Importance of biochemical markers in placentation at the end of the first trimester

Abstract

Our objective was to study some aspects of placental development at the end of the first trimester of pregnancy and assessment of biochemical markers in terms of placentation. We studied 64 pregnant women at the end of the first trimester of pregnancy. Pregnant women were grouped according to the double test results into two groups: those with genetic risk (study group, n=7) and without genetic risk (control group, n=57). We measured the ratio between placental volume and crown-rump length, the ratio between the distance from the umbilical cord insertion site at the placenta and fundical edge of placentation and the distance between the umbilical cord insertion site at the placenta and cervical edge of placentation. We obtained biochemical data by double-test (pregnancy-associated plasma protein A and free beta human chorionic gonadotropin). The data obtained were processed with Student's t Test and Chi-Test. We did not noticed statistically significant difference between the group with positive double-test and control group on terms of placentation by the end of the first trimester of pregnancy. Low pregnancy-associated plasma protein A values associate significantly with smaller placental volume and a small amount of amniotic fluid. Interestingly, we observed a higher frequency of eccentric umbilical cord insertion in women with pregnancy-associated plasma protein A <.5 MoM compared to the control group (OR=10.9, p=.002). The results showed that biometric data measured with ultrasound at the end of the first trimester correlates positively with pregnancy-associated plasma protein A levels and this could help us screening high risk pregnancies in the near future.

Keywords: *placentation, placental volume, umbilical cord, PAPP-A*

Turos Janos Levente[1], Lucian Puscasiu[1], Kiss Szilard Leo[1], Bereczky Lujza Katalin[1], Rozsnyai Florin Francisc[2], Szabo Bela[1]

1. University of Medicine and Pharmacy, Târgu-Mureș, Romania
2. County Emergency Clinical Hospital Târgu-Mureș, Romania

Correspondence:
Turos Janos Levente
e-mail: jturos@yahoo.com

Introduction

The placenta has an important role in the further development of the pregnancy. It combines the functions of the endocrine system, the excretory system, respiratory and absorption system. Circulatory function appears in the early stage of embryo-placental development and fetal growth, and is closely linked to the size of the placenta, uterine artery blood flow and umbilical arteries blood flow[(1)].

Trophotropism, normally, is defined as a preferential proliferation of trophoblastic placental villi in endometrial areas with better blood supply, together with atrophy of the villi in areas with lower blood irrigation. This enables the placenta to change position and shape with the evolution of pregnancy. At the beginning, the placentation site is round with the umbilical cord insertion in the center of this area. Different proliferation rates due to trophotropism can lead to an eccentric insertion of the umbilical cord at the placenta, although the insertion of the umbilical cord has not changed from the underlying endometrium. Thus insertion of the umbilical cord can reach the edge of the placenta (*insertio marginalis*), or even at a distance from the edge of the placenta (*insertio velamentosa*). Trophotropism can explain the development of different forms of placenta: placenta bilobata, succenturiata etc.

Prospective cohort studies reveal that some of placentation abnormalities can be detected since the late first trimester. Pregnancies that had the umbilical cord insertion in the lower third of the uterus (distance between the fundus of uterus and internal cervical os divided into three equal part) show significantly more anomalies at birth in terms of placenta and the umbilical cord insertion at the placenta (low insertion of the umbilical cord at birth 26%, placenta praevia 23%, velamentous/marginal insertion of the umbilical cord 29%, accessory placenta 14%). In these pregnancies, emergency cesarian section were five times more frequent[(1)].

Some authors report a very good prenatal detection of velamentous umbilical cord insertion at 11-14 weeks of pregnancy by routine screening at the end of first trimester. This allows closer follow-up of these pregnancies, knowing that this anomaly is associated with some obstetrical pathology[(2,3,4)].

In a prospective cohort study (more than 1000 placentas), relative chorionic vascular densities were measured (digital photo postpartum and mathematical methods). With the eccentricity of the placental cord insertion more than 50% of the placental radius, blood transport efficiency was significantly lower than the control group (even if that placenta was round). In these patients, newborn birth weight was lower[(5)].

Placental volume was studied as a predictive factor in further development of pregnancies. For a 10% false positive rate, placental volume measurement in the first trimester of pregnancy (11-14 weeks) reveals 20% of women that will develop early and severe preeclampsia requiring birth before 35 weeks[(6)].

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Studies show that the reproducibility of measurements in utero-placental circulation and placental volume at the end of the first trimester of pregnancy (11-14 weeks) is very good. In women with smaller placental volume and a poor placental vascularization in the first trimester of pregnancy, the impedance to flow in the uterine arteries was higher in the second trimester[7].

This period is characterized by some properties. Most genetic abortions usually occur before this period, so it is a milestone in prenatal screening: screening of chromosomal abnormalities (nuchal translucency, presence of nasal bone, double-test), and placentation in a dynamic phase.

The purpose of this study was (a) to investigate the aspects of placentation with ultrasound at the end of the first trimester of pregnancy, and (b) to develop methods for early diagnosis (first trimester) of high-risk pregnancies.

Materials and methods

We studied 64 women at the end of the first trimester of pregnancy (11w.-13w.+6d.).

First, we measured the following:

- crown-rump lenght (CRL, 60.0+/-8.5 mm);
- gestational sac diameter (GSD, simple average of diameters measured in three dimensions), location of the placenta, placental volume (PV);
- GSD/CRL ratio;
- PV/CRL ratio (placental quotient);
- the distance between the umbilical cord insertion at the placenta and the cranial (fundical) rim of the placenta (F);
- the distance between the umbilical cord insertion at the placenta and the caudal (cervical) rim of the placenta (C);
- F/C ratio. Umbilical cord insertion at the placenta was considered eccentric if F/C ratio was <.33 or >3 (eccentricity of the placental cord insertion more than 50% of placental radius)[5].

The placental volume was calculated following the formula and Figure 1, as below:

$$V= (3R^2+H^2)\Pi*H/6 \quad (1)$$

where:

V - spherical segment of one base;

R - radius;

H - height of spherical segment of one base (in which Π=3.14).

$$R= (F+C)/2 \quad (2)$$

where:

F - the distance between the umbilical cord insertion at the placenta and the cranial (fundical) rim of the placenta;

C - the distance between the umbilical cord insertion at the placenta and the caudal (cervical) rim of the placenta.

Placental volume: $PV=[3(F+C)^2+4H^2]\Pi*H/24$.

Pregnancy-related biochemical data were obtained by double-test: free beta-human chorionic gonadotro-

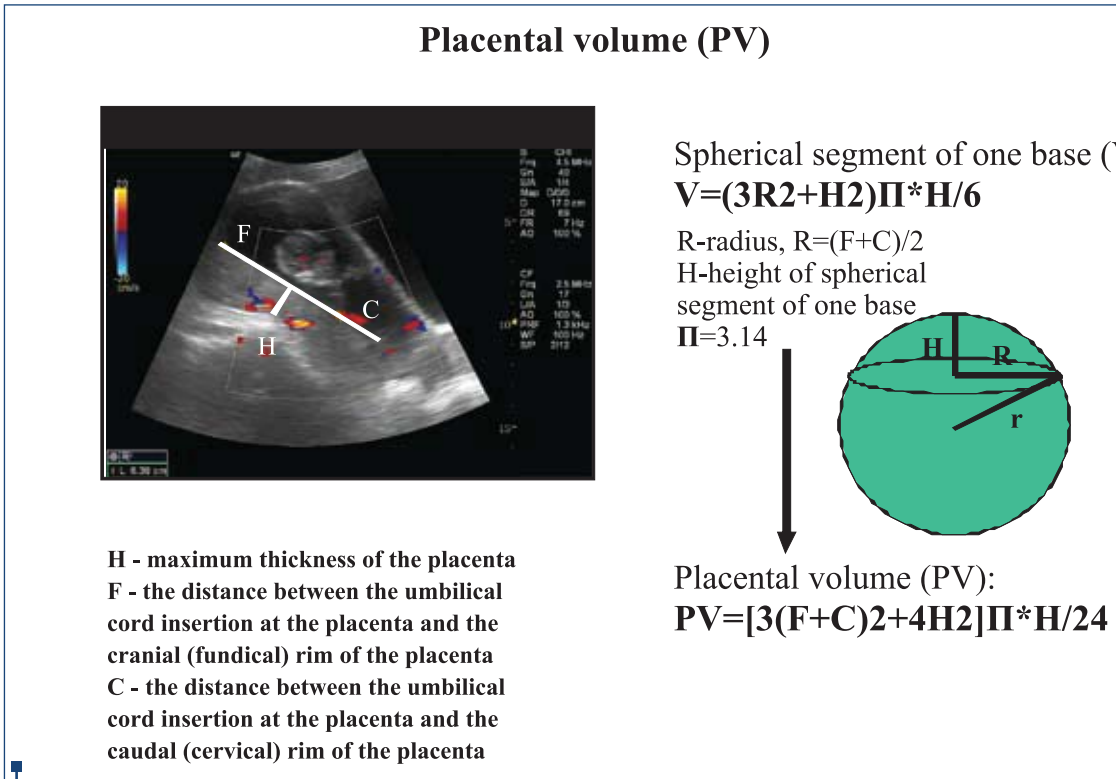

Figure 1. The measures of the placental volume

pin (fb-hCG), pregnancy-associated plasma protein-A (PAPP-A). Double-test cut off was 1:250 measured by PRISCA, nuchal translucency measurements were done according to accepted guidelines.

Uteroplacental circulation was studied by Duplex Color Doppler: resistance index (RI) and pulsatility index (PI) bilateral in uterine arteries (simple average). The equipment used was General Electric S_7 on abdominal probe.

The data were also analyzed in EXCEL, using Student t and Chi-square tests. When p <.05, the data where consider significant.

Results

Pregnant women studied were grouped according to the double-test results into two groups: those with genetic risk (study group, above the cut off 1:250) and those without genetic risk (control group, below the cut off 1:250). Table 1 shows the aspects of placemtation in study group.

There wasn't any significant difference between study and control groups regarding PV, PV/CRL ratio or impedance to flow in the uterine arteries (RI, PI). However, there was a smaller amount of amniotic fluid (GSD/CRL ratio) in pregnancies with genetic risk.

Table 1 Aspects of placentation in study group (women with genetic risk) in the late first trimester of pregnancy

	Double test with genetic risk (study group, nr = 7)	Double test without genetic risk (control group, nr = 57)	p (t-test)
PV (cm^3)	43.4±25.85	48±22.65	p=.11
PV/CRL(cm^2)	7.41±4.3	7.83±3.19	p=.06
GSD/CRL	0.9±0.14	1.22±0.12	p<.08
Uterine a. RI	0.76 ±0.05	0.72±0.07	p=.07
Uterine a. PI	2.02±1.01	1.54±0.51	p=.12

Table 2 Aspects of placentation in women with fb-HCG>2.5 MoM in the late first trimester of pregnancy

	fb-HCG>2.5 MoM (study group, nr = 9)	fb-HCG<2.5 MoM (control group, nr = 55)	p (t-test)
PV (cm^3)	42.43±23.97	46.54±24.17	p=.13
PV/CRL(cm^2)	7.36±3.84	7.56±3.5	P=.17
GSD/CRL	1.14±0.16	1.22±0.12	p<.09
Uterine a. RI	0.73±0.05	0.72±0.07	p=.06
Uterine a. PI	1.67±0.6	1.59±0.62	p=.15

Table 3 Aspects of placentation in women with PAPP-A <.5 MoM in the late first trimester of pregnancy

	PAPP-A<0.5 MoM (study group, nr=7)	PAPP-A>.5 MoM (control group, nr=57)	p (t-test)
PV (cm^3)	30.59±15.21	49.65±22.85	p<.05
PV/CRL(cm^2)	5.14±1.99	8.12±3.29	p<.04
GSD/CRL	1.11±0.14	1.22±0.12	p<.05
Uterine a. RI	0.74± 0.08	0.72±0.07	p=.13
Uterine a. PI	1.60±0.47	1.61±0.63	p<.08

Table 4 Umbilical cord insertion at the placenta in women with low PAPP-A (<0.5 MoM) in the late first trimester of pregnancy

F/C ratio	PAPP-A<.5 MoM (study group)	%	PAPP-A>.5 MoM (control group)	%
<.33 / >3	4	57.14	6	10.9
.33-3	3	42.86	51	89.1
Total	**7**	**100**	**57**	**100**

Depending on the values of fb-HCG, pregnant women were grouped accordingly, following Table 2.

We didn't find any significant difference between those with fb-HCG>2.5 MoM and control group regarding PV, PV/CRL ratio, GSD/CRL ratio or impedance to flow in the uterine arteries (RI, PI). Table 3 shows the values of PAPP-A in the late first trimester of pregnancy.

In this case, also, we didn't find any significant difference (p<.05) between those with PAPP-A< .5 MoM and control group regarding PV, PV/CRL ratio, GSD/CRL ratio. However, it wasn't observed the same thing regarding impedance to flow in the uterine arteries (RI, PI). In pregnancies with PAPP-A< .5 MoM placental volume, PV/CRL ratio and the amount of amniotic fluid (GSD/CRL) were significantly lower to control group (PV 30.59±15.21 *versus* 49.65±22.85, p=.03; PV/CRL 5.14±1.99 *versus* 8.12±3.29, p=.02; GSD/CRL: 1.11±.14 versus 1.22± .12, p=.03). Table 4 shows F/C ratio in the late first trimester of pregnancy, in women with low PAPP-A (<.5 MoM).

In group with PAPP-A <.5 MoM, eccentricity of the placental cord insertion was more frequent compared to the control group (57.14% *versus* 10.9%, OR=10.9, p=.002, Chi-test - statistically significant).

Discussion

Our data show that low serum PAPP-A levels (</=.50 MoM) associate with smaller PV and smaller placental quotient, yet we couldn't found any correlation between low serum PAPP-A levels and impedance to flow in the uterine arteries.

Rizzo et al.[8] measured the first trimester placental volume and 3D power Doppler vascularization of pregnancies with low serum PAPP-A levels (</=.40 MoM). Small amounts of PAPP-A associate with smaller placental volume. Lower index of placental vasculature in the first trimester of pregnancy, significantly associate with intrauterine growth retardation and increased resistance index in umbilical artery in the third trimester of pregnancy.

Another study in 11-13 weeks of pregnancy, with low levels of PAPP-A (</=.30 MoM), shows that small PV and increased levels of alpha-fetoprotein in the second trimester identify women with high obstetrical risk. These pregnancies show significantly more frequent suboptimal development (IUGR and premature birth before 32 weeks four times more frequent, intrauterine demise six times more frequent)[9].

In this regard, we could say that measuring placental quotient at the end of the first trimester can give us data about the future development of pregnancies.

PV/CRL ratio was measured at 12 weeks of pregnancy versus presence of prothodiastolic notch at 22 weeks, for predicting pre-eclampsia and IUGR in a low-risk population (screening criteria: PV/CRL ratio <or=10th centile, PI of >or=90th centile and a bilateral notch at 22 weeks). The study revealed that in both cases the sensitivity of the methods were low (for pre-eclampsia: 38.5% *versus* 44.8%, for IUGR: 27.1% *versus* 28.1%). Although the sensitivity of screening methods was almost identical, placental quotient has the advantage that it can be measured in the first trimester of pregnancy[10].

It is well known that oligoamnios associate with poor prognosis. Our data show that low serum PAPP-A levels (</=.50 MoM) associate with smaller amount of amniotic fluid (GSD/CRL ratio) at the end of the first trimester of pregnancy. Measuring GSD/CRL ratio could help us in risk stratification of pregnancies.

Studies revealed that low serum PAPP-A levels associate with suboptimal pregnancy development. This marker, however, is not always measured (except those undergoing double test). We found that low serum PAPP-A levels (</=.50 MoM) associate with eccentricity of umbilical cord insertion at the placenta in the late first trimester of pregnancy[11,12,13,14].

The benefits of early detection of high-risk pregnancies are well defined. Early identification and risk stratification of pregnant women help prevent severe complications and reduce the impact on patients. In this process, some substances secreted by the fetus or placenta in maternal blood can be helpful. Maternal blood tests are expected to predict the onset of diseases before the manifestation of clinical symptoms. Negative effects of biochemical screening are those linked to false positivity (e.g. uncomplicated pregnancies previously labeled as high obstetrical risk pregnancies), causing anxiety to both pregnant and obstetrician[15,16,17,18].

Conclusions

Our study revealed that there was no significant difference between studied women with or without genetic risk regarding the characteristics of placentation at the end of the first trimester of pregnancy. Also, no significant difference were observed between the group with fb-HCG>2.5 MoM and control (fb-HCG<2.5 MoM).

Low PAPP-A values were significantly associated with lower PV or PV/CRL ratio and a smaller amount of amniotic fluid at the end of the first trimester of pregnancy (GSD/CRL ratio). Moreover, there was a higher frequency of eccentric umbilical cord insertion in women with PAPP-A values <.5 MoM compared to control (OR=10.9, p=.002).

The results showed that biometric data measured with ultrasound at the end of the first trimester correlates positively with PAPP-A levels and this could help us screening high-risk pregnancies in the near future. ■

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