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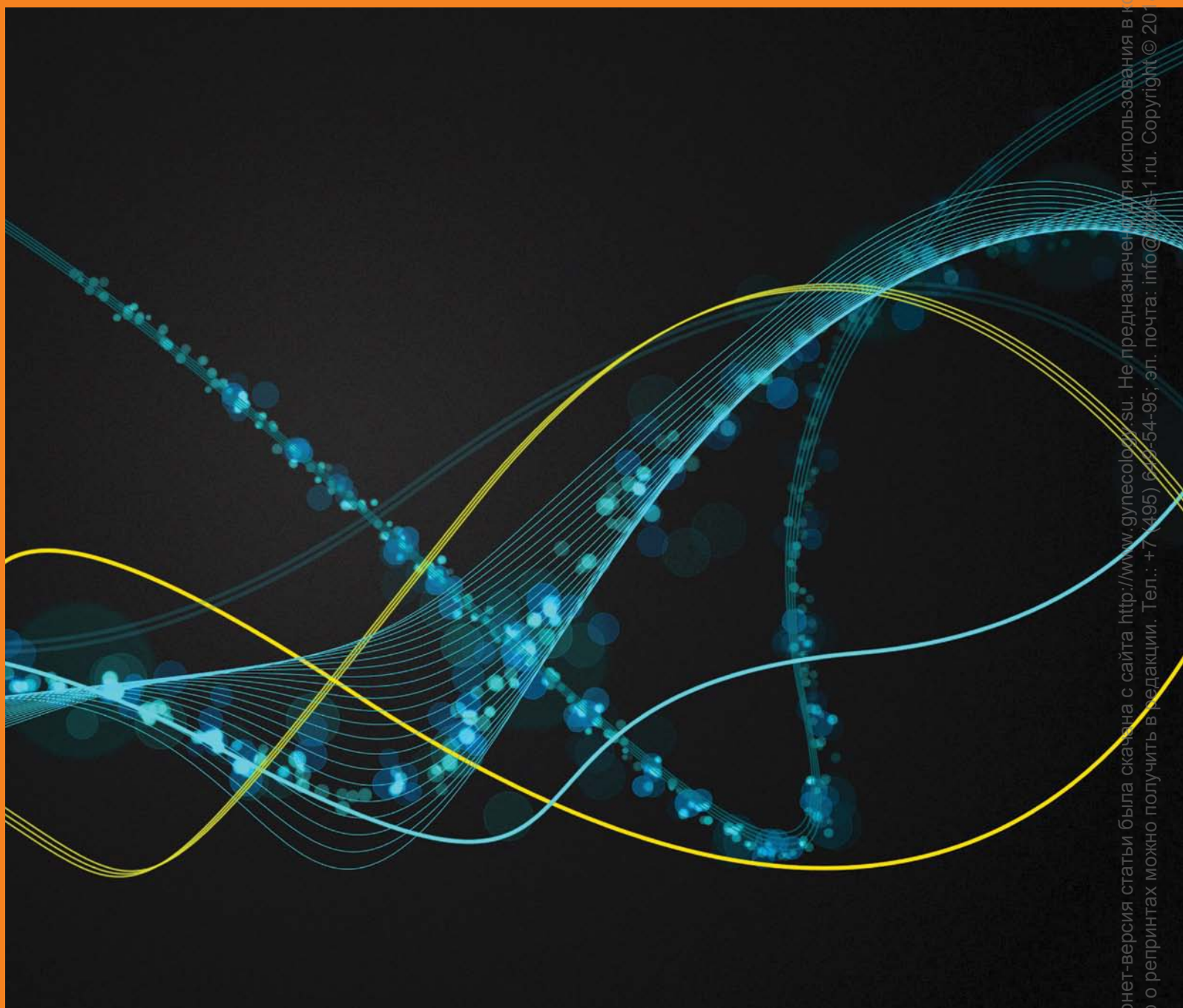

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The relationships between pregnancy-associated protein A levels, placental localization and fetal birth weight

Aşkin E. Güler[1], Melahat Atasever[2], Ulaş Fidan[3], Erhan Artürk[4], Mehmet F. Kinci[3], Serkan Bodur[3]

[1] Lokman Hospital, Fethiye, Turkey;

[2] Giresun University, Giresun, Turkey;

[3] University of Health Sciences; Keçiören-Ankara, 06010 Turkey;

[4] Hospital Gynecology and Obstetrics, Sisli, İstanbul, Turkey

Corresponding author: *Serkan Bodur, e-mail: drserkanbodur@gmail.com*

Abstract

Aim. *This study was designed to determine the relationship between pregnancy-associated protein A (PAPP-A), placenta localization and fetal birth weight (FBW).* ***Materials and methods.*** *First trimester PAPP-A levels, second trimester placental localization and birth weights of 1145 infants were obtained through a retrospective review of the patient follow up charts in Koru Hospital. Serum PAPP-A levels were recorded as the multiple of median (MoM) values, the FBW values of infants were recorded in grams, and the placental localization was recorded under seven different pre-defined categories: 1. placenta anterior; 2. placenta posterior; 3. placenta fundal; 4. placenta fundal-anterior; 5. placenta fundal-posterior; 6. placenta lateral-right; 7. placenta lateral-left. The data were analyzed using the Statistical Package for Social Sciences (SPSS) program (SPSS Inc., Chicago, IL, USA).* ***Results.*** *There was no significant difference between the FBW and PAPP-A levels. The comparison of seven placental localizations shows that the anterior and posterior localizations have an impact on FBW of the infants.* ***Conclusion.*** *The FBW was highest in the cases where the placenta was located in the corpus uteri. We believe this finding is consistent with the fact that the corpus uteri receives the largest blood supply.*

Key words: *fetal birth weight, placental localization, pregnancy-associated protein A*

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Conflict of interests

The authors declare they have nothing to disclose regarding the funding or conflict of interests with respect to this manuscript.

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Взаимосвязь между содержанием ассоциированного с беременностью протеина А, локализацией плаценты и весом плода при рождении

Гюлер А.Е.[1], Атасевер М.[2], Фидан У.[3], Артюрк Е.[4], Кинчи М.Ф.[3], Бодур С.[3]

[1] Госпиталь Локман, Фетхие, Турция;

[2] Гиресунский университет, Гиресун, Турция;

[3] Университет медицинских наук; Турция 06010, Кечиорен-Анкара;

[4] Госпиталь гинекологии и акушерства, Шишли, Стамбул, Турция

Для корреспонденции: *Серкан Бодур, e-mail: drserkanbodur@gmail.com*

Резюме

Цель исследования: *выяснить взаимосвязь между ассоциированным с беременностью протеином А (PAPP-A), локализацией плаценты и весом плода при рождении.* ***Материалы и методы.*** *Значения PAPP-A в I триместре, локализацию плаценты во II триместре и вес 1145 младенцев при рождении определяли посредством ретроспективного анализа карт наблюдения пациенток в госпитале Кору (Анкара). Уровень PAPP-A в сыворотке рассчитывали как кратное медианы (коэффициент, показывающий степень отклонения значения показателя от среднего значения), вес плода измеряли в граммах, а локализацию плаценты определяли по 7 градациям: 1. плацента по передней стенке матки; 2. плацента по задней стенке; 3. плацента в дне матки; 4. плацента в нижнем переднем положении; 5. плацента в нижнем заднем положении; 6. плацента в правом боковом положении; 7. плацента в левом боковом положении. Данные были проанализированы с использованием программы Statistical Package for Social Sciences (SPSS Inc., Чикаго, Иллинойс, США).* ***Результаты.*** *Достоверных различий между значениями PAPP-A и весом плода при рождении выявлено не было. Сравнение 7 локализаций плаценты показало, что передняя и задняя локализация оказывают влияние на вес младенцев при рождении.* ***Заключение.*** *Установлено, что вес плода при рождении является наиболее высоким, когда плацента расположена в теле матки. Несмотря на то, что объяснение этого наблюдения не входило в задачи нашего исследования, мы полагаем, что данный результат отражает обильное кровоснабжение тела матки.*

Ключевые слова: *вес плода при рождении, локализация плаценты, ассоциированный с беременностью протеин А*

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Конфликт интересов

Авторы заявляют об отсутствии необходимости раскрытия финансовой поддержки или конфликта интересов в отношении данной публикации.
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Introduction / Введение

Pregnancy-associated plasma protein A (PAPP-A) and placental localization have been shown to accompany many physiological and pathophysiological processes and play a critical role in fetal growth and development [1]. PAPP-A is one of the unique pregnancy proteins produced by the decidua and placenta; it is secreted into the maternal bloodstream and speeds up the fetal development by degrading the insulin like growth factor binding protein-4 through protease activity and by increasing local insulin like growth factor levels, which plays an important role in the fetal development by controlling glucose and amino acid uptake in trophoblast cells [2–5].

The placenta is a temporary structure that provides basic interactions between the mother and the fetus.

Implantation of the placenta occurs mainly on either anterior or posterior walls of the corpus uteri, where blood levels are known to be highest. According to the trophotropism theory, regardless of blastocyst implantation site in the uterine cavity on the tenth day of fertilization, the final localization of the placenta can be accurately determined at the end of the second trimester due to the development of the lower uterine segment [6]. Placenta, placental localization and its interactions with surrounding structures are all determined and evaluated meticulously during antenatal ultrasonographic examinations. Since the blood supply throughout the uterus is site specific, the placenta localization might play a crucial role in fetal development by influencing fetal physiology and pathophysiology [7, 8].

Although very low levels of PAPP-A and abnormal placental localizations have been linked to various risks for pregnancy and fetal development, no specific study ever examined the impact of these factors on fetal birth weight (FBW). In this regard, the present study was designed to evaluate the possible effects and relations between serum PAPP-A levels, placental localization and FBW in nulliparous risk-free pregnant women.

Materials and methods / Материалы и методы

The pregnancy follow up charts of nulliparous women, who gave term birth in Sincan Koru Hospital and Ankara Koru Hospital between November, 2012 and December, 2015 were retrospectively evaluated. Only low risk singleton pregnancies of women between 25 and 35 years of age with no identified maternal problems, such as hypertension, diabetes/gestational diabetes, smoking or alcohol consumption were selected for the study. Pregnancies with intrauterine growth restriction, congenital chromosome anomalies, amniotic fluid pathologies such as oligo-polyhydramnios, and placental insertion anomalies such as placenta accrete, placenta previa and births with less than a 2500 gram birth weight were excluded from the study.

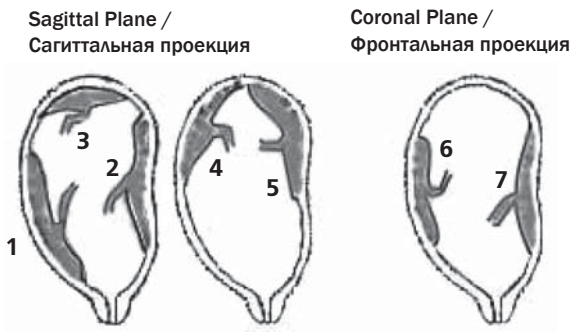

Image 1. Schematization of placental localizations: 1 – placenta anterior; 2 – placenta posterior; 3 – placenta fundal; 4 – placenta fundal-anterior; 5 – placenta fundal-posterior; 6 – placenta lateral-right; 7 – placenta lateral-left.

Рисунок 1. Схема локализаций плаценты: 1. плацента на передней стенке матки; 2. плацента на задней стенке; 3. плацента в дне матки; 4. плацента в нижнем переднем положении; 5. плацента в нижнем заднем положении; 6. плацента в правом боковом положении; 7. плацента в левом боковом положении.

PAPP-A levels in maternal serum were measured using chemiluminescent Siemens kits and an Immulite 2000 XPi analyzer. These measurements were converted to the multiple of median (MoM) data using the PRISCA software. Ultrasonographic examinations were carried out by using a 5 MHz sector ultrasound probes (Voluson 730 pro/expert, General Electric Medical System). Second trimester records were evaluated and placental localizations were classified under one of the seven pre-defined localizations (**Image 1**) at the uterus as anterior wall, posterior wall, lateral (right or left), and fundus uteri (fundal anterior or fundal posterior). The PAPP-A values were categorized under four different quantile ranges: (0–1 MoM, 1.1–2 MoM, 2.1–3 MoM and > 3 MoM).

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) program (SPSS INC., Chicago, IL, USA). Data distribution was evaluated using the Kolmogorov–Smirnov test. The significance of the differences between PAPP-A levels and FBW was determined through two-group comparisons. The Kruskal–Wallis test was used in the cases where the data did not follow normal distributions and were, therefore, divided into more than two sub-groups. For two-group comparisons, the Mann–Whitney U test with the Bonferroni correction was used. P values below 0.05 were accepted as significant.

Results / Результаты

The mean age of the 1145 pregnant women under study was 28.9 ± 4.3 years, the mean PAPP-A level was 2.66 ±1.3 MoM and the mean fetal weight at the time of birth was 3303.6 ± 395.6 grams. The sex ratio among the newborns was 54 % male (n = 618) and 46 % female (n = 527). The anterior and posterior uterine wall located placentas were diagnosed in 224 (19.6 %) and in 315 (27.5 %) of the cases, respectively, while 246 (21.5 %) and 360 (31.4 %) of the placentas were located on the fundal and lateral part of the uterus (**Image 1**).

The means of maternal age, PAPP-A levels and FBWs in relation to placental localization are shown in **Table 1**. The distribution of maternal ages and fetal weights in relation to four PAPP-A quantiles (0–1 MoM in Group 1, 1.1–2 MoM in Group 2, 2.1–3 MoM in Group 3 and > 3 MoM in Group 4) is shown in **Table 2**. No significant difference was found between the four PAPP-A subgroups with respect to FBW (Kruskal–Wallis, p = 0.43). However, a significant difference was found between the placental localization groups with respect to both PAPP-A levels (Kruskal–Wallis, p < 0.01) and FBWs (Kruskal–Wallis, p < 0.01). Within these groups, significant differences in FBWs were found between the placenta anterior, placenta left anterior and placenta posterior groups (**Table 3**).

Table 1. Distribution of maternal age, PAPP-A levels and newborn weights with respect to placental localizations.

Таблица 1. Возраст матери, значения PAPP-A и вес новорожденных при различных локализациях плаценты.

Parameters / Параметры	Anterior / Передняя стенка (n = 224)	Posterior / Задняя стенка (n = 315)	Fundal / Дно матки (n = 171)	Fundal-anterior / Нижняя передняя стенка (n = 31)	Fundal-posterior / Нижняя задняя стенка (n = 44)	Lateral-right / Боковая правая стенка (n = 214)	Lateral-left / Боковая левая стенка (n = 146)
Maternal age / Возраст матери	30,0 ± 0,75	34,35 ± 2,64	22,6 ± 1,7	21,6 ± 2,5	25,16 ± 0,37	26,6 ± 0,59	28,4 ± 0,48
PAPP-A	2,87 ± 1,29	2,21 ± 1,39	2,77 ± 1,26	2,88 ± 1,3	2,71 ± 1,2	2,84 ± 1,22	2,84 ± 1,23
Newborn weight / Вес младенца	3435,0 ± 403,2	3327,9 ± 377,9	3186 ± 426	3053,5 ± 158,5	3418,8 ± 388,18	3285,2 ± 382,9	3232,67 ± 361,46

Note: *PAPP-A – pregnancy-associated plasma protein A.*

Примечание: *PAPP-A – ассоциированный с беременностью протеин А.*

Table 2. Distribution of maternal age and newborn weights with respect to PAPP-A levels.

Таблица 2. Соотношения между возрастом матери, весом новорожденного и значениями PAPP-A.

Parameters / Параметры	PAPP-A			
	0–1 MoM (n = 67)	1,1–2 MoM (n = 241)	2,1–3 MoM (n = 444)	> 3 MoM (n = 392)
Maternal age / Возраст матери	36,7 ± 4,0	28,7 ± 4,43	28,6 ± 3,8	28,1 ± 3,4
Newborn weight / Вес младенца	3364,0 ± 350,2	3296,0 ± 410,6	3306 ± 400	3295,4 ± 389,1

Note: *PAPP-A – pregnancy-associated plasma protein A.*

Примечание: *PAPP-A – ассоциированный с беременностью протеин А плазмы.*

Table 3. Groups of comparison where significant differences by the Mann–Whitney U–test with the Bonferroni correction were found.

Таблица 3. Группы сравнения, между которыми выявлены статистически достоверные различия по U–тесту Манна–Уитни с поправкой Бонферрони.

Compared groups / Группы сравнения	p (0,00238)
Anterior placenta vs. fundal placenta / Плацента на передней стенке vs. плацента в дне матки	< 0,001
Anterior placenta vs. lateral-right placenta / Плацента на передней стенке vs. плацента в правом боковом положении	< 0,001
Anterior placenta vs. lateral-left placenta / Плацента по передней стенке vs. плацента в левом боковом положении	< 0,001
Posterior placenta vs. lateral-left placenta / Плацента на задней стенке vs. плацента в левом боковом положении	< 0,001
Posterior placenta vs. lateral-right placenta / Плацента на задней стенке vs. плацента в правом боковом положении	< 0,001
Posterior placenta vs. fundal anterior placenta / Плацента на задней стенке vs. плацента в нижнем переднем положении	0,001
Posterior placenta vs. fundal placenta / Плацента на задней стенке vs. плацента в дне матки	< 0,001
Fundal anterior placenta vs. lateral-right placenta / Плацента в нижнем переднем положении vs. плацента в правом боковом положении	< 0,001
Fundal posterior placenta vs. lateral-right placenta / Плацента в нижнем заднем положении vs. плацента в правом боковом положении	< 0,001
Lateral-right placenta vs. lateral-left placenta / Плацента в правом боковом положении vs. плацента в левом боковом положении	< 0,001

Discussion / Обсуждение

This study evaluates the effects of PAPP-A levels and placenta localizations on fetal weight of newborn babies. According to our findings, there was no correlation between PAPP-A levels and fetal weight; however, FBW was consistently tending to be higher when the placenta was located on the anterior and posterior uterine walls. Recently, S. Canini et al. evaluated the relationship

between PAPP-A levels and FBW by comparing 149 control subjects and found PAPP-A levels to be significantly lower among small for gestational age (SGA) newborns and significantly higher among large for gestational age (LGA) newborns [9]. As the present study was designed to identify the effect of placentation on fetal growth, the fetuses affected by obstetric complications were all excluded from the study. That is why, correlations between PAPP-A levels and SGA/LGA fetuses could not be confirmed in our study. In another study, the first trimester PAPP-A and beta-human chorionic gonadotrophin (β-hcG) levels had a positive correlation with fetal growth parameters like the femur length and the abdominal circumference; however, no relationship between fetal weight and PAPP-A levels were tested there [10]. Here in the current study, we found no significant correlations between the first trimester PAPP-A levels and the fetal weight.

From another standpoint, K. Devarajan et al. reported no significant correlations between he placenta location and fetal weight by categorizing the placental locations under three different sites [11]. They found that the fetal weight was not significantly higher for placenta anterior, placenta posterior or placenta fundal anterior localizations. Based on our data, we believe that having only three categories may be masking some less obvious relationship between the placenta localization and the fetal growth rate. In our study, we had 7 placental localization subgroups, which helped identify the significant effect of localization on fetal weight. Probably, this specific subdivision reflected the differences in placental blood supply in these specific locations. On the other hand, identifying the placental localizations under similar terms like placenta anterior, posterior and fundal, shouldn't be considered as the same entities when the issue evaluated under three or seven different placental localizations. However, these results would be different if the placental localizations were grouped more specifically, as in the current study.

Furthermore, we found it inappropriate to evaluate the nulliparous and multiparous women in the same setting, as the uterine vasculature is somewhat different between the primiparous and multiparous uterus. That factor may explain why the results of K. Devarajan et al. [11] did not corroborate with ours as they included all singleton gestations in their analyses without discriminating between primiparous and multiparous pregnancies, whereas we included primiparous cases only.

The number of studies on the relationship between PAPP-A levels and fetal weights in normal pregnancies is quite low. Reports on the effects of first trimester placenta hormones or placenta localizations on obstetric complications, such as preeclampsia, eclampsia, intrauterine growth restriction and gestational diabetes, are more common [12–15]. In the present study, only primiparous pregnancies with no obstetric problems were examined, and the data were collected retrospectively. According to the results, the fetal weight was significantly higher when the placenta was anteriorly or posteriorly localized, probably because these regions have the highest blood supply and are most appropriate for blastocyst implantation. This is a clinical conclusion supporting the trophotropism hypothesis [6].

Conclusion / Заключение

Placenta anterior and posterior localizations have an impact on fetal weight of newborns. The level of PAPP-A, which is secreted from the placenta during early pregnancy, cannot be used for reliable fetal weight predictions. Further studies on the relationship between the more sophisticated macroscopic and microscopic characteristics of the placenta and the newborn weight could bring more specific scientific results in the future. And also, clinical studieson specific effects of placenta-related molecules should take into account the role of placental localizations as it is demonstrated in this study.

References / Литература:

1. Fidan U., Ulubay M., Bodur S. et al. The effect of anatomical placental location on the third stage of labor. *Clinical Anatomy*. 2017;3(4):508–11.
2. Sun I.Y., Overgaard M.T., Oxvig C., Giudice L.C. Pregnancy associated plasma protein A proteolytic activity is associated with the human placental trophoblast cell membrane. *J Clin Endocrinol Metab*. 2002;87:5235–40.
3. Giudice L.C., Conover C.A., Bale L. et al. Identification and regulation of the IGFBP-4 protease and its physiological inhibitor in human trophoblasts and endometrial stroma: evidence for paracrine regulation of IGF II bioavailability in the placental bed during human implantation. *J Clin Endocrinol Metab*. 2002;87:2359–66.
4. Kniss D.A., Shubert P.J., Zimmerman P.D. et al. Insulin-like growth factors. Their regulation of glucose and amino acid transport in placental trophoblasts isolated from first trimester chorionic villi. *J Reprod Med*. 1994;39(4):249–56.
5. Çoskun B., Kokanali D., Çoskun B. et al. Association between second trimester maternal serum markers and birthweight. *J Turk Ger Gynecol Assoc*. 2016;17:S313.
6. Obstetrics: normal and problem pregnancies. Eds. S.G. Gabbe, J.R. Niebyl, J.L. Simpson. 5th edition. *Churchill Livingstone*, 2007. 1416 p.
7. Gonser M., Tillack N., Pfeiffer K.H., Mielke G. Placental location and incidence of preeclampsia. *Ultraschall Med*. 1996;17(5):236–8.
8. Newton E.R., Barass V., Cetrulo C.L. The epidemiology and clinical history of asymptomatic midtrimester placenta previa. *Am J Obstet Gynecol*. 1984;148(6):743–8.
9. Canini S., Prefumo F., Pastorino D. et al. Association between birth weight and first-trimester free β-human chorionic gonadotropin and pregnancy-associated plasma protein A. *Fertil Steril*. 2008:89(1):174–8.
10. Leung T.Y., Chan L.W., Leung T.N. et al. First-trimester maternal serum levels of placental hormones are independent predictors of second-trimester fetal growth parameters. *Ultrasound Obstet Gynecol*. 2006;27(2):156–61.
11. Devarajan K., Kives S., Ray J.G. Placental location and newborn weight. *J Obstet Gynaecol Can*. 2012;34(4):325–9.
12. Torricelli M., Vannuccini S., Moncini I. et al. Anterior placental location influences onset and progress of labor and postpartum outcome. *Placenta*. 2015;36(4):463–6.
13. Osmundson S.S., Wong A.E., Gerber S.E. Second-trimester placental location and postpartum hemorrhage. *J Ultrasound Med*. 2013;32(4):631–6.
14. Magann E.F., Doherty D.A., Turner K. et al. Second trimester placental location as a predictor of an adverse pregnancy outcome. *J Perinatol*. 2007;27(1):9–14.
15. Kalem M.N., Yildirim S., Onaran Y. et al. Low birth weight and perinatal risk factors. *Yeni Tıp Dergisi*. 2015;32:152–6.

About the authors:
Aşkin E. Güler – MD, Gynecology and Obstetrics Department, Lokman Hospital, Fethiye, Turkey.
Melahat Atasever – Associate Professor, Faculty of Medicine, Department of Obstetrics and Gynecology, Giresun University, Giresun, Turkey. ORCID: https://orcid.org/0000-0001-8232-4719.
Ulaş Fidan – Associate Professor, Gülhane Medical Faculty, Department of Obstetrics and Gynecology, University of Health Sciences, Ankara, Turkey. ORCID: https://orcid.org/0000-0001-7603-597X.
Erhan Artürk – MD, Hospital Gynecology and Obstetrics, Sisli, İstanbul, Turkey.
Mehmet F. Kinci – MD, Gülhane Medical Faculty, Department of Obstetrics and Gynecology, University of Health Sciences, Ankara, Turkey.
Serkan Bodur – MD, Associate Professor, Gülhane Medical Faculty, Department of Obstetrics and Gynecology, University of Health Sciences. Address: 06010, Keçiören-Ankara, Turkey. E-mail: drserkanbodur@gmail.com. ORCID: https://orcid.org/0000-0003-4461-9174. Scopus Author ID: 16743475900.

Сведения об авторах:
Гюлер Аскин Эврен – врач, отделение гинекологии и акушерства, Госпиталь Локман.
Атасевер Мелахат – доцент медицинского факультета, отделение акушерства и гинекологии Гиресунского университета. ORCID: https://orcid.org/0000-0001-8232-4719.
Фидан Улаш – доцент медицинского факультета Гюльхане, отделение акушерства и гинекологии Университета медицинских наук. ORCID: https://orcid.org/0000-0001-7603-597X.
Артюрк Эрхан – врач, Госпиталь гинекологии и акушерства.
Кинчи Мехмет Ферди – врач, медицинский факультет Гюльхане, отделение акушерства и гинекологии Университета медицинских наук.
Бодур Серкан – врач, доцент медицинского факультета Гюльхане, отделение акушерства и гинекологии Университета медицинских наук. Адрес: 06010, Кечиорен-Анкара, Турция. E-mail: drserkanbodur@gmail.com. ORCID: https://orcid.org/0000-0003-4461-9174. Scopus Author ID: 16743475900.