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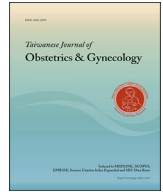
Original Article

The significance of clinical symptoms of subchorionic hematomas, "bleeding first", to stratify the high-risk subgroup of very early preterm delivery

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A R T I C L E   I N F O

A B S T R A C T

Objective: To investigate the factors that stratify high-risk cases among subchorionic hematomas (SCHs) patients with persistent vaginal bleeding in early pregnancy.

Materials and methods: A total of 56 patients who required hospitalization for SCH with vaginal bleeding in early pregnancy were classified into two groups: 1) no hematoma by ultrasonography when vaginal bleeding occurred, and then hematoma was observed by ultrasonography "bleeding to hematoma (BH group, n = 15)" and 2) no vaginal bleeding when hematoma was observed by routine ultrasonography, and then vaginal bleeding occurred later "hematoma to bleeding (HB group, n = 41)". Retrospective cohort study was performed and maternal and neonatal outcomes were evaluated.

Results: The duration of SCHs and/or vaginal bleeding was significantly longer in the BH group than in the HB group (mean: 60.8 days [BH group] vs. 33.3 days [HB group], p = 0.015). BH group patients delivered earlier than HB group patients significantly (mean: 27.3 weeks [BH group] vs. 35.6 weeks [HB group], p = 0.0028). The frequency of chronic abruption and oligohydramnios sequence (CAOS) was significantly higher in the BH group than in the HB group (3/15; 20.0% [BH group] vs. 0/41; 0.0% [HB group], p = 0.016). The frequency of sever fetal distress (Apgar score <4 points) was significantly higher in the BH group than in the HB group (4/15; 26.7% [BH group] vs. 0/41; 0.0% [HB group], p = 0.0037). The levels of factor XIII were relatively lower in the BH group than in the HB group (mean: 54.8% (n = 4) [BH group] vs. 76.1% (n = 7) [HB group], p = 0.077).

Conclusion: The order of the symptoms, bleeding first, is an important feature that reflects the subsequent prolonged duration of SCHs/vaginal bleeding, resulting in very early preterm delivery. Continuous hemorrhage consumes coagulation factor XIII, which further worsen the hemostasis.

Introduction

Subchorionic hematomas (SCHs) are relatively common complications, which usually occur in early pregnancy, and the reported incidence varies from 1.7% to 18.4% [1–3]. SCHs are defined as a crescent-shaped, hypoechoic or anechoic area between the chorionic membrane and the myometrium, which are usually detected by ultrasonography and Magnetic Resonance Imaging (MRI) [4,5]. Most of SCHs appear only transiently in early pregnancy and have little effect on the clinical course of pregnancy or delivery outcomes. However, less frequently, they can be associated with the development of severe pregnancy-related diseases that lead to poor outcomes [6]. Vaginal bleeding is also a common cause of an early-pregnancy emergency-room visit [7,8]. In addition to miscarriage in early pregnancy, the clinical significance of early pregnancy vaginal bleeding has also been implicated in pregnancy-related diseases occurring in the middle and late term [9,10].

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Especially, preterm birth, preterm prelabor rupture of membranes (pPROM) and chronic abruption-oligohydramnios sequence (CAOS) have been reported to be strongly associated with both SCHs and early pregnancy vaginal bleeding [1,2,9–15]. Once pPROM and CAOS occur, premature labor sets in eventually, resulting in preterm delivery. To date, there is no effective way of prolonging the duration of pregnancy after the onset of pPROM and/or CAOS. Therefore, if we can identify the SCH patients who are potentially at high risk of developing pPROM and CAOS, prophylactic treatment can be administered, thereby preventing the occurrence of these conditions.

Several reports suggest that preterm birth, pPROM and CAOS are more likely to occur in SCH patients with bleeding than in those without [1,2,11–15]. However, even when both these symptoms are present, the subsequent development of serious diseases is not very frequent. The need for more useful markers that can identify the high-risk groups and predict the onset of pPROM and CAOS more efficiently among SCH cases is evident. Thus, in the present study, we aimed to investigate the factors that help stratify high-risk cases among SCH patients with persistent vaginal bleeding who underwent hospitalization in early pregnancy. In particular, we focused on the order in which symptoms occur, namely, bleeding followed by hematoma or vice versa. Furthermore, we evaluated coagulant-related factors including factor XIII in this study.

Materials and methods

Study design, period, and participants

This was a retrospective observational cohort study involving women with singleton gestations who required hospitalization for the treatment of SCH and vaginal bleeding. We included patients who were diagnosed with SCH and underwent hospitalization at our department after 14 weeks of gestation, from January 2008 to December 2018. The decision of hospitalization was made by doctors in charge. Usually, we consider hospitalization for patients with SCH and persistent vaginal bleeding together. The diagnosis of SCH was confirmed via ultrasound or magnetic resonance imaging (MRI). We perform ultrasound screening of the fetus in all cases as appropriate, and there was no case of fetal morphological abnormality noted in this study. We excluded patients who had been hospitalized in other hospitals and came to us after 14 weeks of gestation. We also excluded patients who did not know when SCH and/or vaginal bleeding had started. We also excluded patients who underwent artificial abortion. Those with congenital coagulation disorders were also excluded from the study.

We focused on the order in which the first symptom/finding occurred, namely, whether vaginal bleeding preceded hematoma or vice versa. We divided the patients into two groups: the group in which vaginal bleeding occurred prior to the SCH (bleeding to hematoma: BH group) and that in which the SCH developed prior to vaginal bleeding or both developed simultaneously (hematoma to bleeding: HB group). Patients were followed up until delivery and assessed for adverse outcomes. Neonatal findings were also assessed.

In the present study, patients were not required to give informed consent to the study because we used anonymous clinical data which were obtained after each patient agreed to treatment by written consent. This study was approved by the Institutional Review Board of Kyoto University Hospital (number: R2276).

Context of treatment for patients

The context of treatment was determined according to the symptoms and findings of each patient. For patients experiencing regular uterine contractions, we recommended bed rest initially. We then continuously administered tocolytic agents intravenously in cases where doctors, after assessing fetal–maternal well-being believed that the patient's gestational period could be extended. As for tocolytic agents, we used either ritodrine or magnesium sulfate, even both, depending on the situation of patients including the degree of side effects, their gestational weeks and the degree of uterine contraction. Steroids were administered if the gestational weeks are less than 34 and delivery was highly probable. We defined this treatment as "continuous tocolysis" in this study. We administered antibiotics in case of pPROM. We mostly started with Ampicillin Sodium and sometimes change to others depending on the patient situation. The indications for cesarean section were determined by the doctors in charge based on a comprehensive evaluation of the fetal–maternal status. Blood tests were conducted appropriately to check side effects such as hepatic or renal dysfunction caused by tocolytic agents and to evaluate the degree of inflammation.

Study outcomes

The primary outcome of this study was the gestational week at delivery. The time of delivery was divided into three classes: <22 weeks of gestation (spontaneous abortion, SA), from 22 to 27 weeks of gestation (very early preterm delivery, VE), and after 28 weeks of gestation (preterm and term delivery [P + T]). In addition, we investigated the frequency of maternal events that occurred during pregnancy and the neonatal findings at delivery as the secondary outcomes. We investigated the following maternal events: duration of vaginal bleeding/hematoma, pPROM, CAOS, the need for continuous tocolysis and acute abruption. We also investigated the following neonatal findings at delivery: pH of the umbilical cord arterial blood, Apgar score (1 min and 5 min) and birth weight.

Among coagulation-related factors, we evaluated fibrinogen, D-dimer, ATIII and factor XIII between 14 and 18 weeks of gestation. If the samples were collected more than once, the minimum or maximum value was used according to factors. Specifically, the maximum value of fibrinogen and D-dimer were evaluated, and the minimum value of ATIII and factor XIII were evaluated.

Analysis of maternal background and the clinical course of hematoma/bleeding

Clinical data were collected from patients' medical records. We recorded factors related to the maternal background, including maternal age, gravidity, parity, history of spontaneous abortion, history of infertility treatment, and underlying diseases. Vaginal bleeding and SCH were investigated when they first appeared. For SCH, we also investigated the maximum volume of each of patients during their clinical course. We estimated the SCH volume as described in supplementary text.

A database including all data on maternal background, the primary and secondary outcomes mentioned above was created using Microsoft Office Excel 2011 (Microsoft, Santa Rosa, CA, USA). All statistical analyses were performed using PRISM version 6.0 (GraphPad Software, San Diego, CA, USA). A descriptive analysis of the characteristics of the patients in this study was performed to determine the frequency of categorical variables and the mean, standard deviation, median, and range of continuous variables. The study population was categorized into two groups, the HB and BH groups, as mentioned above. Next, we compared the various parameters between the groups. The chi-square test or Fisher's exact test was used to examine the associations among categorical variables, and an unpaired t-test was used to examine the associations

among continuous variables. Statistical significance was set at p < 0.05.

Results

Classification of SCHs based on the clinical findings

A total of 56 patients were included in the study. First, we examined the order in which the first symptom/finding occurred in all cases: vaginal bleeding preceding SCH or vice versa (Fig. 1A). The results showed that in 41 patients, the presence of SCHs was confirmed simultaneously with the occurrence of vaginal bleeding or before the occurrence of vaginal bleeding (hematoma to bleeding: HB group). On the other hand, 15 patients had no SCHs when they complained of vaginal bleeding, and the SCH was later identified on imaging tests (bleeding to hematoma: BH group). Thereafter, we compared the maternal backgrounds, clinical course, and adverse outcomes between these two groups.

We first compared several maternal backgrounds between two groups, and there was no significant difference (Table 1). Next, we compared the symptoms and findings of SCHs and bleeding. Regarding the onset time of vaginal bleeding, there was no significant difference between the two groups (Fig. 1B). On the other hand, the onset of SCHs was significantly later in the BH group than in the HB group (mean: 14.1 weeks [BH group] vs. 10.0 weeks [HB group], p = 0.0015, Fig. 1C). Regarding the estimated maximum volume of the SCH during pregnancy, there was no significant difference between the two groups (Fig. 1D).

The duration of SCHs and/or vaginal bleeding was then examined. The results showed that the presence of SCH and/or vaginal bleeding continued until delivery at a significantly higher frequency in the BH group compared to the HB group. (10/15; 66.7% [BH group] vs. 6/41; 14.6% [HB group], p = 0.0003, Fig. 2A). When we compared the duration of SCHs and/or vaginal bleeding between the two groups, the duration of SCHs and/or vaginal bleeding was significantly longer in the BH group than in the HB group (mean: 60.8 days [BH group] vs. 33.3 days [HB group], p = 0.015, Fig. 2B).

Primary outcome: a comparison of the delivery times

As the primary outcome, the time of delivery between the BH and HB groups was assessed. The results showed that BH group patients delivered significantly earlier than HB group patients

Table 1
Clinical maternal background in BH and HB groups.

	BH (n = 15)	HB(n = 41)	p-value
Age (mean)	32	35	0.3
Parity			
≧2 (n)	3	5	0.67
1 (n)	3	11	1
0 (n)	9	25	1
Previous spontaneous abortion			
≧1 (n)	5	21	0.36
Fertility treatment			
no fertility treatment (n)	7	15	0.55
Timing and AIH (n)	1	6	0.66
IVF, ICSI (n)	7	20	1
History or co-existence of myoma or adenomyosis (n)	3	7	1
Autoimmune disorder (n)	0	7	0.17

AIH: artificial insemination of husband's semen, BH: bleeding to hematoma group, HB: hematoma to bleeding group, ICSI: intracytoplasmic sperm injection, IVF: in vitro fertilization.

(mean: 27.3 weeks [BH group] vs. 35.6 weeks [HB group], p = 0.0028, Fig. 2C). In addition, we performed an analysis after dividing the time of delivery into three periods: SA (<22 weeks), VE (22−28 weeks) and P + T (more than 29 weeks). The distribution was significantly different between the two groups (p = 0.0002). The frequency of VE was significantly higher in the BH group than in the HB group (6/15; 40.0% [BH group] vs. 1/41; 2.4% [HB group], p = 0.0009, Fig. 2D). In contrast, the frequency of P + T was significantly higher in the HB group than in the BH group (5/15; 33.3% [BH group] vs. 34/41; 82.9% [HB group], p = 0.0024, Fig. 2D).

Association of adverse maternal/neonatal outcomes

Next, we investigated the perinatal adverse outcomes. There was no significant difference in the frequency of pPROM between the two groups (3/15; 20.0% [BH group] vs. 7/41; 17.1% [HB group], p = 0.7, Table 2A). Although it is not significant, all three pPROM cases in the BH group occurred at <28 weeks of gestation, whereas only four out of seven pPROM cases (57.1%) in the HB group occurred at <28 weeks. Regarding CAOS development, the frequency of CAOS was significantly higher in the BH group than in the HB group (3/15; 20.0% [BH group] vs. 0/41; 0.0% [HB group], p = 0.016, Table 2A). The frequency of continuous tocolysis was also
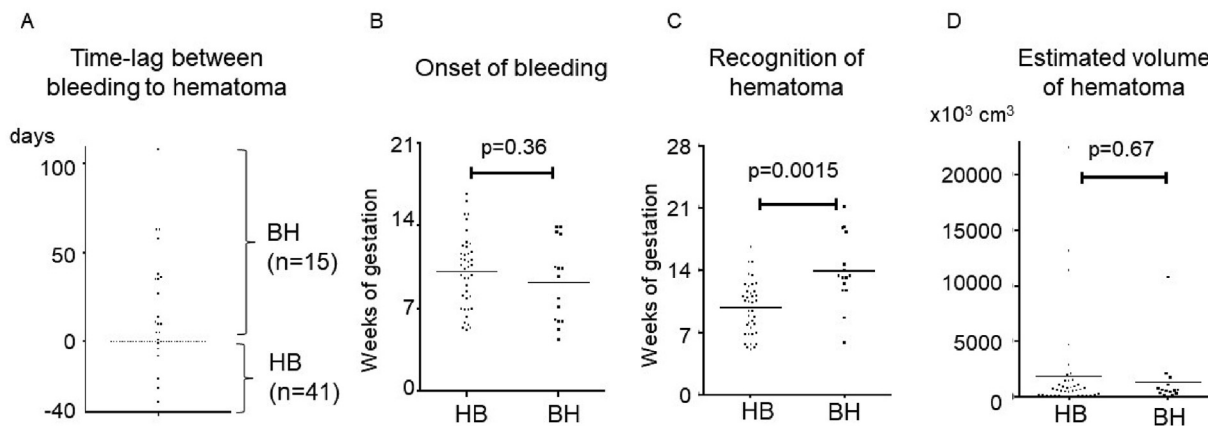

Fig. 1. BH: bleeding to hematoma group, HB: hematoma to bleeding group. A: Time-lag between bleeding to hematoma. All cases were divided into hematoma-to-bleeding group (n = 41) and bleeding-to-hematoma group (n = 15). B: Comparison of onset time of vaginal bleeding. C: Comparison of timing of recognition of hematoma. D: Comparison of estimated volume of subchorionic hematoma (SCH) between HB and BH group.
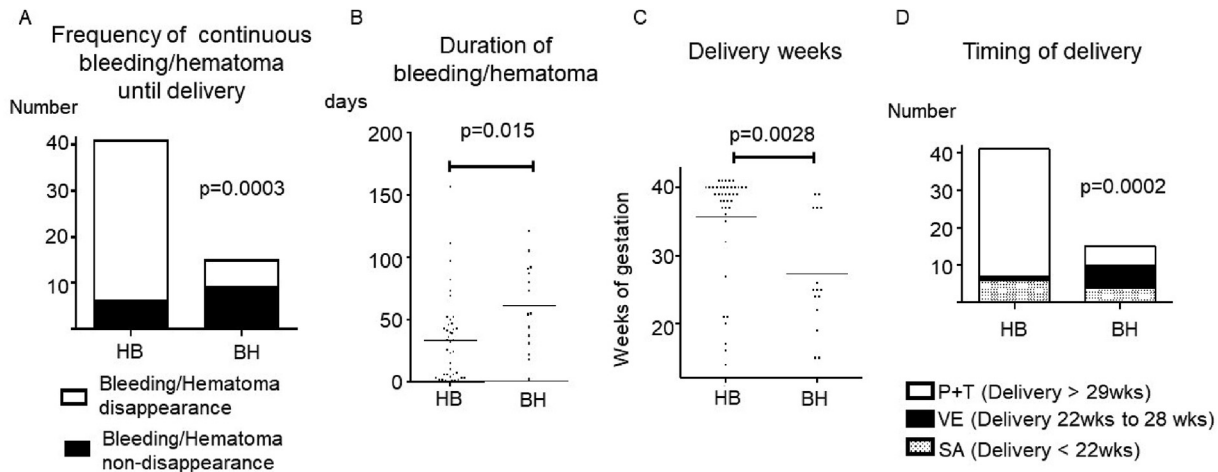
Fig. 2. BH: bleeding to hematoma group, HB: hematoma to bleeding group, P + T: preterm and term delivery, SA: spontaneous abortion, VE: very early preterm delivery. A: Comparison of frequency of continuous bleeding and/or hematoma until delivery between HB and BH group. B: Comparison of duration of bleeding and/or hematoma between HB and BH group. C: Comparison of delivery weeks between HB and BH group. D: Delivery weeks are divided into three group; SA (delivery before 22 weeks), VE (delivery between 22 and 28 weeks) and P + T (delivery after 29 weeks). Comparison about their frequency between HB and BH group.

Table 2
Maternal and neonatal outcomes in BH and HB groups.

A: Maternal clinical outcome in the antepartum.

	BH (n = 15)	HB(n = 41)	p-value
pPROM	3	7	1
onset <28wks	3	4	0.37
onset ≧28wks	0	3	0.56
CAOS	3	0	0.016
onset <28wks	3	0	0.016
onset ≧28wks	0	0	1
Continuous tocolysis	5	2	0.012
start <28wks	5	0	0.0008
start ≧28wks	0	2	1
HDP	0	2	1
Placental abruption	0	0	1

B: Neonatal clinical outcome.

	BH (n = 15)	HB(n = 41)	p-value
Ap 5min < 8	6	3	0.0078
Ap 5min < 4	4	0	0.0037
umbilical artery pH	7.328	7.29	0.32
SGA (<-2.0SD)	0	1	1
LGA (>2.0SD)	0	2	1

Ap: Apgar score, CAOS: chronic abruption and oligohydramnios sequence, HDP: Hypertensive disorder during pregnancy, LGA: large-for-gestational-age, pPROM: preterm premature rupture of membranes, SGA: Small-for-gestational-age.

significantly higher in the BH group than in the HB group (5/15; 33.3% [BH group] vs. 2/41; 4.9% [HB group], p = 0.012, Table 2A). When the frequency of initiation of tocolysis before 28 weeks was further investigated, all five patients in the BH group were found to have been administered before 28 weeks of gestation, whereas there were no such cases in the HB group (5/15; 33.3% [BH group] vs. 0/41; 0.0% [HB group], p = 0.0008, Table 2A). There were no cases of placental abruption in either group (Table 2A).

Next, we studied the adverse neonatal outcomes. First, we compared the Apgar score at 5 min between the groups. The frequency of Apgar score <8 points was significantly higher in the BH group than in the HB group (6/15; 66.7% [BH group] vs. 3/41; 7.3% [HB group], p = 0.0078, Table 2B) as was the frequency of severe fetal distress (Apgar score <4 points) (4/15; 26.7% [BH group] vs. 0/41; 0.0% [HB group], p = 0.0037, Table 2B). As for umbilical artery pH, there was no significant difference between the groups (Table 2B). Regarding birth weight, there was no significant

difference in the frequency of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) neonates in the two groups (Table 2B).

Analysis of coagulation-related factors and supplementation of factor XIII

As shown, the major differences in the clinical findings after 14 weeks of gestation were that the BH group had a significantly longer period of vaginal bleeding and/or presence of SCHs than the HB group. Therefore, we evaluated some coagulation-related factors.

Fibrinogen and D-dimer were investigated first. However, there was no significant difference in them between the BH and HB groups (Fig. 3A and B). We also examined the activity of anti-thrombin III (ATIII), a relatively common cause of congenital coagulopathy, and there was no significant difference between the two groups, either (Fig. 3C). Next, we examined factor XIII, which is known to decrease secondary to chronic inflammation [16]. Although the study was underpowered due to the limited number of cases, the levels of factor XIII were relatively lower in the BH group than in the HB group (mean: 54.8% (n = 4) [BH group] vs. 76.1% (n = 7) [HB group], p = 0.077, Fig. 3D).

We therefore tried supplementation XIII therapy for a SCH patient who required hospitalization (BH group). Her clinical course was described in Supplementary Appendix.

Discussion

In this retrospective cohort study, we investigated whether the order of the symptoms, bleeding prior to hematoma, was related to the practical clinical course of pregnancy. The results showed a significantly higher frequency of VE (delivery between 22 and 28 weeks of gestation) in the BH group than in the HB group. This was mainly due to the development of pPROM or CAOS because all cases of pPROM and CAOS in the BH group also showed early onset of regular uterine contractions, requiring continuous tocolysis and eventually resulting in premature birth. The prognosis of preterm birth before 28 weeks remains unfavorable and even worsens in the setting of CAOS. Thus, the clinical finding of "bleeding first" can be a very useful marker to stratify high-risk groups likely to develop
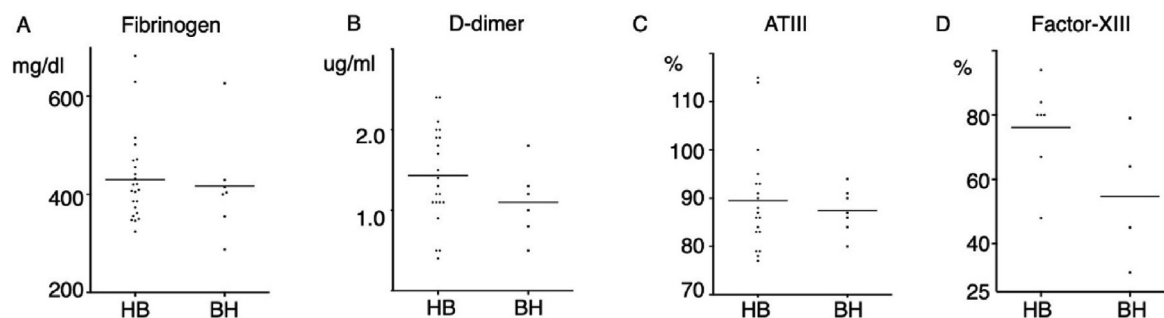
Fig. 3. Comparison of coagulation-related factors between HB and BH group. A: Comparison of the maximum Fibrinogen level. B: Comparison of the maximum D-dimer level. C: Comparison of the minimum ATIII level. D: Comparison of the minimun factor XIII level. ATIII: antithrombin III, BH: bleeding to hematoma group, HB: hematoma to bleeding group.

pPROM/CAOS in early pregnancy, especially as these conditions carry a poor prognosis.

To date, the only consensus is that cases with long-standing SCHs and/or vaginal bleeding are strongly associated with the development of pPROM and CAOS [9,10,17,18]. Therefore, we compared the duration of SCHs or vaginal bleeding in the BH and HB groups and found that it was significantly longer in the BH group. This implies that the symptom of "bleeding first" predicts a prolonged presence of subsequent SCH or vaginal bleeding, resulting in the early development of pPROM or CAOS. Since the duration is only known after the findings have persisted for a while, it cannot be a useful marker for the early prediction of pPROM or CAOS. Our proposed method focusing on the order of symptoms (bleeding first or hematoma first) can easily be adapted in clinical practice and is very useful in predicting pPROM or CAOS early.

Considering the more prolonged presence of SCH and/or vaginal bleeding in BH group, we assume that there is a significant abnormality in coagulation ability around membrane in the BH group, which might cause the difference of clinical symptoms, "bleeding prior to hematoma". The fetal membrane of BH group can eventually be exposed to blood components for a long period, which can be the reason of development of pPROM and/or CAOS. Although the precise mechanism is still to be elucidated [19,20], we assume that thrombin, a key coagulation factor, is one of main key factors. We have previously shown that thrombin plays an important role in determining the vulnerability of the amniotic membrane and uterine contraction via its receptor, protease-activated receptor-1 (PAR-1) [21,22]. Thrombin can have a direct effect on the development of pPROM and/or CAOS.

In this study, we therefore evaluated several coagulation-related factors, and we found that factor XIII seemed to be relatively decreased in BH group. Factor XIII is an endogenous coagulation factor that is activated by thrombin in the final stages of the coagulation cascade and plays a role in fibrin stabilization. It is known to decrease secondary to a decrease in its production or increase in its utilization due to massive bleeding, liver diseases, and disseminated intravascular coagulation [16]. A decrease in factor XIII levels is known to cause bleeding and delayed wound healing [23–25]. In the field of obstetrics, congenital deficiency of factor XIII can cause pregnancy-related diseases, including abruption [23,26,27]. However, the clinical significance of secondary factor XIII deficiency in obstetrics has not been elucidated. Despite the limited number of cases in the present study, secondary factor XIII deficiency may be involved to some extent in the development of long-standing SCHs observed in the BH group.

We therefore tried factor XIII supplementation therapy for the first time against a SCH patient. However, the role of factor XIII supplementation in the prevention of pPROM and premature uterine contractions is limited. Factor XIII does not seem to be only factor that involves in the occurrence of pPROM and early uterine contractions caused by prolonged exposure to blood components.

There are some limitations to this study. In this study, we assessed only those patients who required hospitalization. Sample size was therefore small. In addition, more precise investigation about coagulation-related factors is needed to elucidate the difference of the order of symptoms, bleeding first or hematoma first.

In conclusion, we found that the order of the symptoms, bleeding first, reflects the subsequent duration of SCHs/vaginal bleeding and the very early development of pPROM and CAOS. This finding can be useful in early pregnancy. The secondary deficiency of factor XIII may underlie this difference, but its supplementation only had a limited effect. Further investigation into the pathogenesis involved in the conditions affecting BH group patients, who could be at a higher risk than HB group patients, will help in not only detecting more reliable markers for the early stratification of high-risk groups, but also identifying more effective prophylactic treatment methods.

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Declaration of competing interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2022.02.011.

References

[1] Nagy S. Clinical significance of subchorionic and retroplacental hematomas detected in the first trimester of pregnancy. Obstet Gynecol 2003;102:94–100.
[2] Norman SM, Odibo AO, Macones GA, Dicke JM, Crane JP, Cahill AG. Ultrasound-detected subchorionic hemorrhage and the obstetric implications. Obstet Gynecol 2010;116:311–5.
[3] Naert MN, Khadraoui H, Muniz Rodriguez A, Naqvi M, Fox NS. Association between first-trimester subchorionic hematomas and pregnancy loss in singleton pregnancies. Obstet Gynecol 2019;134:276–81.
[4] Johns J, Hyett J, Jauniaux E. Obstetric outcome after threatened miscarriage with and without a hematoma on ultrasound. Obstet Gynecol 2003;102:483–7.

[5] Linduska N, Dekan S, Messerschmidt A, Kasprian G, Brugger PC, Chalubinski K, et al. Placental pathologies in fetal MRI with pathohistological correlation. Placenta 2009;30:555—9.

[6] Karacor T, Bulbul M, Nacar MC, Kirici P, Peker N, Agacayak E. The effect of vaginal bleeding and non-spesific pelvic pain on pregnancy outcomes in subchorionic hematomas cases. Ginekol Pol 2019;90:656—61.

[7] Indig D, Warner A, Saxton A. Emergency department presentations for problems in early pregnancy. Aust N Z J Obstet Gynaecol 2011;51:257—61.

[8] Wittels KA, Pelletier AJ, Brown DF, Camargo Jr CA. United States emergency department visits for vaginal bleeding during early pregnancy, 1993-2003. Am J Obstet Gynecol 2008;198:523 e1—e6.

[9] Dadkhah F, Kashanian M, Eliasi G. A comparison between the pregnancy outcome in women both with or without threatened abortion. Early Hum Dev 2010;86:193—6.

[10] Ananth CV, Oyelese Y, Prasad V, Getahun D, Smulian JC. Evidence of placental abruption as a chronic process: associations with vaginal bleeding early in pregnancy and placental lesions. Eur J Obstet Gynecol Reprod Biol 2006;128:15—21.

[11] Elliott JP, Gilpin B, Strong Jr TH, Finberg HJ. Chronic abruption-oligohydramnios sequence. J Reprod Med 1998;43:418—22.

[12] Xiang L, Wei Z, Cao Y. Symptoms of an intrauterine hematoma associated with pregnancy complications: a systematic review. PLoS One 2014;9:e111676.

[13] Palatnik A, Grobman WA. The relationship between first-trimester subchorionic hematoma, cervical length, and preterm birth. Am J Obstet Gynecol 2015;213:403 e1—e4.

[14] Tuuli MG, Norman SM, Odibo AO, Macones GA, Cahill AG. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. Obstet Gynecol 2011;117:1205—12.

[15] Al-Memar M, Vaulet T, Fourie H, Bobdiwala S, Farren J, Saso S, et al. First-trimester intrauterine hematoma and pregnancy complications. Ultrasound Obstet Gynecol 2020;55:536—45.

[16] Kohler HP, Ichinose A, Seitz R, Ariens RAS, Muszbek L. Diagnosis and classi-fication of factor XIII deficiencies. J Thromb Haemostasis 2011;9:1404—6.

[17] Sharami SH, Faraji Darkhaneh R, Zahiri Z, Milani F, Asgharnia M, Shakiba M, et al. The relationship between vaginal bleeding in the first and second trimester of pregnancy and preterm labor. Iran J Reproductive Med 2013;11:385—90.

[18] Naqvi M, Naert MN, Khadraoui H, Rodriguez AM, Namath AG, Ali M, et al. Subchorionic hematomas and adverse pregnancy outcomes among twin pregnancies. Am J Perinatol 2021;38:779—83.

[19] Ilhan N, Celik E, Kumbak B. Maternal plasma levels of interleukin-6, C-reactive protein, vitamins C, E and A, 8-isoprostane and oxidative status in women with preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2015;28:316—9.

[20] Menon R, Polettini J, Syed TA, Saade GR, Boldogh I. Expression of 8-oxoguanine glycosylase in human fetal membranes. Am J Reprod Immunol 2014;72:75—84.

[21] Mogami H, Keller PW, Shi H, Word RA. Effect of thrombin on human amnion mesenchymal cells, mouse fetal membranes, and preterm birth. J Biol Chem 2014;289:13295—307.

[22] Nishimura F, Mogami H, Moriuchi K, Chigusa Y, Mandai M, Kondoh E. Mechanisms of thrombin-Induced myometrial contractions: potential targets of progesterone. PLoS One 2020;15:e0231944.

[23] Shi DY, Wang SJ. Advances of coagulation factor XIII. Chin Med J 2017;130:219—23.

[24] Saeki H, Masuda T, Okada S, Ando K, Sugiyama M, Yoshinaga K, et al. Impact of perioperative peripheral blood values on postoperative complications after esophageal surgery. Surg Today 2010;40:626—31.

[25] Tahlan A, Ahluwalia J. Factor XIII: congenital deficiency factor XIII, acquired deficiency, factor XIII A-subunit, and factor XIII B-subunit. Arch Pathol Lab Med 2014;138:278—81.

[26] Asahina T, Kobayashi T, Okada Y, Itoh M, Yamashita M, Inamato Y, et al. Studies on the role of adhesive proteins in maintaining pregnancy. Horm Res 1998;50(Suppl 2):37—45.

[27] Sharief LA, Kadir RA. Congenital factor XIII deficiency in women: a systematic review of literature. Haemophilia 2013;19:e349—57.