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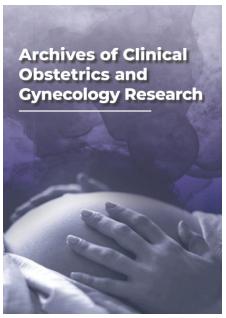

Risk Factors for Poor Perinatal and Neonatal Outcomes in Pregnant Women With Subchorionic Hematoma

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Abstract

Objectives: *Subchorionic hematoma (SCH) increases the risk of miscarriage, preterm birth, preterm premature rupture of membranes (pPROM), and neonatal chronic lung disease. The present study examined perinatal/neonatal outcomes in pregnant women with SCH and investigated risk factors for poor outcomes.*

Methods: *Subjects were 45 pregnant women who developed SCH in the 1st to 2nd trimester of pregnancy, requiring hospital management due to genital bleeding at our hospital between January 2013 and December 2020. Eight patients, consisting of 5 with neonatal death and 3 whose neonates developed chronic lung disease, were assigned to the poor neonatal outcome group and the other 37 to the good neonatal outcome group. We compared maternal background factors, pregnancy-related complications, perinatal outcomes, and pathological findings of the placenta between the two groups.*

Results: *Hematoma diameters were significantly longer in the poor neonatal outcome group than in the good neonatal outcome group, while the rate of patients with bleeding after Week 16 of pregnancy was significantly higher in the former than in the latter. In the poor neonatal outcome group, pPROM occurred in 5 (62.5%) of 8 patients, and chronic abruption-oligohydramnios sequence in 6 (75%). Of the 27 patients from whom pathological findings of the placenta were obtained, chorioamnionitis (Blanc's stage II or higher) was observed in 3 (37.5%) of 8 patients in the poor neonatal outcome group and in 6 (31.5%) of 19 patients in the good neonatal outcome group, with no significant difference. A multivariate analysis showed that the presence of bleeding after Week 16 of pregnancy was an independent risk factor for poor outcomes in SCH patients' neonates.*

Conclusions: *Pregnant women with SCH have generally favorable perinatal outcomes. On the other hand, SCH with bleeding after Week 16 of pregnancy is associated with poor neonatal outcomes; therefore, careful and close management is necessary.*

Background

Subchorionic hematoma (SCH) is a pregnancy-related complication that is routinely encountered in the first trimester of pregnancy. It is characterized by a crescent-shaped hypoechoic lesion around the gestational sac on ultrasonography. Although its etiology remains unclear, partial chorionic exfoliation from the uterine wall has been implicated [1]. The incidence of SCH ranges between 2 and 28.3%. In most cases, SCH spontaneously disappears after 1 to 3 months and does not affect the subsequent course of pregnancy [2]. On the other hand, previous studies reported that the risk of pregnancy-related complications, such as miscarriage, preterm birth, preterm premature rupture of membranes (pPROM), and chronic abruption-oligohydramnios sequence (CAOS), increased in pregnant women with SCH [3,4]. Once pPROM or CAOS occurs, there is no effective method to subsequently prolong the pregnancy period, contributing to a poor neonatal outcome. However, few studies have performed a detailed investigation on which patients show poor subsequent perinatal outcomes among those who develop SCH in the first trimester of pregnancy. The purpose of this study was to stratify and identify perinatal/neonatal outcome-associated risk factors among pregnant women who developed SCH in the 1st to 2nd trimester of pregnancy, requiring hospital management.

Methods

We retrospectively examined 45 patients with SCH who had been hospitalized at Wakayama Medical University Hospital between January 2013 and December 2020. Patients with an echo-free space around the gestational sac on ultrasonography were diagnosed with SCH. Subjects were patients with genital bleeding

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who had been hospitalized. Patients without bleeding, those with spontaneous abortion, and multiple pregnancy patients were excluded.

Patients with SCH were divided into two groups based on the neonatal outcome after delivery (good or poor). Eight patients consisting of 5 with neonatal death and 3 whose neonates developed chronic lung disease (CLD) were assigned to the poor neonatal outcome group and the other 37 to the good neonatal outcome group. Treatment was selected in accordance with each patient's clinical symptoms. Patients with regular uterine contractions were rested. Tocolytics, such as ritodrine hydrochloride or magnesium sulfate, were then intravenously administered to those with the possibility of a prolonged pregnancy period. Antimicrobial agents were administered to patients in whom pPROM, chorioamnionitis, or intrauterine infection was suspected. When the possibility of delivery at <34 weeks was high, steroids were administered. The indication of Cesarean section was dependent on the fetal or maternal condition.

Clinical data were collected from medical records. The age, parity, presence or absence of miscarriage, body mass index (BMI), presence or absence of assisted reproductive technologies (ART), gestational age at the time of the SCH diagnosis, long diameter of SCH (maximum during the clinical course), presence of bleeding after Week 16 of pregnancy, leukocyte count, and C-reactive protein (CRP) level were used as maternal factors. As perinatal outcomes, gestational age at the time of delivery and birth weight were examined. As pregnancy-related complications, the presence or absence of pPROM, preterm birth, placental abruption, CAOS, hypertensive disorder of pregnancy (HDP), and small for gestational age (SGA) were investigated. A pathological examination of the placenta was performed on 27 patients. The incidences of Blanc's stage II or higher chorioamnionitis (CAM) and diffuse chorioamniotic hemosiderosis (DCH) were examined. This study was conducted with the approval of the Ethics Committee of Wakayama Medical University (authorization ID: 4339). Informed consent was obtained from each of the patients. The study was carried out in compliance with the principles of the Helsinki Declaration.

Results

Maternal factors in the good and poor neonatal outcome groups are shown in Table 1. There were no significant differences in primiparity, miscarriage, or ART rates between the two groups. Age (31 vs. 26.6 years, respectively, p=0.004) and BMI (22.3 vs. 19.3, respectively, p=0.009) were significantly lower in the poor neonatal outcome group. SCH was diagnosed in Week 5.6 to 25.7 of pregnancy, and there was no significant difference in gestational age at the time of diagnosis between the two groups. Leukocyte counts at the time of the SCH diagnosis in the good and poor neonatal outcome groups were 8,640 (4,010-18,700) and 8,450 (8,370-11,270)/μL, respectively (p=0.494), while CRP levels were 0.15 (0.02-4.29) and 0.15 (0.03-2.69) mg/dL, respectively (p=0.923), with no significant differences. Furthermore, the long diameter of SCH (46.6 vs. 74.1 mm, respectively, p=0.017) was significantly longer and the rate of patients with a long SCH diameter of ≥50 mm (51.4 vs. 87.5%, respectively, p=0.038) was significantly higher in the poor neonatal outcome group. In addition, the presence of bleeding after Week 16 of pregnancy (16.2 vs. 87.5%, respectively, p<0.001) was significantly more frequent in the poor neonatal outcome group.

Table 1. *Maternal factors in pregnant women with SCH in good and poor neonatal outcome groups*

	Good outcome (n=37)	Poor outcome (n=8)	P value
Maternal age	31 (22-41)	26.6 (24-33)	0.004
Primiparity	12 (32.4%)	4 (50%)	0.347
History of miscarriage	10 (27.0%)	1 (12/5%)	0.385
BMI (kg/m^2)	22.3 (16-35.8)	19.3 (17.1-24.4)	0.009
ART	6 (16.2%)	0 (0%)	0.221
Gestational age (week) at the time of SCH diagnosis	12.6 (5.6-25.7)	12.6 (8.0-15.9)	0.801
SCH size at the time of diagnosis (mm)	46.4 (15-100)	74.1 (45-110)	0.017
SCH size >50 mm	19 (51.4%)	7 (87.5%)	0.038
Vaginal bleeding after 16 weeks of pregnancy	6 (16.2%)	7 (87.5%)	<0.001

ART: assisted reproductive technologies, BMI: body mass index, SCH: subchorionic hematoma

Table 2. *Perinatal outcomes and pregnancy-related complications in pregnant women with SCH in good and poor neonatal outcome groups*

	Good outcome (n=37)	Poor outcome (n=8)	P value
Gestational age at the time of delivery (week)	37.9 (28.8-41.4)	29.0 (25-31.0)	<0.001
Birth weight (g)	2839 (1134-3815)	655.6 (397-1167)	<0.001
pPROM	4/37 (10.8%)	5/8 (62.5%)	0.009
Preterm labor at <34 weeks of pregnancy	3/37 (8.1%)	8/8 (100%)	<0.001
Placental abruption	1/37 (2.7%)	0/8 (0%)	0.638
CAOS	0/37 (0%)	6/8 (75%)	<0.001
HDP	1/37 (2.7%)	0/8 (0%)	0.638
SGA	2/37 (5.4%)	6/8 (75%)	<0.001

pPROM: preterm premature rupture of membranes, CAOS: chronic abruption-oligohydramnios sequence, HDP: hypertensive disorder of pregnancy, SGA: small for gestational age

Perinatal outcomes and pregnancy-related complications in the two groups are shown in Table 2. There were significant differences between the good and poor neonatal outcome groups in the gestational age at the time of delivery (37.9 vs. 29.0 weeks, respectively, p<0.001), birth weight (2,839 vs. 655.6 g, respectively, p<0.001), the incidence of pPROM (10.8 vs. 62.5%, respectively, p=0.009), the incidence of preterm birth at <34 weeks (8.1 vs. 100%, respectively, p<0.001), the incidence of CAOS (0 vs. 75%, respectively, p<0.001), and the incidence of SGA (5.4 vs. 75%, respectively, p<0.001). On the other hand, there were no significant differences in the incidence of placental abruption or HDP.

Table 3. *Multivariate analysis of risk factors for poor neonatal outcomes in pregnant women with SCH*

		Odds ratio (95%CI)	P value
Age	<31	3.41	0.372
	≥31	(0.23-50.7)	
BMI	<21.8	28.6	0.051
	≥21.8	(0.98-836.6)	
SCH size (mm)	≥50	3.56	0.403
	<50	(0.18-69.7)	
Bleeding after 16 weeks of pregnancy	Present	42.2	0.009
	Absent	(2.5-706.0)	

The multivariate analysis was performed to determine the risk factors predicting poor neonatal outcome using 4 parameters (Age, BMI, SCH size, Bleeding after 16 weeks) that showed significant differences between the 2 groups on the univariate analysis. Among the factors, the presence of bleeding after Week 16 of pregnancy was an independent risk factor for poor outcomes in SCH patients' neonates (p=0.009) (Table 3).

A pathological examination of the placenta was performed on 27 patients (Table 4). There were no significant differences in the presence or absence of CAM (Blanc's stage II or higher) or DCH between 19 patients in the good neonatal outcome group and 8 in the poor neonatal outcome group. In 4 of the 6 patients with CAM in the good neonatal outcome group, preterm birth (at 32 to 36 weeks) was noted. DCH was observed in patients with a long SCH diameter of 80 to 100 mm. Of the 3 patients with CAM in the poor neonatal outcome group, neonatal sepsis led to fatal outcomes in 2 patients, and in 1 patient, neonatal cardiac arrest during delivery resulted in a fatal outcome despite resuscitation immediately after birth. In 4 of the 6 patients with CAOS in the poor neonatal outcome group, pathological findings of the placenta suggested DCH. In 3 patients of the 6 with CAOS, neonatal CLD occurred.

Table 4. *Pathological findings of the placenta in good and poor neonatal outcome groups*

	Good outcome (n=19)	Poor outcome (n=8)	P value
CAM	6/19 (31.5%)	3/8 (37.5%)	0.767
DCH	3/19 (13.7%)	4/8 (50%)	0.064

CAM: chorioamnionitis, DCH: diffuse chorioamniotic hemosiderosis

Discussion

SCH is a disease that is often encountered in routine practice in the 1st trimester of pregnancy. However, few studies have investigated its etiology or effects on pregnancy outcomes in detail. The incidence of SCH with bleeding in the first trimester ranges between 2 and 28.3%, but it spontaneously disappears after 1 to 3 months in most cases, not affecting the subsequent course of pregnancy [2]. Regarding the pathogenesis of SCH, a venous sinus is present below the decidua at the margin of the placenta, and venous pressure may increase with blood flow stagnation, resulting in rupture of the sinus [5]. Although SCH spontaneously disappears in many cases, some lesions remain after the second trimester, while others newly appear after the second trimester. Although the mechanisms underlying the development of these lesions remain unclear, a previous study identified abnormal coagulation fibrinolysis and ART operations as risk factors [6]. In the present study, 45 SCH patients, requiring hospital management, with genital bleeding were divided into two groups: good and poor neonatal outcome groups, and risk factors were analyzed to clarify which patients with SCH showed poor neonatal outcomes.

Tuuli et al. performed a meta-analysis of SCH and control groups, and reported that the incidences of miscarriage, pPROM, and preterm birth significantly increased in the SCH group, whereas there was no increase in the incidence of HDP or SGA [4]. In the present study, the incidences of preterm birth and pPROM were higher in the poor neonatal outcome group; however, the incidence of SGA also increased in this group. According to a meta-analysis by Qin et al., the incidence of fetal growth restriction (FGR) increased in the SCH group [2]. Although the underlying mechanisms have yet to be elucidated in detail, the presence of SCH around Week 16 of pregnancy when the placenta is formed might affect trophoblast invasion into the decidua and muscle layer as well as vascular remodeling of the spiral arteries, leading to FGR through a circulatory disorder [7]. Regarding HDP, the present results revealed no increase between the two groups. This is consistent with previous findings showing no increase in the incidence of HDP in SCH patients [2,4].

The risk of miscarriage is high in patients with a very long SCH diameter [8]. Furthermore, spontaneous abortion occurs in many patients in whom the ratio of SCH to the gestational sac is high [9]. The present study also showed that the rate of patients with a very long SCH diameter was significantly higher in the poor neonatal outcome group. These findings suggest that a close follow-up is necessary in patients with a large diameter of SCH. On the other hand, it is noted that hematoma sizes do not accurately reflect the volume of blood loss. Briefly, more attention must be paid when vaginal bleeding is present. Seki et al. reported that patients in whom SCH remained until delivery with symptoms, such as bleeding, accounted for 0.46% of all pregnancies, and that the risk of miscarriage or preterm birth was high in these patients [10]. Furthermore, Aki et al. [11] showed that the duration of SCH or bleeding was prolonged in patients in whom vaginal bleeding occurred prior to hematoma among SCH patients, and also that the risk of pPROM or CAOS was high in these patients. Hosseini et al reported that bleeding induces preterm birth or pPROM through destruction of the space with the chorioamniotic membrane and chronic inflammation [12]. In the present study, the multivariate analysis showed that the presence of bleeding after Week 16 of pregnancy was a risk factor for a poor neonatal outcome. Our results suggest that in patients with a very long SCH diameter and SCH patients with bleeding persisting after the 2nd trimester of pregnancy, perinatal outcomes may be poor.

CAOS is a condition proposed by Eliott et al. [13]. This serious disease leads to an adverse perinatal outcome [14]. Diagnostic criteria for CAOS include: (1) genital bleeding persisting for ≥7 days in the absence of a clear source of bleeding, such as placenta previa, (2) the amniotic fluid volume is normal at the start of bleeding, and (3) oligohydramnios (amniotic fluid

index ≤5) deteriorates in the absence of obvious proof for the premature rupture of membranes. Regarding the pathogenesis of CAOS, bleeding from the marginal venous sinus may result in the formation of retroplacental hematoma; however, external bleeding is a primary symptom, with no progression of placental abruption during the clinical course [15]. A previous study reported that patients with progression from SCH development in the 1st to 2nd trimester of pregnancy to CAOS accounted for 66.7% (10/15) of CAOS patients [12]. In the present study, CAOS occurred in 6 (75%) of 8 SCH patients in the poor neonatal outcome group. Taken together with that the presence of bleeding after 16 weeks is a risk factor for a poor outcome, in SCH patients in whom bleeding persists over a long period after the 2nd trimester of pregnancy, the possibility of progression to CAOS must be considered.

Seki et al. reported that the incidence of CAM in SCH patients was 27.3% [10]. In the present study, no significant difference was observed in the incidence of CAM between the two groups. However, it is noted that in the even good neonatal outcome group, preterm birth was noted in 5 of 6 patients with CAM. Furthermore, the hematoma size was ≥50 mm in 4 of 6 patients with CAM in the good neonatal outcome group.

The treatment strategy of "resting" may be advantageous in most patients with SCH. However, no management guidelines for which a consensus has been reached other than resting have been established, and conservative treatment similar to that for threatened miscarriage or threatened preterm delivery is performed. Although progesterone has been used, concrete evidence for the efficacy of this strategy has not yet been obtained [16]. Furthermore, a recent study reported a mechanism in which intra-hematoma thrombin induces uterine contractions by promoting inflammatory cytokine and prostaglandin production via protease-activated receptors [17]. Therefore, treatments, such as tranexamic acid administration and coagulation factor replacement therapy, are adopted to suppress thrombin release [11].

There are several limitations that need to be addressed. This was a single-center study and the number of SCH patients in the poor neonatal outcome group was small. Furthermore, this was a retrospective study, and the management of SCH patients varied depending on the degree of clinical findings, which may have had a patient selection bias. More patients need to be accumulated for further risk stratification.

Conclusion

In conclusion, the present study showed that bleeding persisting after Week 16 of pregnancy in SCH patients was a risk factor for poor neonatal outcomes. These patients need to be carefully managed from the early stage, recognizing that the risks of pPROM and CAOS are high.

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Study Registry

This study was conducted with the approval of the Ethics Committee of Wakayama Medical University (authorization ID: 4339).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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