

Preterm placental calcification: maternal calcium, magnesium, 25(OH)D levels and adverse obstetric outcomes in low-risk pregnant women

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ABSTRACT

Aim: The aim of our study is to examine early and late preterm placental calcification (PPC) and compare their relationship with maternal calcium, magnesium and 25(OH) D levels and adverse obstetric outcomes.

Material and Method: This prospective cohort study was conducted by examining the pregnant women at their 24th to 36th gestational weeks who applied to the Gynecology Department of Okmeydanı Training and Research Hospital. In this study, 207 patients were selected as the study group.

Results: When the early and late PPC groups were compared, rates of low birth weight (LBW) was statistically higher in the early PPC group. (p=0.022) Oligohydramnios was more common in the early and late PPC patients compared to non-PPC pregnant women. However, oligohydramnios and LBW were not found statistically significant difference in logistic regression analysis. There was also no statistically significant difference in maternal calcium, magnesium and vitamin D levels between the groups.

Conclusion: Preterm placental calcifications might be associated with fetal and maternal complications. But the diagnosis of PPC alone is not effective in determining fetal prognosis.

Keywords: Calcium, low birth weight, magnesium, preterm placental calcification, vitamin D

INTRODUCTION

Placenta acts as a basic endocrine organ while providing nutrient transfer between mother and fetus during pregnancy. Placental calcification (PC) is a condition frequently detected in ultrasonographic examination during pregnancy. The echogenic focus image in the placenta occurs as a result of calcium accumulation in the placental tissue and is generally seen on the maternal aspect and perivillous areas. Possible causes of tissue calcification can be physiological, dystrophic and metastatic (1). When calcium accumulates in the basement membrane and lobules, a linear or lobulated echogenic image is formed. Using the maturational changes in placenta, Grannum et al. created a grading system (2). The indentations and ring formation are seen in Grade III placenta, and they found in 39.4% of pregnancy at term (3,4). Calcifications seen before the 36 weeks of gestation are called preterm placental calcifications (PPC) and have

been found to be associated with obstetric complications (5). There are studies showing that low birth weight (LBW) and abnormal Doppler ultrasound findings are more frequently seen in this group (6).

Calcium and magnesium have a role in the regulation of myometrial activity and maternal serum levels decrease with advancing gestational weeks (7). In the second trimester, premature uterine contraction in women may be related to the homeostasis of calcium-phosphorus-magnesium (8). Maternal calcium and vitamin 25 (OH) D levels were found to be associated with PC and it was concluded that the placenta is important in vitamin D regulation (9,10).

The aim of our study is to examine PPC and compare their relationship with maternal calcium, magnesium and vitamin D levels and adverse obstetric outcomes.

MATERIAL AND METHOD

The study was initiated with the approval of the Okmeydanı Training and Researches Hospital Ethics Committee (Date: 23/12/2019, Decision No: 48670771-514.10./1511). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

This prospective cohort study was conducted by examining the pregnant women at their 24th to 36th gestational weeks who applied to the Gynecology Department of Okmeydanı Training and Research Hospital and had antenatal follow-ups between January 1,2020 and December 31,2020. Gestational age was calculated according to the last menstrual period or findings of ultrasound performed before the 20th gestational week. Gravida, parity, abortion numbers, maternal height, weight values, gestational week of all patients were recorded. Multiple pregnancy, smokers, alcohol users, pregnant women under 18 years old, those with diagnosed chromosomal anomalies, maternal chronic diseases, asthma, pregestational diabetes, and placenta previa, pregnant women receiving calcium, magnesium and vitamin D supplementations were excluded from the study.

From antecubital vein of the mothers, we obtained blood samples and calcium, magnesium and vitamin D levels were measured. Obstetric ultrasound was performed to evaluate the status of placenta. Placental maturity was determined using the Grannum classification: Grade 0: uniform echogenicity with smooth chorionic plate; Grade I: Hyperechoic area or parenchymal calcification and indentations of chorionic plate; Grade II: Occasional hyperechoic areas or basal calcification and deeper indentations of the chorionic plate; Grade III: Basal plate calcification, chorionic plate interrupted by indentations that invate to the basal plate (2). All ultrasonographic examinations were performed by one qualified obstetrician using a Esaote My Lab Seven equipped with a 1–8 MHz convex-arrayabominal transducer to avoid interobserver bias.

Grade III placental calcifications detected at earlier than 36th gestational weeks were recorded as preterm placental calcification (PPC). Patients were followed up until delivery. Although the study started with 246 pregnant women, 207 patients were selected as the study group because birth records of 39 patients were not available. Weeks of delivery, fetal weight, delivery type, cesarean indications and gender of the newborns were recorded. Besides, maternal, and obstetric outcomes as preeclampsia, oligohydramnios, polyhydramnios, small for gestational age (SGA), preterm birth, postterm birth, preterm premature rupture of membrane

(PPROM), premature rupture of membrane (PROM), low birth weight (LBW), preeclampsia, gestational diabetes mellitus (GDM), mort de fetus, macrosomia were recorded.

According to the time when placental calcification was initially confirmed women were classified into one of three groups as follows: an early PPC (Group 1, n=43), in whom PPC was found prior to 32. gestational week, and a late PPC (Group 2, n=62), in whom PPC was found between 32. and 36. gestational weeks; and a control group (Group 3, n=102), in whom PPC was not seen between 24. and 36. gestational weeks.

Maternal calcium, magnesium, vitamin 25 (OH) D levels, and adverse obstetric outcomes were compared with placental grades. Reference ranges for serum magnesium (1,8-2,6 mg/dl) Vitamin 25(OH)D (20-50 µg) calcium (8.8–10,6 mg/dl) were determined as indicated.

Preterm labor was defined as delivery with cervical dilatation and effacement accompanying with uterine contractions before 37. gestational weeks. Deliveries after 42. gestational week were evaluated as postmature births. Low birth weight was defined as fetal weight of less than 2500 g and fetal macrosomia as over 4000 g. Fetal demise was determined as intrauterine fetal death after 24.weeks of gestation.

In polyhydroamnios, the amount of amniotic fluid is 8 cm above the single quadrant or 20 cm above the sum of four quadrants in ultrasonography. In oligohydramnios, amount is 2 cm below the single quadrant measurement or 5 cm below the total of four quadrants. With the criteria defined by the International Society for the Study of Hypertension in Pregnancy, the diagnosis of gestational hypertension and preeclampsia was made (11). Diagnosis of gestational hypertension was made when blood pressures measured twice at 4 hour intervals were systolic ≥ 140 mmHg, and diastolic ≥ 90 mmHg, in a normotensive pregnant woman who had not significant proteinuria after the 20th gestational week. Diagnosis of preeclampsia was made in consideration of above mentioned findings and also high levels of protein (≥ 300 mg) in 24 hour urine samples or 2 (+) proteinuria at 2 different occasions were detected. As recommended by the American College of Obstetricians and Gynecologists (AGOC), we made the diagnosis of GDM in 2 steps (12). SGA was defined when birth weight below the 10th percentile for gestational age. PROM was defined as rupture of the membranes before the onset of labor. PPRM was defined as spontaneous rupture of the amniotic membrane before the 37. gestational week and the release of amniotic fluid before the onset of labor.

Statistical Evaluation

Using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program, the statistical analyzes were performed. With the Shapiro - Wilk normality test, in the evaluation of the data, descriptive statistical methods (mean, standard deviation, median, interquartile range), the distribution of the variables was examined. Tukey multiple comparison test were used in the intergroup comparisons of variables with normal distribution one-way analysis of variance, and for their subgroup comparisons. Dunn's multiple comparison test were employed for intergroup comparisons of variables without normal distribution Kruskal Wallis test, and for their comparisons of subgroup. For comparisons of qualitative data chi-square test was utilized. To determine the risk factors of early and late PPC groups, logistic regression analysis was performed. The results were evaluated with the significance level of $p < 0.05$.

RESULTS

The demographic characteristics of the women and pregnancy outcomes are shown in **Table 1**. The test week values of the early PPC group were statistically significantly lower than the test week averages of the late PPC and non- PPC groups. ($p=0.0001$, $p=0.012$).

The fetal weight of the non-PPC group were found to be statistically significantly lower than the fetal weight values of the late PPC group ($p=0.011$), but there was no statistically significant difference in fetal weights between the other groups ($p > 0.05$). There was no statistically significant difference between the early PPC, late PPC and non- PPC groups in terms of mean values for birth weeks, body mass index (BMI), gender distributions ($p=0.168$, $p=0.09$, $p=0.741$ respectively) and calcium, magnesium, vitamin 25 (OH) D levels were not significantly different ($p=0,680$, $p=0,616$, $p=0,839$ respectively).

When the perinatal outcomes were evaluated, there was no statistically significant difference between the groups in terms of preeclampsia, SGA, fetal demise, GDM, oligohydramnios, polyhydramnios, PROM, PPROM, macrosomia, preterm birth, postterm birth and abruptio placenta, while a statistically significant difference was observed between the LBW distributions ($p=0.024$). When the early and late PPC groups were compared, rates of LBW was statistically higher in the early PPC group. ($p=0,022$)

Adjusted by maternal age, body mass index, and parity, the analysis was performed by logistic regression to compare the differences in pregnancy outcomes among the three groups, (**Table 2**).

Univariate risk analysis has been made for early PPC, and none of the variables were statistically significant ($p > 0.05$) regarding preeclampsia (OR, 1.2; 95% CI, 0.28-5.03) LBW (OR, 0.14; 95% CI, 0.007-2.61), SGA (OR, 1.2; 95% CI, 0.29-5.04), GDM (OR, 1.02; 95% CI, 0.25-4.13), oligohydramnios (OR, 3.75; 95% CI, 0.61-13.03), and premature birth (OR, 0.91; 95% CI, 0.30-2.71). Age, parity and BMI were adjusted by performing a multivariate risk analysis with variables with an OR value above 2; and none of the variables were found to be statistically significant.

Univariate risk analysis has been made for late PPC, and none of the variables were statistically significant ($p > 0.05$) regarding preeclampsia (OR, 1.40; 95% CI, 0.41-4.81), LBW (OR, 2.55; 95% CI, 0.70-9.32), SGA (OR, 0.12; 95% CI, 0.006-2.14), GDM (OR, 0.69; 95% CI, 0.17-2.77), oligohydramnios (OR, 2.54; 95% CI, 0.41-15, 66), premature birth (OR, 0.35; 95% CI, 0.09-1.26)). In addition, in the multivariate risk analysis, none of the variables were found to be statistically significant.

	Group 1		Group 2	
	Univariate Risk	Multivariate Risk	Univariate Risk	Multivariate Risk
	OR (%95 CI)	OR (%95 CI)	OR (%95 CI)	OR (%95 CI)
Preeclampsia	1.2 (0.28-5.03)		1.40 (0.41-4.81)	
LBW	0.14 (0.007-2.61)	0.99 (0.98-1.02) $p=0.237$	2.55 (0.70-9.32)	1.02 (0.00-1.28) $p=0.998$
SGA	1.2 (0.29-5.04)		0.12 (0.006-2.14)	
GDM	1.02 (0.25-4.13)		0.69 (0.17-2.77)	
Oligohydramnios	3.75 (0.61-13.03)	1.01 (0.99-1.02) $p=0.455$	2.54 (0.41-15.66)	0.98 (0.00-1.14) $p=0.998$
Preterm birth	0.91 (0.30-2.71)		0.35 (0.09-1.26)	

LBW: Low birth weight, SGA: Small for gestational age, GDM: Gestational diabetes mellitus
 Group 1, women with early preterm placental calcification (noted at 24-32 week's gestation); Group 2, women with late preterm placental calcification (noted at 32-36 week's gestation); Odds ratios compared to control group (women with no placental calcification noted on ultrasound at 24-36 week's gestation) calculated by logistic regression analysis and adjusted by maternal age, body mass index and parity in multivariate analysis

Table 1. Characteristics and pregnancy outcomes								
		Group 1 n:43		Group 2 n:62		Group 3 n:102		p
Age (years)		29.09±5.8		28.71±5.91		29.98±6.16		0.393*
Type of Delivery								0.897+
	Vaginal	18	41.86%	28	45.16%	42	41.58%	
	Cesarean	25	58.14%	34	54.84%	59	58.42%	
Indications for Cesarean Sections								0.230+
	Previous Cesarean	13	52.00%	19	55.88%	35	59.32%	
	Fetal Distress	3	12.00%	5	14.71%	12	20.34%	
	Progress failure	4	16.00%	4	11.76%	5	8.47%	
	Cephalopelvic disproportion	3	12.00%	0	0.00%	5	8.47%	
	Macrosomia	1	4.00%	4	11.76%	0	0.00%	
	Malpresentation	1	4.00%	2	5.88%	2	3.39%	
Gravida								0.185‡
	Mean (SD)	2.81±1.39		2.32±1.14		2.56±1.61		
	Median (IQR)	3 (2-4)		2 (2-3)		2 (1-3.25)		
Parity								0.918‡
	Mean (SD)	1.19±1.1		1.11±0.96		1.28±1.29		
	Median (IQR)	1 (0-2)		1 (0-2)		1 (0-2)		
Placenta Grade								0.0001+
	1	0	0.00%	0	0.00%	70	68.63%	
	2	0	0.00%	0	0.00%	32	31.37%	
	3	43	100.00%	62	100.00%	0	0.00%	
Test week		30.16±1.76		35.16±0.64		31.48±3.34		0.0001*
Fetal Weight (g)		3213.6±560.67		3405.48±404.58		3205.54±368.27		0.01*
Gestational age at delivery (weeks)		38.35±2.08		38.94±1.12		38.67±1.54		0.168*
BMI		26.12±5.01		27.48±4.51		25.84±4.67		0.09*
Calcium (mg/dl)		8.75±0.39		8.7±0.49		8.75±0.33		0.680*
Magnesium (mg/dl)		1.78±0.15		1.77±0.21		1.75±0.13		0.616*
25(OH)D (µg)		14.5±7.46		13.92±7.29		14.66±8.37		0.839*
Gender	Female	17	39.53%	29	46.77%	43	42.16%	0.741+
	Male	26	60.47%	33	53.23%	59	57.84%	
Preeclampsia	No	40	93.02%	57	91.94%	96	94.12%	0.863+
	Yes	3	6.98%	5	8.06%	6	5.88%	
LBW	No	38	88.37%	62	100.00%	97	95.10%	0.024+
	Yes	5	11.63%	0	0.00%	5	4.90%	
SGA	No	40	93.02%	62	100.00%	96	94.12%	0.128+
	Yes	3	6.98%	0	0.00%	6	5.88%	
Fetal demise	No	42	97.67%	62	100.00%	102	100.00%	0.147+
	Yes	1	2.33%	0	0.00%	0	0.00%	
GDM	No	40	93.02%	59	95.16%	95	93.14%	0.855+
	Yes	3	6.98%	3	4.84%	7	6.86%	
Oligohydramnios	No	40	93.02%	59	95.16%	100	98.04%	0.321+
	Yes	3	6.98%	3	4.84%	2	1.96%	
Polyhydramnios	No	42	97.67%	61	98.39%	102	100.00%	0.351+
	Yes	1	2.33%	1	1.61%	0	0.00%	
PROM	No	42	97.67%	61	98.39%	94	92.16%	0.136+
	Yes	1	2.33%	1	1.61%	8	7.84%	
PPROM	No	43	100.00%	61	98.39%	101	99.02%	0.708+
	Yes	0	0.00%	1	1.61%	1	0.98%	
Macrosomia	No	41	95.35%	56	90.32%	100	98.04%	0.082+
	Yes	2	4.65%	6	9.68%	2	1.96%	
Preterm birth	No	38	88.37%	59	95.16%	89	87.25%	0.250+
	Yes	5	11.63%	3	4.84%	13	12.75%	
Postterm birth	No	42	97.67%	62	100.00%	99	97.06%	0.406+
	Yes	1	2.33%	0	0.00%	3	2.94%	
Abruptio Placantae	No	41	95.35%	62	100.00%	101	99.02%	0.125+
	Yes	2	4.65%	0	0.00%	1	0.98%	

* One-way Analysis of Variance, ‡ Kruskal Wallis Test, +Chi-Square test, Group 1, women with early preterm placental calcification (noted at 24-32 week's gestation); Group 2, women with late preterm placental calcification (noted at 32-36 week's gestation); Group 3 controls.i.e. women with no placental calcification noted on ultrasound at 24-36 week's gestation, BMI: Body mass index (kg/m²), LBW: Low birth weight, SGA: Small for gestational age, GDM: Gestational diabetes mellitus, PROM: Premature rupture of membrane, PPRM: Preterm premature rupture of membrane

DISCUSSION

Placental calcification (PC) is a common condition showing maturation and aging of the placenta and smoking low parity, and young age are the most important predisposing factors (9). When seen before the 36th gestational week, it is called preterm placental calcification (PPC) and PPC was determined as 3.8% at 36 weeks and 23.7% between 31-34 gestational weeks (5). In our study, LBW was observed more frequently in the early PPC group than in the late PPC group. Oligohydramnios was more common in the early and late PPC patients compared to non-PPC pregnant women. However, oligohydramnios and LBW were not found statistically significant in logistic regression analysis. In addition, we observed no statistically significant difference regarding other adverse obstetric outcomes such as SGA, preeclampsia, fetal death, GDM, polyhydramnios, PROM, PPRM, macrosomia, preterm birth, postterm birth and abruptio placenta.

Some histological changes in placenta may be related to pregnancy complications (13-15). Goswami et al. (16) explained that PCC occurs as an inadequate uteroplacental blood flow, and one of the factors playing a role in insufficient uteroplacenta is excessive calcium accumulation in villus. Considering this mechanism, we investigated the relationship between calcium, magnesium and vitamin D and PPC in our study. In a study, the authors were not found any difference between the late preterm and term pregnancies for placental pathologies. (17). Yin et al. (18) examined placentas after birth and found that this grading in term placentas did not reflect the functional capacity of the placenta.

After synthesized in placenta, vitamin 24-25 (OH) D have a role in ossification in fetus and absorption of calcium from fetal intestines (19). We can also demonstrate that the deficiency of vitamin D is common among women. Certain hormones such as vitamin D, parathyroid hormone and calcitonin may play a role in PC (20,21). In some of the studies, calcium levels in fetus and pregnant women were found to be higher in patients with PC (9). Both deficiency of vitamin D and PC were found to be associated with intrauterine growth retardation (IUGR) (2), GDM (22) and pre-eclampsia (23). Hypovitaminosis D during pregnancy was found to be associated with preeclampsia and GDM, and it was stated that it could increase the risk of osteoporosis in the post-pregnancy life of the patient (24,25). Unlike other studies, we did not find any correlation between magnesium, calcium, vitamin D levels and PPC.

In the study of Vosmar et al. (22), it was stated that when PPC was seen, 60% SGA cases were born. However, while SGA was observed at a rate of 6.98% in our pregnant

group with early PPC, SGA was not found in late PPC. In present study, with the comparison of 3 groups, there was no significant intergroup difference as for SGA.

There are also studies showing the relationship between abnormal Doppler ultrasonography imaging and IUGR with placental pathology (26,27). For evaluating the effects of placental mineral deposition, noninvasive imaging techniques are needed (28). Rossi et al. (29) proposed a new histopathological scoring system based on calcification pattern and grading, and evaluated IUGR with this scoring system.

In the study by Mc Kenna et al. (13) pregnant women with grade III placenta at 36th gestational week were examined and they found 3-fold increase in the risk of SGA and 5-fold increase in the risk of preeclampsia. In our study, preeclampsia was observed with a rate of 6.98% in the early PPC and 8.06% in the late PPC groups. In patients without PPC, preeclampsia rate was 5.88% and between the groups there was no significant difference.

When the relationship between PC and longterm cardiovascular health is examined, the calcification of coronary artery increases the risk 3.5 times when there was a history of preeclampsia. (14,30). In another study, pregnant women with grade III PC between 31th and 34th gestational weeks were examined and increases in incidence of IUGR (6.20%), fetal distress (7.8%), and LBW (34.37%) were observed (31).

In a study examining the relationship between LBW and the pathological changes of the placenta, deposition of subchorionic fibrin and calcification were seen in significantly higher numbers from LBW delivered patients than controls (32). However in another study, they found that the risk of oligohydramnios, and LBW increased in pregnant with PC at their <37 gestational weeks (33). In our study, oligohydramnios increased 3.75 times in the early PPC group and 2.54 times in the late PPC group compared to the non-PPC group. However, increase in the risk was not found significant in multivariate analysis.

In the study of Chen et al. (5) although hemorrhage, abruption of placenta and maternal intensive care unit admission (ICU), preterm birth and LBW were more common in early PPC group. But in the late PPC group adverse obstetric problems were not observed. In our study, we observed a statistically significant difference between LBW distributions ($p=0.024$). While no LBW was found in the late PPC group, LBW was found in the 11.63% of the pregnant in the early PPC group at <32 gestational weeks. When the early and late PPC groups were compared, the rate of LBW was higher in the early PPC. ($p=0.022$) However, any statistically significant difference was not detected in logistic regression analysis.

A relationship was found between excessive placental calcification and gestational hypertension, placental abruption and IUGR (34). When the authors were examined the liaison between intravillous and intrafibrinous microcalcification and obstetric problems, they found that the risk for intrauterine death increased. (35). In another study, when PPC occur at 28 weeks of gestation, there was a correlation with demise of fetus (36). In the meta-analysis, they found that placental calcification was seen with LBW, labor induction and death of the fetus (37). In our study, fetal demise was observed at a rate of 2.33% in the early PPC group, while no fetal demise was observed in the late PPC group and the group without PPC.

We acknowledge that this study has some limitations. Data related to race, socioeconomic status, education and nutritional status of the mother were not analyzed. The results might be affected by these factors.

CONCLUSION

In conclusion, preterm placental calcifications might be seen with obstetric complications. However, in our study early and late PPC did not increase the risk for adverse outcomes such as preeclampsia, SGA, fetal demise, GDM, oligohydramnios, polyhydramnios, PROM, PPRM, macrosomia, preterm birth, postterm birth and abruptio placenta. Although LBW was observed significantly more frequently in the early PPC group; increase in the risk associated with PPC was not observed in multivariate analysis and there was also no significant difference in maternal calcium, magnesium and vitamin D levels between the study groups. We think that PPC alone is not effective in determining fetal prognosis. Our study differs from previous studies in that it is a prospective study with a large patient group, where we examined the relationship between maternal calcium, magnesium and vitamin D levels with PPC. However, large-scale studies, in which maternal and fetal prognosis can be examined after birth are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Okmeydanı Training and Research Hospital Ethics Committee (Date: 23/12/2019, Decision No: 48670771-514.10./1511).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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