nagamatsu T, Yanagisawa M, Fujii T, Shibuya M. Hypoxia-inducible factor-1β is essential for upregulation of the hypoxia-induced FLT1 gene in placental trophoblasts. Mol Hum Reprod. 2021 Nov 27; 27(12): gaab065. doi: 10.1093/molehr/gaab065.

21. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, *et al*. Predictive Value of the sFlt-1: PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016 Jan 7;374(1):13-22. doi: 10.1056/NEJMoa1414838.

22. Wojcik M, Karouni F, Jindal S, Kapaya H. Implementing placental-growth-factor (PLGF) measurements in suspected pre-eclampsia-Challenges in clinical practice. Eur J Obstet Gynecol Reprod Biol. 2021 Nov; 266:157-162. doi: 10.1016/ j.ejogrb. 2021.10.006.

23. Gao J, Huang X, Di W, Dong X, Gou W, Shi H, Wang Z, Dietl A, Grill S, Hund M. Short-Term Prediction of Preeclampsia in Chinese Women Using the Soluble fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio: A Sub-Analysis of the PROGNOSIS Asia Study. Front Cardiovasc Med. 2021 Aug 23; 8:602560. doi: 10.3389/fcvm.2021.602560.

24. Chantraine F, Van Calsteren K, Devlieger R, Gruson D, Keirsbilck JV, Dubon Garcia A, Vandeweyer K, Gucciardo L. Enhancing the value of the sFlt-1/PlGF ratio for the prediction of preeclampsia: Cost analysis from the Belgian healthcare payers' perspective. Pregnancy Hypertens. 2021 Dec; 26: 31-37. doi: 10.1016/j.preghy. 2021.08.113.

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