Clinical importance of placental membrane microscopic chorionic pseudocysts in preeclampsia

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Summary

Objective: To determine the importance of placental membrane microscopic chorionic pseudocysts (MCP) in preeclamptic and normal placentas and evaluate the association between MCP and neonatal complications in preeclamptic patients. *Materials and Methods:* In this prospective case-control study, microscopic examination of placentas was performed, including MCP count, in 33 preeclamptic and 35 normal control pregnant women from December 2008 to May 2009. The MCP were counted in placentas for each patient and modeled as a continuous variable to assess the difference between the two groups. *Results:* The mean MCP count was similar for preeclamptic (7 ± 2) and control patients (7 ± 2; not significant). A weak positive correlation was noted between placental weight and MCP ($r = 0.253$; $p \leq 0.04$). In the preeclamptic patients, mean MCP count was significantly higher for neonates that did not have neonatal respiratory distress syndrome (NRDS) ($p \leq 0.05$) and who did not admitted to neonatal intensive care unit (NICU) than admitted to NICU ($P \leq .03$). The risk for developing NRDS was 20.3-fold greater in neonates of preeclamptic patients who did not have than had MCP (odds ratio, 20.3 95% confidence interval, 1.0 to 48; $P \leq .05$). The MCP count cutoff value was ≤ 1 for developing NRDS (sensitivity 83%; specificity, 70%). *Conclusion:* The absence of MCP was significantly associated with the development of NRDS in neonates. The MCP count was inversely associated with the risk of NRDS in newborns of high-risk pregnancies caused by preeclampsia.

Key words: Pregnancy; Complications; Hypoxia; Neonatal respiratory distress syndrome.

Introduction

Prematurity, growth restriction, and intrauterine fetal demise are the most serious complications of high-risk pregnancies such as preeclampsia. The main causes of these complications include uteroplacental insufficiency and intrauterine fetal hypoxia [1]. The placenta of a high-risk pregnancy gives clues about the intrauterine condition of the fetus. Despite experience in examining the placenta in utero by ultrasonography, there are limited studies about the importance of different placental microscopic features ex utero [2-7].

Human placental cystic lesions located on the fetal surface are known as subchorionic, chorionic, or membrane cysts [8-10]. These cysts are formed by extravillous trophoblastic degeneration and may be single or multiple. The subchorionic cysts can be seen by macroscopic or microscopic (chorionic pseudocysts) examination of the placenta. Gross subchorionic cysts are present in 5% to 7% of mature placentas [8]. These cystic formations that are located adjacent to extravillous trophoblastic cells may be associated with perivillous fibrin aggregation, placental edema, or infarcts of the placental bed [8-10].

Microscopic chorionic pseudocysts (MCP) are lined with migratory trophoblasts and mostly located in chorionic layer of the placental membrane [3]. The MCP are present in 4.3% to 18% of normal and 14.9% of preeclamptic placentas [3, 4]. The importance is even less clear for MCP than gross subchorionic cysts. The MCP are regarded as lesions associated with chronic hypoxia [3, 6, 7]; however there is no study that evaluates the association of MCP in the placenta with neonatal outcomes of these pregnancies. The purpose of this study was to compare the number of the MCP in normal and preeclamptic pregnancies and secondly to evaluate the relation between MCP and neonatal complications in preeclamptic pregnancies, if there is any.

Materials and Methods

Subjects

The study was performed at the Departments of Obstetrics and Gynecology and Pathology of a tertiary care university hospital between December 2008 and May 2009. There were 68 third-trimester pregnant women who were recruited from the patients who were treated at the antenatal clinic. The study participants included 33 preeclamptic women and 35 healthy pregnant control women who were matched for body mass index. The women were classified as having preeclampsia (PE) when they had $\geq$ two occasions with elevated blood pressure in 12 hours period (systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg) plus proteinuria > 300 mg in a 24-hour urine collection. Preeclampsia was defined as severe if any of these conditions existed in otherwise PE patient; blood pressure >160 mm Hg systolic

Table 1. — *Maternal, fetal, and neonatal demographic characteristics.*

Feature	Control group n =35	Preeclampsia group n =33	p
Age	30.89±0.94	31.7±0.98	>0.05
Gravida	2.17±0.22	2.67±0.20	0.030
Parity	0.74±0.10	1.06±0.16	>0.05
BMI (kg/m^2)	24.65±0.80	26.27±1.11	>0.05
Weight gain (%)	14.06±0.87	13.45±0.79	>0.05
Gestation length (days)	270.69±1.86	242.15±4.75	<0.001
Amniotic Fluid Index	124. 03±10.38	90.27±5.77	0.013
Systolic BP (mmHg)	108.86±1.58	149.06±4.59	<0.001
Diastolic BP (mmHg)	69.43±1.29	95.45±2.69	<0.001
ESBACH (gr/24 st)	0.12±0.02	3.11±0.51	<0.001
Umbilical Artery PI	0.95±0.02	1.26±0.04	<0.001
Umbilical Artery RI	0.55±0.01	0.70±0.02	<0.001
Birth Weight of Neonate	3461.71±57.71	2273.18±160.51	<0.001
Mode of delivery			<0.001
Vaginal	17 (48.6%)	3 (9.1)	
C/S	18 (51.4)	30 (90.9)	
Meconium presence	3 (8.6%)	3 (9.1%)	> 0.05
PROM (min)	148.71±43.59	27.67±13.48	0.002
APGAR Score (5 min)	9.29±0.26	8.12±0.32	0.001
Fetal umbilical blood			
pH	7.36±0.01	7.32±0.02	> 0.05
pO2	32.46±2.70	25.92±2.17	0.040

Values were presented as mean±st. error of mean and n(%).

Table 2. — *Neonatal findings of the preeclamptic patients.*

	+/-	Control Group n =35	Preeclampsia Group n=33	p
Prematurity	-	35 (100)	23 (69.7)	<0.001
	+	0 (0)	10 (30.3)	
NRDS	-	35 (100)	27 (81.8)	0.010
	+	0 (0)	6 (18.2)	
Neonatal sepsis	-	34 (97.1)	23 (69.7)	0.002
	+	1 (2.9)	10 (30.3)	
TTN	-	35 (100)	26 (78.8)	0.004
	+	0 (0)	7 (21.2)	
NICU admission	-	33 (94.3)	16 (48.5)	<0.001
	+	2 (5.7)	17 (51.5)	

Values were presented as n (%), n: case; +: presence; -: absence;
NRDS: neonatal respiratory distress syndrome;
TTN: Transient tacypne of neonate.

and >110 mm Hg diastolic, proteinuria > five grams /24 hours or the presence of oliguria or thrombocytopenia. Patients were excluded from the study for multiple pregnancies, fetal anomalies, placental anomalies (either invasion or localization anomalies), coexisting disease such as diabetes or connective tissue disease, maternal or fetal infectious disease, or absence of antenatal follow-up at our institution. The study protocol was approved by the Research Ethics Committee of the School of Medicine (Ethic Committee Number 2008-19/9). All participants gave written informed consent for the study.

Clinical evaluation

Gestational age was calculated by last menstrual period and ultrasonographic data obtained during the first or second trimester of pregnancy in patients who had irregular cycles. Data recorded included demographic characteristics, laboratory findings, ultrasonographic and umbilical artery Doppler measurements of the fetus, umbilical cord blood gas values, birth weight, APGAR scores, and any neonatal complications such as prematurity, neonatal respiratory distress syndrome (NRDS), sepsis, transient tachypnea of the neonate, admission to the neonatal intensive care unit (NICU), or need for neonatal resuscitation.

Pathologic evaluation

The placentas were analyzed in the pathology department by two gynecological pathologists who were blinded to the study groups. All the placentas were fixed in 10% formaldehyde after birth and examined macroscopically by the pathologist within 24 hours. The weight, height, and volume of the placenta, and the length and insertion site of the cord were measured. The placentas were examined for subchorionic fibrin aggregation, calcifications, infarct areas, and cystic formations. Placental membrane (ten sections), umbilical cord (three sections), and paracentral full-thickness chorionic disc sections (≥ two sections when no gross lesions were identified) were fixed in buffered formalin, embedded in paraffin, cut, and stained with hematoxylin and eosin for light microscopic examination. At histologic evaluation, the numbers of MCP were recorded by the pathologists.

Statistical analysis

Data analysis was performed with statistical software (SPSS, version 13). Normality of variables was tested with Shapiro-Wilk test. Descriptive data were reported as mean ± SEM and categorical data were reported as number (%). Comparisons of continuous variables between groups were evaluated with *t*-test for independent samples. Categorical variables were compared with χ^2 test (chi-square test). Binary logistic regression was performed to evaluate independent risk factors for NRDS. The associated risk factors, significance of the model, odds ratios, confidence intervals, and *p* values were determined. The MCP cutoff value for NRDS was determined from a receiver operating characteristic curve; the threshold value for MCP, sensitivity, specificity, area under the curve, confidence intervals, and *p* values were determined. The relation between continuous variables was determined with Pearson product moment correlation. Statistical significance was defined by $p \leq 0.05$.

Results

There were no significant differences between the preeclamptic and control groups with regards to age or parity (Table 1). Gestational age at birth was smaller in the preeclamptic than control group (Table 1). Mean neonatal weight and APGAR scores at five minutes were significantly lower for babies of preeclamptic than control patients and neonatal complications were more frequent in the preeclamptic patients (Table 2).

Macroscopic examination of placentas showed that mean placental weight and volume were lower in preeclamptic than control patients (Table 3). Microscopic examination showed diffuse placental infarcts, decidual vasculopathy, and chorionitis in the placentas from preeclamptic patients (Table 3). Figure 1 shows an example of MCP. The mean numbers of MCP were similar between preeclamptic and

Table 3. — *Placental characteristics of the preeclamptic patients.*

	Control group n =35	Preeclampsia group n =33	*p*
Weight (gr)	646.11±19.94	502.42±32.87	<0.001
Volume (cm³)	685.38±34.32	483.52±42.52	<0.001
Infarct (%)	0	4.85±1.96	-
Fibrin (%)	12.67±2.64	20.02±3.53	>0.05
MCP count	7.46±2.31	7.06±2.09	>0.05
Chorionitis			0.050
Present	0 (0)	4 (12.10)	
Absent	35 (100)	29 (87.90)	
Decidual vasculopathy			0.050
Present	0	4 (12.10)	
Absent	35 (100)	29 (87.90)	
Diffuse placental infarcts			0.012
Present	1 (2.90)	8 (24.20)	
Absent	34 (97.10)	25 (75.80)	

Values are presented as mean ± st. error of mean and n (%).

Table 4. — *Risk factors and MCP count of preeclamptic group.*

		MCP count [a]	*p*
Betametazone administered	No	3.64±1.54	>0.05
	Yes	8.77±3.01	
Preeclampsia	Mild	8.5±3.16	>0.05
	Severe	6±2.84	
AFD	No	5.96±1.92	>0.05
	Yes	10.5±6.39	
Cigarette	No	6.54±2.12	>0.05
	Yes	10±7.76	
NICU admission	No	11.13±3.96	0.050
	Yes	3.24±1.12	
NRDS	No	8.33±2.48	0.030
	Yes	1.33±1.15	
Inter villous fibrin	No	7±2.82	>0.05
	Yes	7.22±1.79	
Diffuse placental infarcts	No	6.04±1.91	>0.05
	Yes	10.25±6.44	

AFD: acute fetal distress; NICU: Neonatal Intensive Care Unit;
NRDS: neonatal respiratory distress syndrome.
Values were presented as mean ± st. error of mean.

Figure 1. — Histologic appearance of placental membrane microscopic chorionic pseudocyts (white arrow) (hematoxylin-eosin, original magnification ×10).

Figure 2. — Total number of MCP to define the risk of developing NRDS (area under curve, 0.79).

control placental membranes (Table 3). There was a significant weak positive correlation between placental weight and number of MCP (r = 0.253; $p \leq 0.04$).

In the preeclamptic patients, the numbers of MCP were evaluated for a relation with risk factors (Table 4). Mean MCP count was significantly higher for neonates who did not have than had NRDS ($p \leq 0.05$) and who were not admitted to to NICU ($p \leq 0.03$). In univariate analyses, NRDS was significantly correlated with the type of preeclampsia, injection of betamethasone, administration of magnesium sulfate to the mother, neonatal sepsis, prematurity, and admission to NICU. Logistic regression analysis showed that total MCP count was inversely related
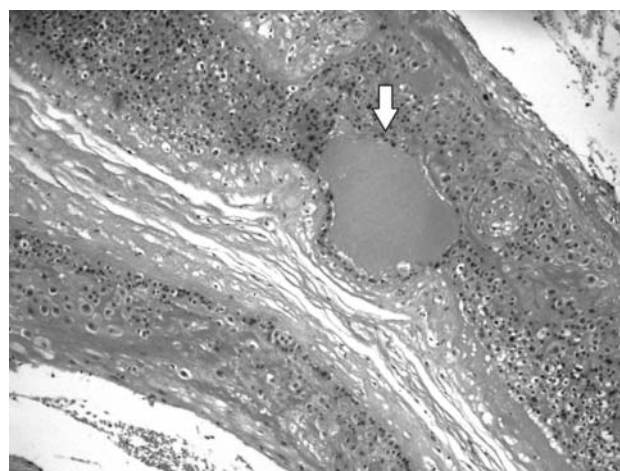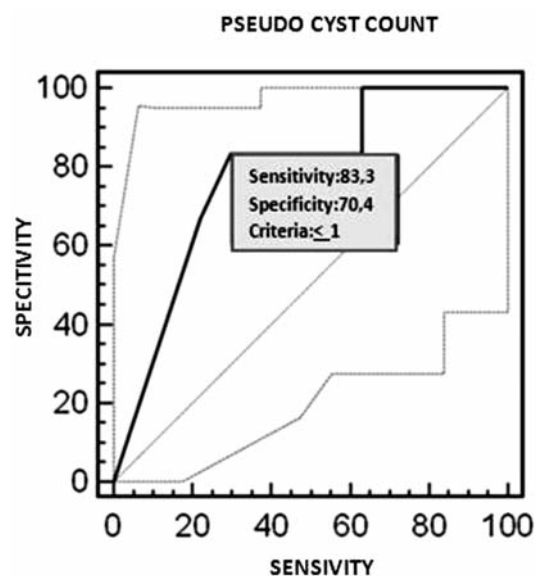
to NRDS (odds ratio, 0.6; 95% confidence interval, 0.43 to 0.96; $p \leq 0.03$).

The effect of total number of MCP on the occurrence of NRDS was evaluated by categorizing patients in two groups based on presence or absence of MCP in their placentas. The presence of MCP and prematurity were significant risk factors affecting the occurrence of NRDS. There was a 20.3-fold increased risk of having NRDS in neonates without than with MCP (odds ratio, 20.3; 95% confidence interval, 1.0 to 48.0; $p \leq 0.05$). There was a 15.8-fold increased risk of having NRDS in premature neonates than

Table 5. — *MCP count and presence of NRDS in preeclamptic group.*

		NRDS		Total n
		Present n=6	Absent n=27	
MCP Count	≤ 1	5 (83.30)	8 (29.60)	6
	> 1	1 (16.70)	19 (70.40)	62

Sensitivity = 83.3% (5/6);
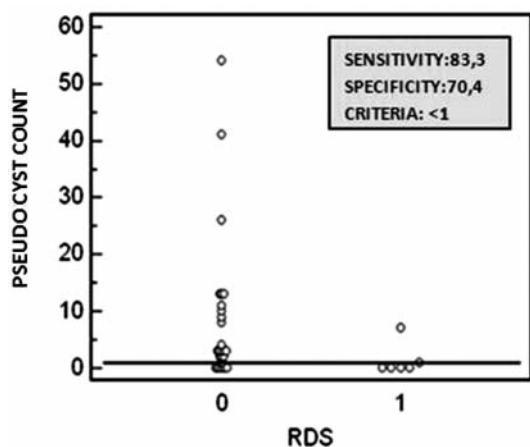Specificity = 70.4% (19/27) AUC [0.79 (0.60-0.90); $p = 0.002$].

Figure 3. — Distribution of neonates (with or without NRDS) in preeclamptic patients according the cutoff value of MCP ≤ 1 (0, absence of NRDS; 1, presence of NRDS).

normal babies (odds ratio, 15.8; 95% confidence interval, 2.3 to 108; $p \leq .005$). The logistic regression model was statistically significant ($p \leq 0.001$).

Evaluation of the relation between total number of MCP and occurrence of NRDS in preeclamptic patients with a receiver operating characteristic curve showed a total number of MCP cutoff for NRDS ≤ 1 (Figure 2). Sensitivity was 83% and specificity was 70% (Table 5 and Figure 3). The area under the curve was significant (area under the curve, 0.79; 95% confidence interval, 0.60 to 0.90; $p \leq 0.002$) (Figure 2).

Discussion

In this study the number of the MCP in normal and preeclamptic pregnancies were compared and the association of MCP with neonatal outcomes was assessed in preeclamptic pregnancies. The absence of MCP was significantly associated with the development of NRDS in neonates. Other placental pathologies including diffuse placental infarcts, decidual vasculopathy, and chorionitis were significantly greater in the preeclamptic than control group, alike previous studies which showed that these placental factors are more frequent in placentas from patients who have preeclampsia [3, 5].

The MCP are placental lesions that can be diagnosed microscopically, but they may be diagnosed incorrectly as fibrous and atrophic chorionic villi [3]. They are caused by increased secretory activity of extravillous trophoblasts [3, 6]. This secretory activity requires a long period of time for accumulation, thus making the process chronic. In previous placental studies, MCP lesions were found to be associated with preeclampsia and maternal diabetes in which the authors postulated that chronic hypoxia may induce the formation of MCP [3, 6]. In both of those studies placentas with more than three MCP were evaluated and authors stated that placentas with one or two MCP generally showed slightly and insignificantly increased percentages of clinical and placental factors associated with in utero hypoxia [3, 6]. In the present study, the authors did not set a cutoff number for MCP, instead analyzed the total number of MCP in placentas. In the previous studies, the placentas of unselected high-risk patients were studied including patients who had diabetes, multiple gestations, and preeclampsia, and these studies did not report any clinical verification of intrauterine hypoxia (such as umbilical cord pH, NICU admission) [3, 6]. Another study did not show any association between MCP and uteroplacental ischemia in an unselected population; clinical conditions related to hypoxia included fetuses small for gestational age and pregnancy-induced hypertension [4]. Similar to the present findings, authors showed no difference in number of MCP between preeclamptic and control patients [4].

Another study showed no significant difference in placentas with or without MCP in patients who had preeclampsia, pregnancy-induced hypertension, or chronic hypertension [7]. In the present study the authors defined a high-risk and low-risk group and there were no differences in clinical findings of uteroplacental hypoxia between preeclamptic and control patients, and the number of MCP was similar between placentas of both groups. In the present study, there was a correlation between placental weight and MCP count (r = 0.253; $p \leq 0.04$), in contrast with other studies [4]. High-risk pregnancies are not always associated with intrauterine hypoxia [1], and placental lesions detected in placentas of high-risk pregnancies cannot be correlated with intrauterine hypoxia in all circumstances. The discrepancies between patient groups in this study may clarify the association between preeclampsia and MCP.

In the analysis of the preeclampsia group, MCP count was different in some subgroups. The neonates in the preeclamptic group who were diagnosed with NRDS and those who were hospitalized in the NICU had placentas with lower numbers of MCP. A greater number of MCP was associated with better fetal respiratory condition. Literature search showed no previous study regarding the relation between NRDS and MCP count. The present results showed a significant relation between NRDS and total MCP count, and neonates without placentas having MCP had 20.3-fold

greater risk of having NRDS. In the receiver operating characteristic curve, the significant threshold was 1. In the preeclamptic patients, when the total MCP count was < 1, the NRDS risk increased by 83%; when total MCP count was > 1, the risk decreased by 30%.

There are many previous studies about chorioamnionitis and NRDS, but there are limited studies that associate placental morphology with neonatal outcomes [11, 12]. The present study provides new evidence about the clinical importance of MCP in neonatal outcomes in preeclamptic patients, and MCP in preeclamptic patients may be a protective factor against developing NRDS. Limitations of the present study include the limited number of placentas evaluated, but it justifies larger prospective studies to evaluate the importance of the placenta in the fetal and neonatal period.

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