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Original Article

**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 week 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 in 13 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 11<sup>th</sup> to the 14<sup>th</sup> 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 <sup>(1)</sup>. 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 <sup>(2)</sup>.

Preeclampsia is a serious complication of the pregnancy and in its most severe form, represents of the principle causes of maternal and associated perinatal morbidity and mortality. It is the best described as “a pregnancy-specific 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 <sup>(3)</sup>.

Preeclampsia and fetal growth restriction (FGR) are associated two obstetric complications. Histopathological and gross placental abnormalities are common in both conditions <sup>(4)</sup>. 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 <sup>(5)</sup>. 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 <sup>(6)</sup>.

## 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 lying 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  $\geq 140/90$  mmHg in previously normotensive women after the 20<sup>th</sup> week of pregnancy and proteinuria  $\geq 300$  mg/24hr urine collection) <sup>(7)</sup> and/or delivery of SGA neonate (defined as birth weight below 10<sup>th</sup> percentile according to gestational age and sex of a standard birthweight curve) <sup>(8)</sup>. 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) <sup>(9)</sup>. Based on the formula at least 145 patients were required to detect a significant incidence at a value of 0.05 and power of study 85%. Assumptions used in the formula were based on results of previous studies <sup>(10, 11)</sup>. Accordingly, we included a total of 150 participants

$$N = \frac{p_0q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1q_1}{p_0q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$$q_0 = 1 - p_0$$

$$q_1 = 1 - p_1$$

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

$$N = 145$$

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

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  $2.973 \pm 0.4796$  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  $26.84 \pm 4.66$  years, while body mass index ( $\text{kg}/\text{m}^2$ ) ranged between 25 to  $31 \text{ kg}/\text{m}^2$  (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 gestational 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 11<sup>th</sup> 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 11<sup>th</sup> to the 14<sup>th</sup> weeks of gestation (Table 3).

In the current work, patients with preeclampsia had significantly higher MOM than those without preeclampsia ( $1.16 \pm 0.11$  vs  $1.02 \pm 0.13$ , respectively). In addition, preeclampsia with preterm delivery had higher MOM than those without preeclampsia ( $1.18 \pm 0.12$  vs  $1.02 \pm 0.13$ , respectively). On the other side, females with SGA without preeclampsia had significantly lower MOM than those without ( $0.82 \pm 0.08$  vs  $1.05 \pm 0.13$ , 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  $\leq 0.94$  (Table 5, figures 2 and 3).

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

Variable	Statistics
Fetal sex (n,%)	Male
	Female
Maternal age (years)	Mean $\pm$ SD; min.-max; (median (IQR))
BMI ( $\text{kg}/\text{m}^2$ )	Mean $\pm$ SD; min.-max; (median (IQR))
GA at delivery (weeks)	Mean $\pm$ SD; min.-max; (median (IQR))
Birthweight (kg)	Mean $\pm$ SD; min.-max; (median (IQR))

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)
	Preeclampsia without preterm delivery
	Preeclampsia with small for gestational age
	Small for gestational age
	Normal pregnancies
Mode of delivery	CS
	NVD



**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	<b>4.44</b>	<b>&lt;0.001*</b>
	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 <sup>#</sup>	<b>10.412</b>	<b>&lt;0.001*</b>
	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	<b>4.75</b>	<b>&lt;0.001*</b>
	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

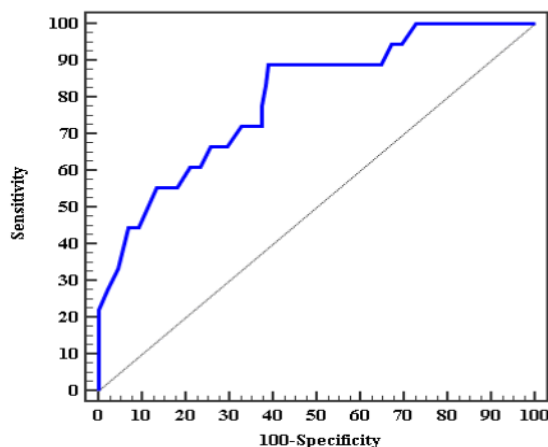


Figure (2): ROC curve for maximum placental thickness to predict preeclampsia (n=18) from none (n = 128)

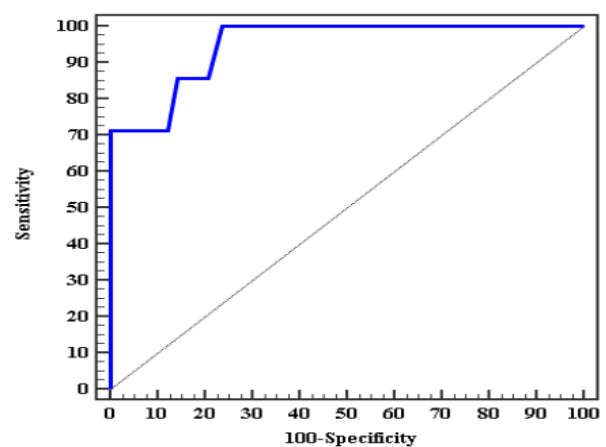


Figure (3): ROC curve for maximum placental thickness to predict small for gestational age (n=7) from none (n=139)

### 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.* <sup>(11)</sup>. 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  $12.7 \pm 0.7$  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.* <sup>(11)</sup> 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.* <sup>(12)</sup> 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.* <sup>(6)</sup> 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.* <sup>(13)</sup> 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 PIGF 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 <sup>(14-16)</sup>, a condition described by pathologists as distal villous hypoplasia. Such pregnancies may secrete less placental growth factor (PIGF) than normal, ultimately presenting with FGR <sup>(17,18)</sup>.

By contrast, preeclampsia may increase placental weight and thickness via reactive changes in placental villi to ischemia <sup>(19)</sup> (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 <sup>(20)</sup> triggering the disease in the third trimester <sup>(21-24)</sup>).

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

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