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Fetuin A level in advanced placental calcification at term pregnancies

Esin Merve Erol Koc[1], Selen Yaman[1], Yasemin Tasci[2], Nihal Omur[3], Fatma Meric Yilmaz[4], Yeksin Helvacioglu Karatas[5], Salim Erkaya[5], Ali Ozgur Ersoy[5], Jale Karakaya[6], Rahime Bedir Findik[1]

[1]Ankara City Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey
[2]Kütahya Training and Research Hospital, Department of Obstetrics and Gynecology, Kütahya, Turkey
[3]Ankara Numune Training and Research Hospital, Department of Biochemistry, Ankara, Turkey
[4]Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Biochemistry, Ankara, Turkey
[5]Ankara Zekai Tahir Burak Women Health Training and Research Hospital, Ankara, Turkey
[6]Hacettepe University, Faculty of Medicine, Department of Biostatistics, Ankara, Turkey

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ABSTRACT

Aim: Fetuin A is a multifunctional protein which is a marker of pathological calcification in several diseases. This study aimed to evaluate serum fetuin A level in term pregnancies with grade 3 placental calcification.

Material and Method: Fifty-seven pregnant women who applied obstetrics outpatient clinic for routine pregnancy follow-up at term were included in this study. The study was designed prospectively. Patients with grade 3 placental calcification (n=29) were compared to patients with non-calcified placenta (n=28) in terms of serum fetuin A levels.

Results: Maternal serum calcium levels of pregnant women with grade 3 calcified was significantly increased compared to pregnant women with non-calcified placenta. There was no significant difference between the fetuin A levels of study and control groups. The fetuin A level was not found to be correlated with maternal serum calcium level.

Conclusion: Fetuin A has been targeted as a marker for pathological calcification. The findings of the current study may support the thought that term placental calcification may be physiological rather than a pathological process.

Keywords: Placental calcification, term pregnancy, calcium, fetuin A

INTRODUCTION

Fetuin A is a plasma glycoprotein which exists in all vertebrates and takes role in metabolic events as mineralization, inflammation, cell adhesion, proliferation, and differentiation. It is mainly synthesized in liver and sequestered at physiological and pathological calcification areas (1-3). Fetuin A is a potential inhibitor of ectopic calcification, as well as takes role in normal osteogenetic activity of bone tissue (2, 4). Increased serum fetuin A levels were shown to be significantly related with gestational and type 2 diabetes mellitus (GDM and DM), preeclampsia, cardiovascular diseases (CVD), chronic kidney disease, hypertension (HT), metabolic syndrome and cigarette smoking (5-8).

Placental calcification is a widespread calcium deposition of placenta. The calcification can be clinically detected through ultrasonographic evaluation. Grannum et al. established the grading scale for placental maturity. Advanced degree (grade 3) placental calcification was indicated to be related with pulmonary maturity (9). The placental calcification at third trimester was shown to indicate adverse pregnancy outcomes including preeclampsia, intrauterine growth restriction and stillbirth. Besides, its clinical significance was reported as more prominent when it is detected at early weeks of the third trimester (10-14).

Despite the studies reporting the adverse outcomes of grade 3 placental calcification at the third trimester of pregnancy, the pathophysiology of placental calcification at term is not clearly elucidated yet. In this study, we aimed to evaluate the change in serum fetuin A levels in grade 3 placental calcification at term pregnancies.

Corresponding Author: Esin Merve Erol Koc, esinmerve87@gmail.com
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MATERIAL AND METHOD

This study was performed by participation of 57 Caucasian singleton pregnant women who consecutively applied to Ankara Dr. Zekai Tahir Burak Women Health and Research Hospital, Ankara, Turkey, for routine pregnancy follow-up. Approval for the study was granted by Ankara Zekai Tahir Burak Women Health Training and Research Hospital Ethics Committee (Date: 26.06.2014, Decision No: 8). The study design was prospective, and data collection was completed in six months starting from June 2014. Informed consent was taken from all participants before the data collection. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Healthy pregnant women at term were included in this study. The study group consisted of pregnant women with grade 3 placental calcification (n=29). The control group included pregnant women without grade 3 placental calcification (n=28). Detailed medical history was taken from all participants. Physical examination was performed including systolic blood pressure measurement and body mass index (BMI) calculation. Routine laboratory parameters including complete blood count, liver and kidney function tests were also evaluated whether they are in normal ranges. The clinical characteristics and demographic features of the participants were recorded. Pregnant women with the history of smoking, comorbidities including DM, GDM, HT, preeclampsia, cardiovascular diseases, metabolic syndrome, thyroid dysfunction, connective tissue disorders, inflammatory diseases, active infectious conditions, rupture of membranes, and presence of structural/chromosomal fetal abnormalities were excluded.

Placental calcification was assessed through Grannum's classification (9). Ultrasonographic evaluation was performed with MindrayM5 brand ultrasound scanner (Mindray, Shenzhen, China) by the same obstetrician. Fetuin A level was examined from blood serum samples taken from antecubital vein. Boster brand ELISA kit (USA, Catalog #EK0757) based on quantitative sandwich ELISA principle was used for serum analyses. The results were presented as ng/ml.

Statistical Analyses

Statistical analyses were carried out by IBM-SPSS for Windows V21 (IBM-SPSS, Armonk, NY, USA). Categorical variables were expressed as number and percentages, numerical variables were expressed as mean, median and standard deviation. Independent samples t-test was used for normally distributed numerical variables. Chi-Square test was used to compare categorical variables. Spearman's rho correlation analysis was used to investigate the relationship between not normally distributed numerical variables. Two-tailed P-value <0.05 was considered statistically significant. Binary logistic regression analysis was used to investigate the variables affecting the placental calcification through forward stepwise LR method. G-Power Version 3 was used in for sample size analysis (Universitat Kiel, Kiel, Germany), before the study start. The sample size was found to be 25 for each group with assumed power of 0.84, a significance level of 0.05 and effect size of 0.5. A p value lesser than 0.05 was defined as statistically significant.

RESULTS

This study included 60 pregnant women. However, 3 participants were excluded from the study due to preeclampsia development after their participation in the study. The data of 57 pregnant women were evaluated at final analysis. Demographic features and clinical characteristics of study and control groups were presented in **Table 1**.

Table 1. Demographic features and clinical characteristics of study and control groups

Variables	Placental calcification (n=29)	Control Group (n=28)	P-value
Maternal age (years) Mean±SD	25.03±5.15	27.14±4.9	0.12
BMI (kg/m²) Mean±SD	27±2.66	27.65±3.40	0.87
Gestational age (weeks) Mean±SD	39±1.62	39±1.95	0.93
Birth weight (g) Mean±SD	3417.93±374.26	3281.78±364.42	0.17
APGAR score 5th min <7 n (%)	4/29 (13)	3/28 (10)	0.75

BMI: Body mass index; SD: Standard deviation P-value <0.05 was considered statistically significant

The fetuin A levels were similar for the study and control groups (350.72±63.68 vs. 336.27±56.96, respectively; p=0.370). Maternal serum calcium level was significantly higher in pregnant women with grade 3 placental calcification (p=0.022) (**Table 2**).

Table 2. Maternal serum calcium level and maternal serum fetuin A level of the study group compared to control group

Variables	Placental calcification (n=29)	Control Group (n=28)	P-value
Maternal serum calcium level (mg/dl) Mean±SD	8.51±0.42	8.15±0.70	0.02*
Maternal serum Fetuin A level (ng/ml) Mean±SD	350.72±63.68	336.27±56.96	0.37

SD: Standard deviation, *P-value <0.05 was considered statistically significant

There correlation of fetuin A level with the maternal serum calcium level was not significant (p >0.05) (**Table 3**).

Table 3. Correlation between maternal serum Fetuin A level and the related parameters

Variables	r	P-value
Birth weight (g)	-0.16	0.21
Maternal serum calcium level (mg/dl)	-0.21	0.11

P-value <0.05 was considered statistically significant

Logistic regression analysis indicated that 1 unit (mg/dl) increase at maternal serum calcium level was resulted in 3.58-fold increase at possibility of placental calcification development [CI 95%=3.58 (1.08-11.86), p=0.037].

DISCUSSION

Fetuin A is a marker for pathological calcification in several pregnancy related comorbidities. Grade 3 placental calcification at last trimester of pregnancy may be related with adverse pregnancy outcomes. The current study evaluated serum fetuin A level in grade 3 placental calcification in term pregnancies. Serum fetuin A level was slightly decreased in study group however, the difference was not significant. On the other hand, maternal serum calcium level was found to be an independent estimator of placental calcification with a 3.58-fold increase regarding to 1 unit increase in calcium level.

Actual mechanism of placental calcification is unclear and may be physiological in course of placental aging (15). On the other hand, placental calcification may be the result of a pathological process such as dystrophic changes under ischemic conditions or metastatic calcification related with mineral supersaturation (16, 17). In the current study, maternal serum calcium level of the pregnancies with grade 3 placental calcification was significantly higher than the control group. Maternal serum calcium level was detected as a determinant of placental calcification. However, serum calcium levels of both the study group and control group were within the normal range. Therefore, the significant difference should not be assumed as a pathological increase in calcium level in the study group. The correlation analysis between fetuin A level and maternal serum calcium level was also not reveal a significant relation.

Previous studies on fetuin A have been concentrated on preeclampsia and GDM in pregnant population. Fetuin A executes some cell protective functions by inhibiting receptor tyrosine kinases. However, the inhibitory pathways triggered by increased amount of fetuin A may impair trophoblast invasion in the early weeks of gestation, consequently leading to preeclampsia development (18). Through the inactivation of receptor tyrosine kinase activity, fetuin A also takes role in pathogenesis of GDM and liver diseases (19-21). In addition, fetuin A levels also increase in normal course of pregnancy by advancing gestational age (22). Subsequent studies also shown that fetuin A levels decrease by young maternal age and morbid obesity (18, 21, 23). In this study, the study and control groups were similar in terms of gestational age, maternal age, and maternal BMI.

Fetuin A is known to be a negative acute phase reactant in inflammatory diseases and infectious conditions besides to be a calcification marker (24, 25). Previous studies have shown that serum fetuin A level is significantly lower in preeclamptic patients with hemolysis-elevated liver enzymes-low platelets (HELLP) syndrome compared to the healthy controls and compared to preeclamptic cases without HELLP syndrome. This situation was explained through that fetuin A is a negative inflammatory mediator (26, 27). In this regard, the current study included the pregnant cohort without any systemic inflammatory or infectious condition.

Advanced placental calcification before 36 weeks of gestation is defined as preterm placental calcification. It was indicated to be related with pregnancy complications as preeclampsia, placental abruption, and stillbirth (11, 13, 15). Advancing gestational age, that is related with the increasing fetuin A level is as well as responsible for increasing amount of placental calcium deposition. On the other hand, prominent placental calcification at term thought to be a physiological process with 39.4 % incidence (28). Similar serum fetuin A levels between the groups also appear as evidence for the physiologic basis of grade 3 calcification at term. The birthweight and 5th minute APGAR score were also similar between the study and control groups. The results of the current study appear to be consistent with the general approach which is towards to accept placental calcification at term as physiological.

The similarity of clinical, and demographic features between the groups and inclusion of healthy subjects appears to be the strongest aspects of the study. On the other hand, the study has a number of limitations. In this study, ELISA method was used to was measure serum fetuin A level. However, some previous studies reported that quantitative measurement of fetuin-mineral complexes may better exhibit calcification stress and give more accurate results (29, 30). Another limitation of the current study is that umbilical cord fetuin A level was not evaluated. Due, possible relations between of umbilical cord fetuin A level with placental calcification could not be evaluated. This study did not examine preterm placental calcification, which may lead to adverse pregnancy outcomes, can be also considered as a limitation. A third study group composed of pregnancies with preterm placental calcification might give us some notable findings regarding the role of fetuin A in pathogenesis of placental calcification.

The study findings supported the general thought that placental calcification at term may not be accepted as a component of fetal wellbeing. This study did not show any significant relation between the placental calcification and serum fetuin A level. There is need for studies designed in pregnant cohort with preterm placental calcification to evaluate the role of fetuin A in pathophysiology of calcified placenta.

CONCLUSION

In this current study, fetuin A, which is a marker of dystrophic calcification, was not found to be increased in advanced degree placental calcification at term. The current findings indicate that the development of placental calcification at term may be based on a physiological course.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by Ankara Zekai Tahir Burak Women Health Training and Research Hospital Ethics Committee (Date: 26.06.2014, Decision No: 8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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