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Placental Size and Uterine Artery Doppler for Prediction of Adverse Pregnancy Outcomes in Women with Low Pregnancy-Associated Plasma Protein-A

Ashraf Jamal [1], Shohreh Vosoogh [2, *], Razieh Sadat Tabatabaei [3] and Fatemeh Salamat [4]

[1]Department of Obstetrics and Gynecology, Perinatology Division, Dr. Ali Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Clinical Research Development Unit (CRDU), Sayad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran
[3]Department of Gynecology and Obstetrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4]Cancer Research Center, Golestan University of Medical Sciences, Gorgan, Iran

[*] *Corresponding author*: Clinical Research Development Unit (CRDU), Sayad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran. Email: shohreh.vosoogh@gmail.com

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Abstract

Background: Patients with a low level of pregnancy-associated plasma protein-A (PAPP-A) experience more placental disorders in the second trimester.

Objectives: We aimed to assess UtA-Doppler and placental size to predict adverse pregnancy outcomes in a woman with placental insufficiency and low PAPP-A.

Methods: Following a cross-sectional design, 83 singleton pregnant women with normal chromosomes and PAPP-A $\leq$ 0.5 were examined at 11 - 13 + 6 weeks of gestation. All participants with PAPP-A $\leq$ 0.5 were tested in the Nilo laboratory of Tehran from 2018 to 2019. The placental size and Doppler uterine artery were assessed at 18 - 20 weeks. Three cases were excluded due to abortion and aneuploidy. All participants were assigned to placenta lengths of < 10 cm and > 10 cm. All comparisons between two groups were assayed by the independent *t*-test, Mann-Whitney U test, χ^2-test or Fisher exact test, and Logistic regression model.

Results: Of 80 women, 48 (60%) had placenta length of < 10 cm and 32(40%) had placenta length of > 10 cm. Fourteen (17.5%) were preterm (< 32 weeks), and 36(45%) were IUGR. According to the logistic regression model, in participants with a placenta length of < 10 cm, the risk of IUGR was higher by 9-time than those with placenta length of > 10 cm (OR = 9, CI95% = 3.20 - 25.29). Also, the risk of preterm labor was 3.47 fold higher in the group with placenta length of < 10 cm, OR: 3.47;(CI95% = 1.27 - 9.44). Sensitivity of placenta length of < 10 cm for predicting IUGR was 75% (CI95% = 56.60 - 88.54).

Conclusions: Placental length measurement in the second trimester can help predict adverse pregnancy outcomes in pregnant women with low PAPP-A. Placenta evaluation can assist in planning future pregnancy care to detect the pathology of fetal growth restriction.

Keywords: Placenta Size, Pregnancy-Associated Plasma Protein-A, Intrauterine Growth Restriction, pregnancy Outcomes

1. Background

Pregnancy-associated plasma protein-A (PAPP-A) is primarily made by the placenta and increases with gestational age (1). PAPP-A facilitates insulin growth factor (IGF) function by breaking down the IGF binding protein enzyme to support placental growth and function. It is a protease glycoprotein, which releases the Insulin-like growth factor from IGFBP 4 (2). Low PAPP-A may indicate improper growth and function of the placenta in the future. PAPP-A $\leq$ 0.45 multiples of the median (MOM) are considered as low-level PAPP-A (3-7).

PAPP-A with BHCG serum level, maternal age, and ultrasound sonography of nuchal translucency measurement in the first trimester of pregnancy (11-13+6 week) have a detection rate of 90 % and a false positive rate of 5% for down syndrome screening (8).

The placental function can be assessed in two ways in the second trimester. First, the length of the placenta, which should be at least 10 cm long in the second trimester, and its thickness, which a thickness less than 2 cm, is considered abnormal. The second is examining uterine artery Doppler (UtA- Doppler) and uterine artery pulsatility index (UtA-PI) in the second trimester, which is considered abnormal if the mean PI of both sides (right and left) is more than 1.45 (1).

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All fetuses whose weight is less than 10% of gestational age on ultrasound weight estimate or birth weight are considered as IUGR (9). Women whose PAPP-A level is below the 5% percentile (0.45 MOM) are at increased risk of IUGR, preterm, preeclampsia, and stillbirth (2).

Numerous studies showed an association between the PAPP-A and IUGR, preterm, preeclampsia, and stillbirth in trisomy 21. Since fetuses with trisomy 21 have a reduced PAPP-A level, women with a false-positive screening test are at increased risk of pregnancy complications. Screening tests for placental insufficiency in high-risk women in the second trimester are UtA- Doppler and placental length measurement (10). Evaluation of placenta morphology can improve screening accuracy for FGR but is not sufficient to justify its cost in low-risk populations (11).

A major challenge in modern obstetrics is early detection of pregnancies at high risk of early-onset preeclampsia (PE) and other adverse pregnancy outcomes (APOs) and undertaking necessary measures to improve placenta and reduce the prevalence of the disease (12, 13). A meta-analysis study showed that PAPP-A cannot routinely be recommended to predict fetal loss, and more research is required with a combination of other biomarkers (14).

2. Objectives

This study aimed to investigate placental pathology and uterine artery Doppler to predict adverse pregnancy outcomes in women with low pregnancy-associated plasma protein-A.

3. Methods

This cross-sectional study was conducted on eighty-three singleton pregnant women with normal chromosomes and PAPP-A $\leq$ 0.5 (9) at 11 - 13 + 6 weeks of gestation based on LMP in the Nilo laboratory of Tehran from 2018 to 2019. We selected low PAPP-A cases with high-risk screening results. In cases where the screening results were high risk, the karyotype was checked, among which three cases with aneuploidy or abortion less than 20 weeks were excluded from the study. Amniocentesis was performed in cases with the results of the high-risk first screening test, which included a set of maternal age over 35 years, increased NT, and abnormal PAPP-A and BHCG. The exclusion criteria were multiple pregnancies. Down syndrome fetuses were excluded, and false positives and healthy fetuses were included in the study. All participants had healthy fetuses.

The adverse pregnancy outcomes evaluated in this study included; Preterm labor (early preterm: < 32 weeks; and late preterm: 32 - 37 week), intrauterine growth restriction (IUGR): All fetuses whose weight was less than 10% of gestational age on ultrasound weight estimate or birth weight were considered as IUGR, stillbirth: Baby loss before or during delivery, infant death: Live birth results in death, preeclampsia (Mild/severe), and C/S delivery.

Background variables included; mother's age, body mass index (BMI), parity: (nulliparity/multiparity), infertility, APO history, ASA use in this pregnancy, heparin use pregnancy, UtA result: (normal/Abnormal), and infant sex: (boy/girl).

Small for gestational age (SGA) were identified based on their birth weight, i.e., below 10% of the population weight at that same gestational age by ultrasound. In this study, we considered a weight percent below 10% for IUGR, and our treatment plan for all IUGR cases was according to the RCOG guideline. Umbilical artery (UA) Doppler and fetal middle cerebral arterial (MCA) Doppler were performed for all IUGR cases during the patient's pregnancy visits. Meanwhile, UtA-Doppler and placenta size were evaluated for all 80 patients. Preeclampsia and hypertension was managment based on the RCOG criteria.

The placental characteristics, such as placenta previa, placenta accreta, vascular lake, or abnormal umbilical cord connections, were not considered abnormal. We did not consider the location of the umbilical cord connection to the placenta; we only considered the shape and connection mode of the umbilical cord to the placenta, and no umbilical cord defects were found in this study.

All participants were taken nuchal translucency (NT) and biochemical markers as screening tests for the first trimester of pregnancy. PAPP-A was estimated using the standard Biochemical method by one device and there was no need for patients to fast. Gestational age was estimated based on the measures of NT in sonography. Placenta length was assessed between 18 - 20 weeks, and the largest longitudinal axis was determined as the placental length in sonography (1).

If the placenta was curved, in the fundus, the measurement was performed as follows: It was measured from one edge of the placenta to the midpoint of the junction of the basal and chorionic plate, the distance was measured in two parts, from the edge of the placenta to a point midway between the chorionic and basal plates, then from this point to the opposite edge of the placenta (1). Placenta length less than 10 cm was considered abnormal. UtA-Doppler was assessed between 18 - 24 weeks. Mean of PI $\geq$ 1.45 was considered abnormal.

If there was evidence of fetal growth restriction or amniotic fluid volume in the serial ultrasounds of each patient, fetal health assessment tests, such as the Non-Stress Test (NST), biophysical profiles, arterial Doppler, and fetal middle cerebral arterial (MCA) Doppler assessment, were performed for the fetus.

Termination of pregnancy or continuation of pregnancy protocol was implemented according to RCOG protocol for fetuses with IUGR.

If pregnancy leads to preterm labor or premature rupture of the membrane, or if preeclampsia occurs at gestational age less than 34 weeks, or if the decision to terminate the pregnancy is made in cases of growth restriction less than 34 weeks full course of betamethasone (corticosteroid) was prescribed.

3.1. Ethical Statement

Ethical approval for this study was obtained from the Ethics and Research Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1396.228). Before registration, all participants read and sign the informed written consent form. A copy of the signed consent form was given to the participant. The guidelines on research involving the use of human subjects (beneficence, non-maleficence, veracity, confidentiality, and voluntarism) were strictly adhered to according to the Helsinki Declaration. Participants did not incur any cost by participating in this study and there was no financial inducement.

Pregnant women with abnormal placenta and Doppler were not overlooked and placed in prenatal care under the supervision of a perinatologist, and management strategy was determined based on risk factors and clinical examinations and ultrasound results. For those with fetal growth restriction and abnormal Doppler, the biophysical profile (BPP) test and Color Doppler Ultrasound were performed twice a week or they were admitted as soon as their high blood pressure was diagnosed.

3.2. Statistical Analysis

Pearson chi-square test, Fisher exact, independent *t*-test, and Mann-Whitney U test were used to determine significant associations. A Logistic regression model was done to determine the adjusted risk of placenta length < 10 cm and other significant variables such as maternal age, infertility, APO history, ASA use, and heparin use on adverse outcomes. The odds ratio presented with 95% CI. Statistical significance was considered when P-value < 0.05. Data analysis was administered using SPSS software ver.21.

4. Results

As shown in Table 1, among all 80 participants, 18 (22.5%) were nuliparity, and 62 (77.5%) were multiparty. The mean age of women was 29.90 ± 6.61 years. Forty eight women (60%) had placenta length < 10 cm and thirty two (40%) had placenta length of > 10 cm. There was a significant association between the proportion of mother age (P = 0.0001), history of heparin use (P = 0.003), history of ASA use (P = 0.013), and placenta length. There was no significant association between parity (nullparity/multiparty) (P = 0.79), infertility history (P = 0.56), APO history (P = 0.056), and abnormal UtA (P = 0.52) in low- and high-risk subgroups.

As shown in Table 2, 24 individuals (30%) were late preterm, 14 (17.5%) were early preterm. There was a significant association between preterm labors IUGR, still birth, infant death, mild preeclampsia, and placenta length (P = 0.0001).

According to the multiple logistic regression, after adjusting all significant variables, the risk of IUGR was higher in participants with a placenta length of < 10 cm, than those with a placenta length of > 10 cm, by 9 fold (OR = 9, CI 95% = 3.20 - 25.29). Also, the risk of preterm labor was 3.47 fold more than those with a placenta length of > 10 cm (Table 3).

As shown in Table 4, sensitivity (CI 95%) of placenta length of < 10 cm for predicting IUGR, preterm labor, and preeclampsia was 75 (56.60 - 88.54), 57.89 (40.82 - 73.69), and 70.59 (52.52 - 84.90), respectively.

5. Discussion

This study showed that the placenta length of < 10 cm increases the risk of IUGR by 9-fold (CI 95%; 3.20 - 25.29). Also, a placenta length of < 10 cm and ASA increase the risk of preterm labor by 3.47 and 4.08-fold, respectively, in patients with low PAPP-A.

Low PAPP-A is associated not only with an increased risk of trisomy 21 but also with poor pregnancy outcomes and placental insufficiency. In the first-trimester screening age, HCG and NT are used along with PAPP-A to get the best results.

Low PAPP-A alone is not acceptable for predicting adverse pregnancy outcomes (APOs); meanwhile, the addition of second-trimester screening increases the accuracy of predicting APOs. Since, both ethically and scientifically, mothers with a history of recurrent miscarriages and a history of autoimmune diseases should be treated with heparin, it was prescribed from the beginning of pregnancy and before placental length measurement, to prevent adverse effects of previous pregnancies. At the end of the study, the effect of heparin consumption on adverse pregnancy outcomes was controlled in the logistic regression model.

It was assumed that the combination of evaluating PAPP-A and placental function on ultrasound can be an accurate test to identify pregnancies with placental insufficiency that leads to preterm delivery, stillbirth, etc. In our study, which was performed on 80 high-risk pregnant

Table 1. Demographic Characteristics and Placenta Length of Study Cases (n = 80) [a,b]

Variables	Total (n = 80)	Placenta Length		P Value
		> 10 cm (n = 48)	< 10 cm (n = 32)	
Mother age	29.90 ± 6.61	27.21 ± 5.75	33.94 ± 5.7	0.001
BMI	25.08 ± 1.99	24.88 ± 2.09	25.38 ± 1.83	0.322
Parity				0.79
Nuliparity	18 (22.5)	10 (20.8)	8 (25)	
Multiparity	62 (77.5)	38 (79.2)	24 (75)	
Infertility	12 (15)	4 (8.3)	8 (25)	0.056
APO history	20 (25)	10 (20.8)	10 (31.3)	0.30
ASA use	18 (22.5)	6 (12.5)	12 (37.5)	0.013
Heparin use	6 (7.5)	0	6 (18.8)	0.003
Abnormal UtA	14 (17.5)	8 (16.7)	6 (18.8)	0.52

Abbreviations: UtA, uterine artery Doppler; APO, adverse pregnancy outcome.
[a] Data presented as Mean ± SD or No. (%).
[b] Independent *t*-test, Mann-Whitney U test, χ^2-test, or Fisher exact test was used to compare demographic characteristics in two groups.

Table 2. Pregnancy Outcomes and Placenta Length of Study Cases (n = 80) [a,b]

Variables	Total (n = 80)	Placenta Length		P Value
		> 10 cm (n = 48)	< 10 cm (n = 32)	
Preterm (week)				0.001
32 - 37	24 (30)	16 (33.3)	8 (25)	
< 32	14 (17.5)	0	14 (43.8)	
IUGR	36 (45)	12 (25)	24 (75)	0.001
Still birth	4 (5)	0	4 (12.5)	0.020
Infant death	6 (7.5)	0	6 (18.8)	0.003
Preeclampsia				0.001
Mild	16 (20)	6 (12.5)	10 (31.3)	
Severe	18 (22.5)	4 (5.3)	14 (43.8)	
C/S delivery	34 (42.5)	16 (33.3)	18 (56.3)	0.64
Infant sex				0.52
Boy	44 (55)	26 (54.2)	18 (56.3)	
Girl	36 (45)	22 (45.8)	14 (43.8)	

Abbreviation: IUGR, intrauterine growth restriction.
[a] Data presented as No. (%).
[b] χ^2-test or Fisher exact test was used to compare pregnancy outcomes in two groups.

women with abnormal Doppler, we found that placental length can strongly determine the pregnancy APOs. According to Krebs et al., reduced blood flow, as evaluated by abnormal Doppler, maybe less than the small placenta, leading to reduced gas exchanging villi. It is significant for predicting APOs (15).

Our findings showed a sensitivity of 75%, of placenta length < 10 cm for predicting IUGR was higher than Proctor et al.'s and Soongsatitanon and Phupong's studies with the sensitivity of 48% and 50%, respectively (1, 16). It can be attributed to the fact that in our study a large number of participants, who were referred to a perinatology center for screening, had a history of previous abnormal pregnancies. Proctor et al. showed that small placenta and increase in αFP in patients with low PAPP-A yields perfect positive predictive value (PPV) (i.e., 100%) and a false-positive rate of zero for severe IUGR (1). Schiott et al. showed that evaluating small placenta and AFP level in women with low PAPP-A

Table 3. Predictors of APOs from the Logistic Regression Model [a]

Adverse Outcome	Adjusted Relative Risk	(CI 95%)
IUGR		
Placenta length < 10 vs. > 10 cm	9	(3.20 - 25.29)
Preterm		
Placenta length < 10 vs. > 10 cm	3.47	(1.27 - 9.44)
ASA use	4.08	(1.14 - 14.63)

[a] The logistic regression model was done to determine adjusted odds risk of placenta length < 10 for some pregnancy adverse outcomes. In this model, the effect of placenta length, mother age, infertility, APO history, ASA use, and heparin use on adverse outcomes have been adjusted.

can be used for intense placental insufficiency syndromes (8).

Evaluating small placenta and AFP levels in women with low PAPP-A also is a cost-effectiveness test because the first and second-trimester screening criteria are used in addition to the placenta length, which can indicate placental insufficiency.

Our study showed that UtA-Doppler in the second trimester is not valuable for determining low PAPP-A, while small placenta length is significantly associated with APOs. Although Pilalis et al. studied the UtA-Doppler evaluation potential in screening for pregnancy outcomes (APOs), this test is not recommended for low-risk individuals. Recently, the combination of low PAPP-A with UtA-Doppler in the first trimester of pregnancy has been proposed as a screening for APOs, versus sole PAPP-A, although it is not recommended for low-risk women (17).

According to Toal et al., Placental size may be important because placental blood flow is clearly increased in the second and third trimesters of normal pregnancy (18).

In previous research performed by Wright et al. in the last 20 years, Akolekar et al., and Mesdaghi-Nia et al., mainly as a consequence of the shift in screening for identifying chromosomal defects from the second to the first trimester of pregnancy, have identified a series of early biophysical and biochemical markers of placenta disorder (19-21).

Lesmes et al. and Odibo et al. reported that elevated maternal serum levels of AFP were associated with small for gestational age (birth weight < 5th centile) with or without preterm delivery (22, 23) and stillbirth due to birth weight < 5th centile, as evidenced by Smith et al. (24). Proctor et al. and Smith et al. showed that low PAPP-A in the first trimester and high AFP in the second trimester are strong predictors of severe FGR (1, 25). According to Gaccioli et al. and Lean et al., free BHCG alone ($\geq$ 2.0 MoM) was not associated with any adverse outcome. In contrast, maternal circulating AFP ($\geq$ 2.0 MoM), inhibin A ($\geq$ 2.0 MoM), and uE3 ($\leq$ 0.5 MoM) were significantly associated with an increased risk of SGA infants (11, 26).

Walter et al. demonstrated that IUGR neonates had a significantly lower placental size (27). We also observed reduced placental size in the early first trimester in cases with IUGR. Mesdaghi-Nia et al. showed that serum PAPP-A levels in women with the thick placenta (> 4 cm or > 50% placental length) were generally low (0.8%). They declared that PAPP-A measurements in the first trimester of pregnancy might be more predictable to evaluate a healthy placenta (21).

A previous study in 2008 by Kagan et al. showed that the abnormal shape and morphology of the placenta in the second trimester of pregnancy was significantly associated with pregnancy complications, while none of the screening cases in the first trimester predicted APOs. They suggested that in high-risk pregnancies, placental function tests in the second trimester appear to be more valuable than the first trimester in predicting pregnancy complications (28, 29).

As reported by Gaccioli et al., focusing on prenatal diagnosis of placental disease helps to differentiate between a healthy small fetus for gestational age (SGA) and a fetus at risk for perinatal complications due to FGR and this is one of the important points about examining the shape of the placenta (11).

Based on the findings of the present study, 14 (17.5%) participants had abnormal UtA-Doppler, of whom 6 (18.8%) had a placenta length of < 10 cm. Also, the findings indicated no significant difference between individuals with a placental length of < 10 cm and > 10 cm and abnormal UtA-Doppler. Based on this finding, it seems that UtA-Doppler measurement in low PAPP-A individuals does not help identify the low placental length, because UtA-Doppler is a costly intervention, its measurement is not necessary for predicting placenta length. Future studies, with an appropriate methodology, are needed to validate this finding.

Despite ultrasound and fetal evaluation tests, other factors such as maternal age, pregnancy with medical conditions, and a history of infertility can increase APOs; therefore, diagnosing placental insufficiency and planning for placental screening is an urgent need.

In this study, pregnant women with a placental length of < 10 cm or with abnormal Doppler were further followed up, and the rest of the cases were followed up according to the routine instructions of pregnancy care. An effective screening program may be needed to assess the need for medical interventions, including fatal monitoring or planning for labor induction. According to the results of this study, evaluation and monitoring of fetal growth were

Table 4. Diagnostic Values (Sensitivity, Specificity, and Positive and Negative Predictive Values) of Placenta Length < 10 cm vs. > 10 cm for IUGR

Adverse Outcome	Total Participant (n = 80)			
	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
IUGR	75 (56.60 - 88.54)	75 (60.40 - 86.36)	66.67 (54.09 - 77.25)	81.82 (70.73 - 89.34)
Preterm	57.89 (40.82 - 73.69)	76.19 (60.55 - 87.95)	68.75 (54.57 - 80.12)	66.67 (57.05 - 75.07)
Preeclampsia	70.59 (52.52 - 84.90)	82.61 (68.58 - 92.18)	75.00 (60.65 - 85.38)	79.17 (68.95 - 86.67)

Abbreviation: IUGR, intrauterine growth restriction.

performed more accurately in patients with small placenta at 18 - 20 weeks.

Usually, the fetal biometrics of normal fetuses should be evaluated at 32 weeks, while in small length-placenta fetuses, biometric ultrasounds and fetal weight estimation should be performed every 4 weeks to provide maternal and fetal care if IUGR symptoms begin. In this study, cases with low PAPP-A did not necessarily had abnormal Doppler, and there was no significant difference between UtA-Doppler results and its cost; Therefore, repeated UtA-Doppler measurement is not necessary for patients with low PAPP-A.

5.1. Conclusions

In pregnant women with low PAPP-A, placental length measurement in the second trimester can help predict adverse pregnancy complications, and pregnancy care should be done more carefully and at shorter intervals. In addition, prescription of drugs such as ASA should be considered in some cases. In future studies, placenta measurement should be performed in the first trimester for cases with low PAPP-A and the results not only should be compared with placental length in the second trimester but also should be compared with pregnancy outcomes. Postpartum care focused on placenta evaluation, as a modifiable risk factor, can assist in planning future pregnancy care to detect pathology of fetal growth restriction.

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Footnotes

Authors' Contribution: AJ and SV: Conceptualized and designed the study, collaborated in the collection of data and quality control, edited and critically reviewed manuscript; RT: Critically reviewed manuscript, interpreted the results; FS: Collaborated in data analysis, wrote the first draft of the manuscript, performed statistical analysis; All authors approved the final draft of the manuscript.

Conflict of Interests: The authors declare no potential conflict of interest in this study.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

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