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Placental Thickness in First Trimester (11-14) Weeks and Correlation with Preeclampsia and Intrauterine Growth Retardation

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ABSTRACT

Background: First trimester trophoblastic invasion has far-reaching consequences for the fetus; failure at this stage may result in fetal growth restriction with morbidity both in the immediate perinatal period, as well as throughout development into adulthood.

Objective: The aim of this study was to estimate the placental thickness in first trimester (11-14) weeks and investigating the correlation with preeclampsia and intrauterine growth retardation. **Patients and methods:** This prospective cross-sectional study was conducted at Al-Azhar University Hospital. The study included 50 patients.

Results: There was a significant increase in the maximal placental thickness (PT) to placental volume ratio in growth restricted fetuses in our study. This may be a reflection of reduction in placental surface area. Further work is required to confirm this finding using more accurate stereological analysis of the placenta in utero. In this study, the MRI appearance of suspected retroplacental haemorrhage, placental infarct, and subchorionic haemorrhage was confirmed by placental histology in 100%, 100%, and 33% of cases respectively.

Conclusion: From our study, it can be concluded that PT can be used as a predictor of the GA, in the women in whom the LMP is unreliable or is not known.

Keywords: Placental thickness, first trimester, preeclampsia, intrauterine growth retardation.

INTRODUCTION

First trimester trophoblastic invasion has far-reaching consequences for the fetus. Failure at this stage may result in fetal growth restriction with morbidity both in the immediate perinatal period, as well as throughout development into adulthood. Pregnancies complicated by fetal growth restriction are characterised by shallow invasion of the trophoblast into maternal tissue, and inadequate conversion of the spiral arterioles, leading to placental ischemia [(1)].

Histological examinations of these malperfused placentae demonstrated a thickened, globular placenta with gross areas of infarct and abruption, as well as microscopic evidence of chronic inflammation and villitis [(2)].

This increases uteroplacental impedance in both the fetal and maternal compartment was evidenced by an increase in the Doppler velocimetry of the umbilical and the uterine arteries respectively on ultrasonography [(1)].

Growth restricted fetuses are at increased risk of perinatal demise and neonatal complications such as intraventricular haemorrhage, periventricular leucomalacia, respiratory distress syndrome, and necrotising enterocolitis [(3)].

Ultrasound assessment of the placenta typically includes an assessment of placental location and maturity, and the presence of placental haemorrhage or intervillous lakes. Although volumetric assessment of the placenta may be performed using 3D ultrasound in the first trimester, it becomes increasingly difficult to perform as gestation progresses due to limitations in the field of view [(4)].

Fetal MRI is now established as an adjunct to ultrasonography in the diagnosis of fetal abnormalities. MRI assessment of the placenta was first used in cases of suspected placenta praevia**.** Its role has expanded and now ranges from the assessment of placental invasion in cases of suspected placenta accreta/increta/percreta in the clinical setting to studies on spectroscopy and perfusion of the placenta in the research setting [(5)].

AIM OF THE WORK

The aim of this study was to estimate the placental thickness in first trimester (11-14) weeks and investigating the correlation with preeclampsia and intrauterine growth retardation.

PATIENTS AND METHODS

This study was conducted at Al-Azhar University Hospital. The study included 50 patients.

Inclusion criteria:

1. Primary gravida "Para 0 +0 PG".
2. Singleton pregnancies, 11-14 weeks.
3. Known last menstrual period.
4. A history of regular menstruation.

Exclusion criteria:

1. Maternal Disease
   a. Gestational Diabetes.
   b. Hypertension (Systemic hypertension and Pregnancy induced hypertension).
   c. Anaemia.
2. Aneuploidy.
3. The presence of in utero infection.
4. The presence of additional structural abnormalities, and suspected genetic syndromes.

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5. Foetal anomalies.
6. Palcenta previa, placental anomalies and poor visualization of the placenta.
7. Multiple pregnancies.
8. Last menstrual period not known or irregular menstrual periods.

Type of the study:

Prospective cross-sectional study.

Methods:

1. **Taking informed consent from all patients included in the study and approval of the Ethical Committee of Al-Azhar University.**
2. Patients were subjected to the following:

- Detailed history :

- Personal history (name, age, socioeconomic status, special habits of medical importance "smoking").
- Complain and present history:
- Presence of bleeding (onset – course – amount – severity – duration, no of the attacks – associated symptoms as pain – need blood transfusion).
- Manifestation of anemia (pallor – easy fatigability – loss of appetite).
- Menstral history: first day of last normal menstrual period.
- Obstetric history :
- Parity, mode of previous delivery (vaginal or cesarean section and its indication), number of previous cesarean section, previous abortion and D & C.
- Antepartum hemorrhage in previous pregnancies.
- Postpartum hemorrhage in previous deliveries.
- Any complication in the previous deliveries.
- Medical and surgical history.

General examination :

- General condition: (level of consciousness, orientation of time and place)
- Vital data measurement (blood pressure, pulse, temperature and respiratory rate).
- Evidence of anaemia (pallor) and cyanosis.

Abdominal examination :

- Evaluation of fundal level, presentation and position.
- Abdominal tenderness.
- Scar of previous operation.

Ultrasonography :

- The examination was done with ultrasonography machine (Voluson 730 Pro V).
- Transbdominal ultrasound was done with partially full bladder. To assess fetal viability, fetal presentation, gestational age, to exclude intrauterine fetal anamolies, amniotic fluid index, placenta localization and placenta adherence.
- Measurement of cervical length with Transvaginal ultrasound (TVS) as follows: ultrasound examination was done by ultrasonography machine containing multifrequancy transvaginal probe (Voluson 730 Pro V). Women evacuated the urinary bladder before the examination. We obtained a true sagittal plane to show the whole length of the cervix and cervical length was measured 3 times by placing the calipers on the internal and external cervical os. The median measurement was taken.

- Routine antenatal investigation:
  - o Blood group, RH.
  - o Complete blood count (CBC), Hb level, hematocrit value.
  - o Coagulation profile (prothrombin time, partial thromboplastin time).
  - o Liver function tests.
  - o Kidney function tests.
- Follow up of all these cases about:
  - Hemorrhage (severity, duration and need to blood transfusion).
  - Any maternal morbidity.
  - Admission to ICU.
- Recording of those who delivered by elective CS & those with emergency CS.

Outcome measures:

Primary outcome:

Type of CS whether emergency CS due to massive antepartum hemorrhage or elective CS and its relation to cervical length.

Secondary outcome:

Maternal morbidity:

- Antepartum hemorrhage (number of attacks from admission to the hospital), severity, duration and need for blood transfusion.
- Operative complications (blood loss, uterine embolization, internal artery ligation, CS hysterectomy).
- Blood loss during and after CS by measuring Hb level before and after CS.
- Admission to intensive care.
- Post-operative complications:
  - (Sepsis, post-partum hemorrhage, blood transfusion and post-operative hysterectomy).
  - ***Fetal condition at delivery :***
- Gestational age (term or preterm).
- Fetal birth weight.
- Apgar score at one and five minutes.
- The need to neonatal ICU admission.
- Neonatal mortality (still birth, early neonatal death).

Methodology in details

Prospective cohort study of women recruited at 11–14 weeks gestation. Participants were followed until delivery for pregnancy outcomes. Placental measurements of participants who developed preeclampsia and/or delivered SGA neonate (defined as birth weight below 10^{th} percentile) were compared to those who did not use non-parametric statistical analyses.

Placental volume, maximal placental thickness, the placental thickness to volume ratio, the placenta to amniotic fluid signal intensity ratio, and the presence of abnormal signal intensity consistent with placental pathology were noted. In a subset of patients, histopathological diagnosis was compared to the MRI appearance of the placenta. A transabdominal scanner (3.5 MHz transducer) was used to determine the fetal anomalies if there was any. The gestation age was determined by measuring the biparietal diameter, the abdominal circumference, the crown rump length, the head circumference and the femur length. The placental thickness was measured at the level of the umbilical cord insertion; the maximum thickness was noted in the cross section. Each placenta was measured to a 1 mm precision, at its greatest thickness, which was perpendicular to the uterine wall. The uterine myometrium and the retroplacental veins were excluded. The subjects were in the supine position with a full urinary bladder while they underwent the ultrasonography.

Data were collected on the severity of fetal growth restriction and pregnancy outcome, including clinical neonatal details, perinatal mortality and birth weight and centile.

Statistical Analysis

Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc, Chicago, IL, USA) and NCSS 11for windows (NCSS LCC, Kaysville, UT, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- ***Independent-samples t-test*** of significance was used when comparing between two means.
- ***Mann Whitney U test*** was used when comparing two means of not normally distributed data.
- ***Chi-square (X^2) test*** of significance was used in order to compare proportions between two qualitative parameters.
- ***Fisher Exact test*** is a test of significance that is used in the place of chi square test in 2 by 2 tables, especially in cases of small samples.
- ***Spearman's correlation coefficient (r) test*** was used for correlating continuous data.

The following regarding ROC curve were done:

- Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. Area Under Curve (AUC) was also calculated, criteria to qualify for AUC were as follows: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at point of maximum accuracy.
- **Sensitivity:** Probability that a test result will be positive when the disease is present (true positive rate, expressed as a percentage).

Sensitivity = (true +ve)/ [(true +ve) + (false –ve)

- **Specificity:** Probability that a test result will be negative when the disease is not present (true negative rate, expressed as percentage).

Specificity = (true –ve) / [(true –ve) + (false +ve)

- **PPV (positive predictive value):** Probability that the disease is present when the test is positive (expressed as a percentage of true positive cases to all positive).PPV = (true +ve) / [(true +ve) + (false +ve)].
- **NPV (negative predictive value):** Probability that the disease is not present when the test is negative (expressed as a percentage of true negative subjects to all negative). NPV = (true –ve) / [(true –ve) + (false –ve)].
- **Accuracy =** [(true +ve) + (false +ve)] / [(true +ve) + (false +ve) + (true –ve) + (false –ve)].
- **Probability (P-value):** P-value $\leq$ 0.05 was considered significant, P-value $\leq$ 0.001 was considered as highly significant and P-value > 0.05 was considered insignificant.

RESULTS

Table (1)*:* Age, BMI and GA distribution among studied groups

	Age	**GA**	**BMI**
Mean ± SD	**24.3 ± 3.28**	**12.22 ± 1.14**	**24.82 ± 3.39**
Median (Median)	**24.0 (18-32)**	**12.0 (11-14)**	**25.2 (23.5-27.5)**

Age was distributed as 24.3 ± 3.28, GA 12.22 ± 1.14 and BMI 24.82 ±3.39

Table (2): Placenta thickness and volume distribution among studied groups

	Placenta thickness mm	**Placenta volume cm**
Mean ± SD	**9.84±2.17**	**79.96±7.12**
Median (Median)	**10.0 (7-13)**	**81.0 (69-90)**

Placenta thickness was 9.84 ± 2.17 mm with minimum 7 and maximum 13, Placenta volume cm was 79.96 ±7.12 with minimum 69 and maximum 90

Table (3): Distribution of abortion, preeclampsia and IUGR

		N	**%**
Abortion	**No**	**43**	**86.0**
	Yes	**7**	**14.0**
Preeclampsia	**No**	**33**	**66.0**
	Yes	**17**	**34.0**
IUGR	**No**	**35**	**70.0**
	Yes	**15**	**30.0**
	Total	**50**	**100.0**

14% aborted , 34% had preeclampsia and 30% had IUGR

Table (4): Correlations between Placenta thickness and volume

		Placenta thickness mm	Placenta volume cm
Placenta volume cm	r	**.525****	**1**
	P	**.000**	
Age	r	**.070**	**-.155-**
	P	**.631**	**.284**
GA	r	**.292***	**.289***
	P	**.040**	**.045**
BMI	r	**.052**	**-.141-**
	P	**.720**	**.329**

Placenta thickness and volume significantly associated with GA and with each other

Table (5): Comparison Preeclampsia

	Preeclampsia	**N**	**Mean**	**Std. Deviation**	**t**	**P**	
Placenta thickness mm	**Yes**	**17**	**8.5294**	**1.37467**	**-3.35**	**0.002***	
	No	**33**	**10.5152**	**2.22375**			
Placenta volume cm	**Yes**	**17**	**76.7059**	**6.15188**	**-2.43**	**0.019***	
	No	**33**	**81.6364**	**7.09673**			

Preeclampsia cases significantly lower

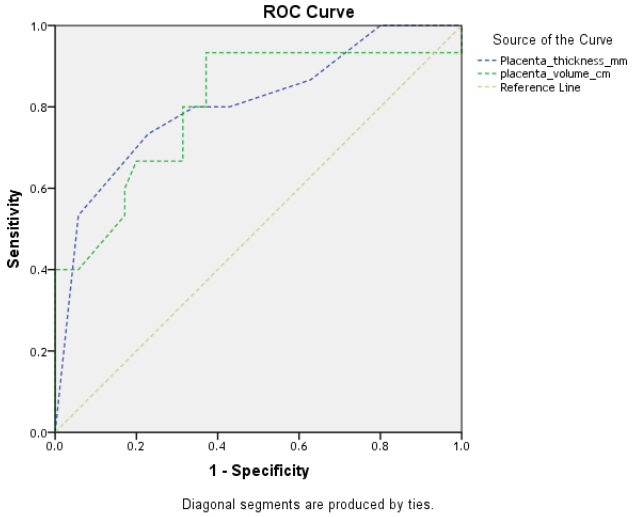
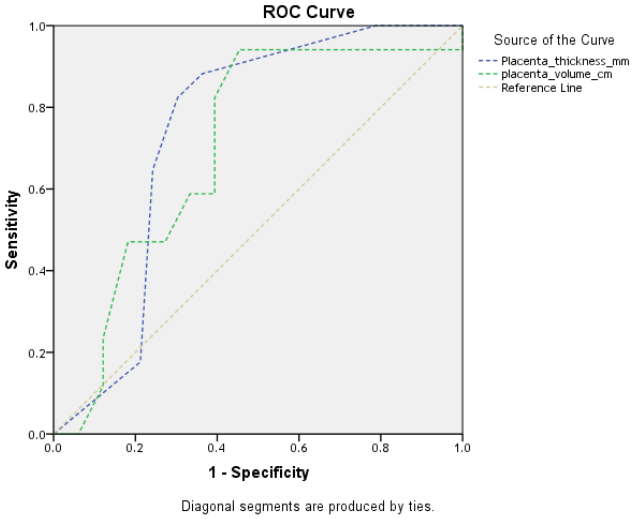


Fig. (1): ROC Curve for cutoff regarding preeclampsia

Area Under the Curve					
Test Result Variable(s)	Area	Cutoff	P	95% Confidence Interval	
				Lower Bound	Upper Bound
Placenta thickness mm	**0.807**	**<9.5 mm**	**0.001****	**0.666**	**0.947**
Placenta volume cm	**0.803**	**< 83 cm**	**0.001****	**0.657**	**0.948**

Significant area under curve with cutoff < 9.5 for thickness and < 83 for volume

Fig. (2): ROC Curve for cutoff regard IUGR



Area Under the Curve					
Test Result Variable(s)	Area	Cutoff	P	95% Confidence Interval	
				Lower Bound	Upper Bound
Placenta thickness mm	**0.739**	**<8.7**	**0.006***	**0.599**	**0.879**
Placenta volume cm	**0.702**	**<79.5**	**0.020***	**0.550**	**..854**

Significant area under curve with cutoff <8.7 for thickness and <79.5 for volume

DISCUSSION

Growth restricted fetuses are at increased risk of perinatal demise, and of neonatal complications such as intraventricular haemorrhage, periventricular leucomalacia, respiratory distress syndrome, and necrotising enterocolitis [3].

The placenta is a materno-fetal organ, which nourishes and protects the fetus and it dies out after the delivery of the baby. Since it is closely related to the fetus and the mother, it acts like a mirror, reflecting the statuses of both the mother and the fetus. **Machado** [6] stated that a PT of < 25 mm at term, was associated with intra-uterine growth retardation (IUGR) [6]. A placental thickness of > 40 mm at term is associated with gestational diabetes, intra- uterine infections and hydrops foetalis. **Wells *et al.*** [7] opined that at no stage of the pregnancy placental thickness exceeded 40 mm indirectly, thus indicating the cut off value for the upper limit. Among the pregnant women with CMV infections, the placental thickness was increased in about 93.3% of the subjects.

The incidence of the perinatal mortality and the fetal anomalies were greater in the subjects with thick placentas. **Pron *et al.*** [8] in their study reported that in PT with 22 mm at 36 weeks in the fetuses which weighed < 2500 gm and in PT with 34.8 mm at 36 weeks in the fetuses which weighed > 2500gm, The PT was a predictor of low- birth weight (LBW) infants.

In our study, the mean placental thickness at 36 weeks was 37.6mm. The placental thickness was increased in the subjects with α- thalassemia type 1 than in their normal counterparts. From the above discussion, it is evident that a decreased PT is associated with IUGR. So, a subnormal PT may be an earliest indicator of IUGR, which can be treated if it is diagnosed early. An enlarged placenta (placentomegaly) is suspected if the PT is > 40 mm at term and if it is associated with gestational diabetes mellitus, intra uterine infections, hydrops fetalis, anaemia and α- thalassemia type [9].

In 19 of 20 growth restricted fetuses in our study, the MRI placental appearance was of a thickened globular structure as opposed to the appearance of a flattened disc with typical tapering edges in the normal pregnancies. **Reiter *et al.*** [10] found an association between sonographically detected globular placentae and adverse perinatal outcome, including fetal growth restriction. In our study, the appearance of a globular thickened placenta was easy to identify on MRI. Increased placental thickness is known to be associated with fetal growth restriction, and all 8 pregnancies that resulted in perinatal mortality demonstrated a globular placenta at the time of MRI scan ($p < 0.01$). Two normally grown fetuses had the appearance of a thickened, globular placenta at the time of MRI scan and both were found on histopathology to have focal haemorrhage and infarct with added chorioamnionitis in the second. It is possible that these 2 patients had an underlying placental pathology that was not of sufficient severity to result in fetal growth restriction. However, it may have contributed to the complications they faced in labour.

There was a significant increase in the maximal placental thickness to placental volume ratio in growth-restricted fetuses in our study. This might be a reflection of reduction in placental surface area, and further work is required to confirm this finding using more accurate stereological analysis of the placenta in utero.

In this study, the MRI appearance of suspected retroplacental haemorrhage, placental infarct, and subchorionic haemorrhage was confirmed by placental histology in 100%, 100%, and 33% of cases respectively. One limitation of this study is the lack of histological examination on all the fetuses studied, and the delay between antenatal MRI assessment of placental pathology and postnatal histological examination of the placenta. Histopathological assessment of the placenta in growth-restricted pregnancies is routine in our hospital, however, as the fetal care unit functions as a tertiary referral center, not all growth restricted pregnancies were delivered in the hospital, and placental histological analysis was not obtained for 7 growth restricted fetuses.

Although at present, ultrasound remains the optimal tool for the evaluation of the placenta in fetal growth restriction, there is growing evidence that MR imaging plays a role in the assessment of the growth-restricted fetus. In this study, MRI was able to predict fetal and neonatal death with a relative risk of 7 (95% CI ¼ 2.96—16.55) using a measure of maximal placental thickness to volume ratio. This is comparable to Ultrasound Doppler studies of the middle cerebral artery and the ductus venosus which are able to predict perinatal mortality with an odds ratio of 10.2 (95%CI ¼ 1.8—57) [(11)]. Recent MRI studies have also demonstrated abnormalities in brain development in growth-restricted fetuses, which include reductions in cortical gray matter and hippocampal volume, abnormalities in diffusion tensor analysis and proton Magnetic Resonance Spectros- copy analysis. These changes within the fetal brain may have implications for longer-term developmental outcome and MR imaging may contribute to management decisions in cases at the threshold of viability in the future [(12)].

IUGR is a problem associated with significant perinatal morbidity and mortality. Level 1 evidence to direct clinicians in practice does exist, but is limited to a few high quality trials. Several demographic factors, including advanced maternal age, assisted conception technologies, and pregnancy with maternal comorbidities, interact to steadily increase of IUGR risk and stillbirth in the third trimester. More effective use of current evidence might reduce this risk, but further studies, especially to evaluate the role of systematic screening of placental function in the second trimester, are needed to improve the perinatal prognosis of IUGR due to placental insufficiency. Since IUGR has many additional causes, when it is suspected, a detailed fetal anatomical ultrasound examination should be performed including further testing when fetal abnormalities are suspected. Soft markers might be seen, or there is no apparent supportive evidence of underlying placental insufficiency [(13)].

In uncomplicated IUGR attributed to placental insufficiency, no pharmacological interventions are of proven benefit, although the accumulated data from several trials and meta-analyses of low-dose aspirin demonstrate some preventive benefit. By contrast, no evidence currently exists to support the preventive use of the parenteral anticoagulant drug heparin for either the prevention or treatment of IUGR. After 36 weeks of gestation, IUGR due to suspected placental insufficiency could be managed, equally effectively, by early delivery or delayed delivery with increased fetal surveillance.

CONCLUSION

From our study, it can be concluded that PT can be used as a predictor of the GA, in the women in whom the LMP is unreliable or is not known. The substitution of any abnormal fetal parameters like BPD in hydrocephalus with PT in USG in the GA estimation can be ventured into. In abnormal PT for the corresponding GA, the disease conditions, which cause an increased or decreased PT, should be addressed. The regression equation can be used to calculate the GA from the other fetal parameters, with minimal error.

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