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Prenatal diagnosis and postnatal outcome of fetal intracranial hemorrhage: a single-center experience

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Objective
To assess prenatal ultrasonographic findings and postnatal outcomes in fetuses with intracranial hemorrhage (ICH).

Methods
This retrospective study included fetuses prenatally diagnosed with ICH between December 2012 and August 2023. Maternal characteristics, prenatal ultrasonographic findings, and postnatal outcomes were reviewed.

Results
Twenty-seven fetuses with ICH were reviewed. Intracranial hemorrhage was classified as grade 3 and 4 in 24 fetuses. Twenty-two fetuses had ICH, four had ICH with subdural hemorrhage, and one had ICH with subarachnoid hemorrhage. Ventriculomegaly was the most common ultrasonographic finding, and was observed in 22 of the 27 (81.5%) fetuses. Seven fetuses were lost to follow-up, and four intrauterine fetal deaths occurred. The remaining 16 fetuses were delivered at a median gestational age of 35+2 weeks. The infants were followed-up for 40.1 months (range, 4-88). Nine of the 16 infants underwent ventriculoperitoneal placement. One infant underwent brain surgery for severe epilepsy. Motor impairment, including cerebral palsy, was observed in 13 infants (81.2%). Neurologic impairment occurred in six infants (37.5%), developmental delay in nine (56.2%), and epilepsy in 11 (68.7%).

Conclusion
Fetal ICH is a rare complication diagnosed during pregnancy, which results in subsequent fetal neurological sequelae or death. This study demonstrated that the common ultrasonographic findings in fetal ICH were progressive ventriculomegaly and increased periventricular echogenicity. Fetuses diagnosed with prenatal ICH, especially those affected by higher-grade ICH, may be at an increased risk of long-term neurodevelopmental problems.

Keywords: Nervous system malformations; Intracranial hemorrhages; Prenatal diagnosis; Ultrasonography

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Introduction

Fetal intracranial hemorrhage (ICH) refers to a hemorrhage that occurs antenatally in the ventricles, subdural space, subarachnoid space, or brain parenchyma. This entity has been reported to affect approximately 0.5-1.0 pregnancies per 1,000 [1,2]. Various maternal and fetal predisposing factors are associated with fetal ICH [3,4]. However, the etiology can be identified in only 20-45% of fetuses [5,6]. Fetal ICH most commonly occurs in the third trimester, mainly due to germinal matrix hemorrhage [7]. Fetuses with a prenatal diagnosis of ICH are at high risk of perinatal mortality and adverse neurodevelopmental outcomes [8]. Sileo et al. [9] reported that perinatal death occurred in 14.6% of fetuses with ICH and 32.0% developed cerebral palsy. Given its strong association with poor outcomes, prenatal detection of fetal ICH is essential for pregnancy management.

Due to the subtle and variable characteristics of hemorrhage on ultrasonography, it is challenging to distinguish fetal ICH from other intracranial lesions [8,10]. The detection rate of fetal ICH has increased in recent years, which can be attributed to advancements in prenatal ultrasonography techniques and the increased utilization of fetal magnetic resonance imaging (MRI) [3,9,11,12]. Nevertheless, several cases of fetal ICH are still being missed, and the incidence varies across regions and studies [8]. Furthermore, depending on the clinician's understanding of fetal ICH, parents may be provided with incorrect or inappropriate clinical advice. Therefore, precise knowledge of the short- and long-term consequences of fetal ICH in conjunction with prenatal ultrasonography findings is required.

This study aimed to investigate the prenatal ultrasonography findings and postnatal outcomes of fetal ICH for pregnancy management and prenatal parental counseling in 27 fetuses with ICH.

Materials and methods

1. Study design and procedure

We performed a retrospective analysis of all patients prenatally diagnosed with fetal ICH between December 2012 and August 2023 at the Department of Obstetrics and Gynecology. Data from the medical records, prenatal ultrasonography and MRI findings, postnatal treatments, and prognoses of 27 fetuses with ICH were collected from the electronic database and analyzed. This study was approved by the Institutional Review Board (YUHS 4-2023-1011) and performed in accordance with the tenets of the Declaration of Helsinki. The need for informed consent was waived due to the retrospective nature of the study.

All fetal ultrasonographic examinations were performed and analyzed using maternal-fetal medicine (MFM) specialists, MFM fellows, and expert sonographers with 10 years of advanced scanning experience in prenatal diagnosis. Ultrasonographic examinations were performed using a multiplanar approach with 27 MHz transabdominal probes. When pregnant women were permitted, transvaginal ultrasonography was also performed in cases of cephalic presentation using a 5-10 MHz probe. Examinations were performed using the ultrasonography systems WS80A or HERA W10 (Samsung Medison, Seoul, Korea) and Voluson E10 (GE Healthcare Ultrasound, Milwaukee, WI, USA).

Fetal cranial examinations were performed in accordance with the International Society of Ultrasound in Obstetrics and Gynecology practice guidelines [13]. This examination evaluated the cavum septum pellucidum, lateral ventricles, choroid plexus, thalamus, cistern magna, and cerebellum in the transventricular, transthalamic, and transcerebellar planes. Additionally, the face, heart, great vessels, intra-abdominal organs, spine, kidneys, bladder, umbilical cord, and extremities were examined to detect any associated lesions. Serial two-dimensional ultrasonographic examinations were performed on patients diagnosed with fetal ICH to investigate fetal well-being and lesion progression.

Intracranial hemorrhage was diagnosed when one or more of the following characteristics were present: increased periventricular echogenicity, echogenic intraventricular foci suggesting clots, ventriculomegaly, with an irregular choroid plexus, parenchymal hyperechogenic avascular mass suggestive of extraventricular extension, increased periventricular white matter echogenicity, or porencephaly [10-14]. Extracranial hemorrhage (subdural hematoma) was diagnosed when a space-occupying lesion with curved boundaries compressing the ipsilateral cerebral structures was observed [10,14]. Location, size, and appearance of all lesions were also evaluated. Intraventricular hemorrhage (IVH) in this study was classified into four categories according to the classification system devised by Papile et al. [15]. Grade 1 was confined to the germinal matrix and subependymal areas; grade 2

involved intraventricular extension, but ventriculomegaly was <15 mm; grade 3 indicated ventriculomegaly >15 mm; and grade 4 included IVH and periventricular lesions with parenchymal involvement. Other types of ICH not included in IVH include cerebellar, epidural, subdural, and subarachnoid hemorrhages.

Prenatal data collected from electronic medical records included maternal age, gestational age at diagnosis, prenatal ultrasonography and MRI findings, and associated chromosomal anomalies. Postnatal data included gestational age at delivery, birth weight, sex, mode of delivery, Bayley scale scores of infant development to assess the level of functioning of the child across various developmental domains (cognitive, language, motor, social-emotional development, and adaptive behavior), postnatal microtomography, and brain MRI findings. We defined outcomes as neurosurgical interventions, including ventriculoperitoneal shunt placement or surgery, motor impairment, neurological impairment, epilepsy, and developmental disabilities. Motor impairment was defined as cerebral palsy, delayed motor milestones, abnormal tone, or paresis. Neurological impairment was defined as a sensorineural hearing loss or ophthalmological sequelae. Epilepsy was defined as recurrent seizures, regardless of the time of onset, including epileptic encephalopathy. Delayed development, such as language, expression, and cognition, which did not fit the above definition of impairment, was assessed using the Bailey's test.

2. Statistical analysis

Quantitative variables are expressed as medians with ranges, whereas categorical variables are expressed as frequencies and percentages. All statistical analyses were conducted using Statistical Package for Social Sciences version 26.0 (IBM Corporation, Armonk, NY, USA). Statistical significance was considered at $P<0.05$.

Results

Twenty-seven fetuses with ICH were identified in our tertiary hospital. Demographic characteristics and ultrasonographic findings of the fetuses are summarized in Table 1. The median age of the women at the time of diagnosis in all the 27 fetuses was 32 years (range, 19-44). Median gestational age of the women at the time of diagnosis was 29 weeks and 4 days (range, 18 weeks 4 days to 36 weeks 6 days). Nineteen fetuses (70.3%) were identified during the third trimester of screening. When comparing postnatal outcomes, there were 16 live births (59.3%), seven lost to follow-up (25.9%), and four intrauterine fetal deaths (14.8%). There were no postnatal deaths among the liveborn infants during postnatal treatment or follow-up. Fetal ICHs was graded as 3-4 in 24 fetuses, while only three fetuses were graded as 1-2. In our study, we observed that fetal ICH occurred unilaterally in 55.5% fetuses (n=15) and bilaterally in 44.4% (n=12). Bilateral ventriculomegaly was present in 75% of fetuses, especially in those with grade 3 or higher ICH. Four fetuses had both subdural and intraventricular involvement (Fig. 1).

Representative ultrasonographic findings of fetal ICH are presented in Figs. 2-5. Fig. 2 shows that progressive ventriculomegaly accounted for most of the findings, as observed in 22 (81.5%) fetuses. Fig. 3 shows increased periventricular

Table 1. Prenatal characteristics and ultrasonography findings of fetal ICH

Variable	Value (n=27)
Maternal age (yr)	32 (19 to 44)
Gestational age at prenatal diagnosis (weeks)	29+4 (18+4 to 36+6)
Loss to follow-up	7 (25.9)
Spontaneous IUFD	4 (14.8)
Classification	
Grade 1-2	3 (11.1)
Grade 3-4	24 (88.9)
Laterality of fetal ICH	
Both	12 (44.4)
Left	5 (18.5)
Right	10 (37.0)
Location of hemorrhage	
Intraventricular	22 (81.5)
Intraventricular+subdural	4 (14.8)
Intraventricular+subarachnoid	1 (3.7)
Ultrasonography findings	
Progressive ventriculomegaly	22 (81.5)
Increased periventricular echogenicity	21 (77.8)
Echogenic intraventricular clot	11 (40.7)
Irregular choroid plexus	8 (29.6)

Values are presented as median (range) or number (%).
ICH, intracranial hemorrhage; IUFD, intrauterine fetal death.

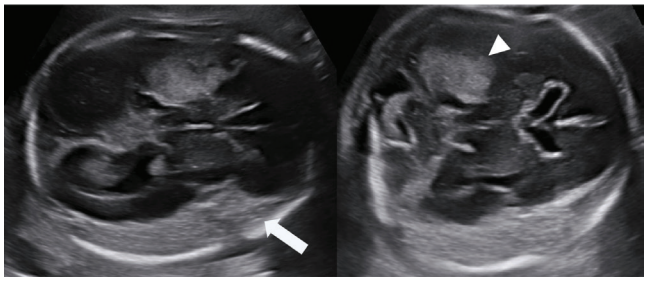

Fig. 1. Image showing subdural hemorrhage. Patient was referred to our hospital due to a history of previous intrauterine fetal death (IUFD). First visit at 26 weeks showed IUFD, ventriculomegaly, left subdural space hemorrhage (arrow), right temporoparietal area hemorrhage (arrowhead), fetal ascites, pleural effusion, scalp edema, and intracardiac hematoma. After hysterotomy, cord next generation sequencing and parental gene screening was performed, but significant result were not found.

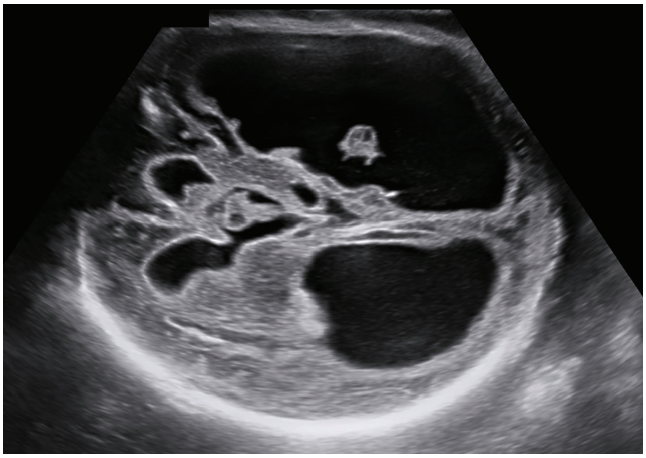

Fig. 3. Image showing increased periventricular echogenicity. Increased periventricular echogenicity accompanied by severe bilateral ventriculomegaly (both sides >30 mm).

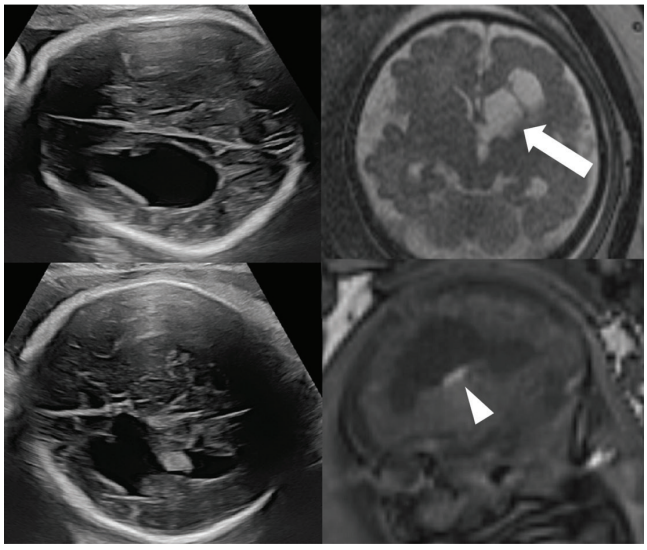

Fig. 2. Image demonstrating progressive ventriculomegaly. Ultrasound image (left) showing left ventriculomegaly with a hyperechogenic blood clot in the lateral ventricle. Magnetic resonance imaging (right) showing the same results, indicating ventriculomegaly (arrow) and a hyperechogenic blood clot (arrowhead).

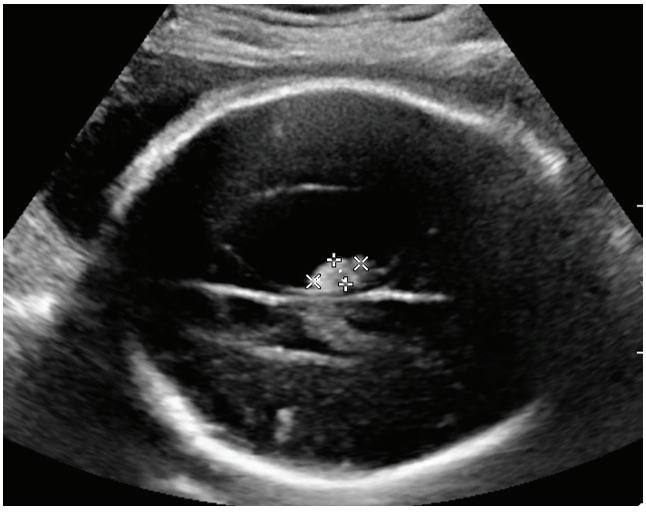

Fig. 4. Image demonstrating echogenic intraventricular clot. Ultrasound image showing an echogenic space-occupying lesion. A blood clot (1.2×0.6 cm) was noted in the ventricle with unilateral ventriculomegaly. Postnatal magnetic resonance imaging confirmed the presence of an old intraventricular hemorrhage.

echogenicity, which was evident in 21 fetuses (77.8%). Fig. 4 shows the echogenic intraventricular clots elicited in 11 fetuses (40.7%). Fig. 5 illustrates the irregular choroid plexus observed in eight fetuses (29.6%). In most fetuses, the prenatal ultrasonography and postnatal MRI findings were consistent, except for one in which cerebral hemorrhage was too small to be detected.

Cesarean delivery is generally indicated in cases of fetal ICH or IVH, depending on the progression of ultrasonography findings and etiology [7]. In this study, cesarean delivery was performed in 14 women (87.5%), and there were two (12.5%) vaginal deliveries. Among the women who underwent vaginal delivery, one fetus was delivered at 38 weeks of gestation with IVH grade 3, and the mother had a history of three previous vaginal deliveries. The other fetus was delivered at 39 weeks of gestation with IVH grade 4 and subdural

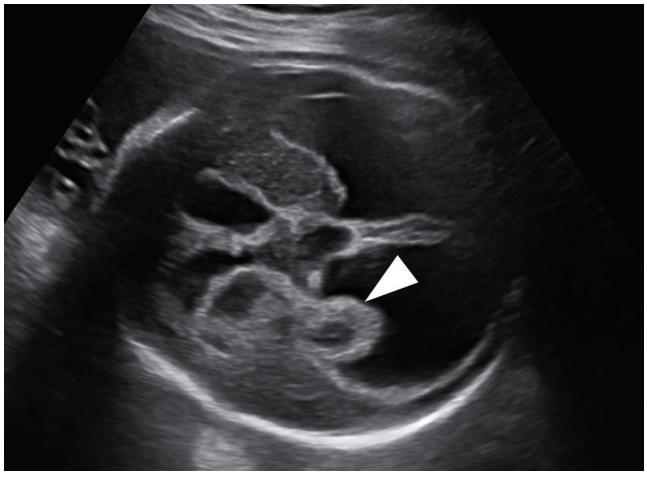

Fig. 5. Image showing an irregular shaped choroid plexus. The patient showed an irregular choroid plexus (arrowhead) with severe bilateral ventriculomegaly and increased periventricular echogenicity.

Table 2. Summary of postnatal outcomes of fetal ICH

Variable	Value (n=16)
Gestational age at delivery (weeks)	35+2 (30+5 to 39+5)
Preterm delivery (<37 weeks)	10 (62.5)
Cesarean section	14 (87.5)
Birth weight (kg)	2.78 (1.30 to 3.85)
Postnatal follow-up period (months)	40.1 (4 to 88)
ICH grade 3/4	16 (100.0)
Neurosurgical intervention	10 (62.5)
Motor impairment	13 (81.2)
Neurological impairment	6 (37.5)
Developmental delay	9 (56.2)
Epilepsy	11 (68.7)

Values are presented as median (range) or number (%).
ICH, intracranial hemorrhage.

hemorrhage, and the mother was nulliparous. Furthermore, the infant developed normally after birth due to the small size of the lesion.

Postnatal outcomes are summarized in Table 2. The median gestational age of the liveborn infants was 35 weeks and 2 days (range, 30 weeks 5 days to 39 weeks 5 days). Of the 16 liveborn infants, ten were delivered prematurely, and the average postnatal follow-up period was 40.1 months (range, 4-88). Ten infants (62.5%), including nine with ventriculoperitoneal shunt placement and one with intracranial

Table 3. Summary of clinical data, ultrasonography findings, and MRI features of the 27 cases of fetal ICH

Case No.	Age (yr)	GA at diagnosis (weeks)	GA at delivery (weeks)	Parity	Delivery mode	Birth weight (kg)	Risk factor (co-condition)	Grade in US	Laterality (ventriculomegaly)	Prenatal MRI	Postnatal outcome
1	32	35+0	35+1	0	CS	1.30	Twin (DCDA) and IUGR	4	Bilateral	NP	Protein C deficiency, CP, and epilepsy
2	29	24+6		0			None	3	Bilateral	Confirmative	FL
3	28	29+2	29+6	0	VD	1.55	Maternal AGC	4	Bilateral	NP	IUFD
4	39	35+1	35+3	1	CS	2.33	R/O G-TCP	4 and SAH	Bilateral	NP	CP, epilepsy, and VPS
5	32	32+5	33+3	1	VD	Unknown	None	4 and SDH	Left	NP	IUFD
6	19	28+4		0				4	Bilateral	NP	FL
7	35	26+6		0				2	Bilateral	NP	FL

Table 3. Summary of clinical data, ultrasonography findings, and MRI features of the 27 cases of fetal ICH (Continued)

Case No.	Age (yr)	GA at diagnosis (weeks)	GA at delivery (weeks)	Parity	Delivery mode	Birth weight (kg)	Risk factor (co-condition)	Grade in US	Laterality (ventriculomegaly)	Prenatal MRI	Postnatal outcome
8	31	32+5	37+6	0	CS	3.43	None	3	Right	NP	CENPJ, COL4A1, ATR, ARFGEF2, EOMES, CP, epilepsy, neurologic impairment, developmental delay, grid insertion, and Lt. occipital lobectomy
9	39	29+0	38+1	0	CS	3.20	None	4	Bilateral	NP	CP and neurologic impairment
10	36	36+6	36+6	1	CS	3.28	None	4	Bilateral	NP	CP, VPS, epilepsy, and developmental delay
11	34	33+1	38+5	3	VD	3.85	None	3	Right		CP, VPS, epilepsy, and developmental delay
12	37	26+3	26+4	1	CS	1.08	Fetal ascites, pleural effusion, scalp edema, and intracardiac hematoma	4 and SDH	Bilateral	NP	IUFD
13	32	30+2	39+5	0	VD	3.53	None	4 and SDH	None	NP	Normal development
14	37	31+3		2			HSV IgM/G (+) and parvovirus IgM/G (+)	3	Right	NP	FL
15	32	32+0	33+2	0	CS	2.17	None	4 and SDH	Bilateral	NP	CP, VPS, epilepsy (west syndrome with intractable epilepsy), and developmental delay
16	34	28+0	30+5	1	CS	1.74	None	3	Bilateral	NP	CP, epilepsy, VPS, neurologic impairment, and developmental delay
17	35	27+3	36+2	0	CS	2.92	None	3	Bilateral	NP	CP, VPS, and epilepsy
18	31	27+1	37+2	0	CS	3.33	HSV (+)	3	Bilateral	NP	CP, epilepsy, and developmental delay
19	31	32+5	33+1	1	CS	2.40	None	3	Bilateral	Confirmative	CP, VPS, developmental delay, and neurologic impairment
20	29	34+4	37+1	1	CS	3.00		4	Left	Confirmative	CP, developmental delay, and neurologic impairment
21	32	29+5		1			None	3	Bilateral		FL

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Table 3. Summary of clinical data, ultrasonography findings, and MRI features of the 27 cases of fetal ICH (Continued)

Case No.	Age (yr)	GA at diagnosis (weeks)	GA at delivery (weeks)	Parity	Delivery mode	Birth weight (kg)	Risk factor (co-condition)	Grade in US	Laterality (ventriculomegaly)	Prenatal MRI	Postnatal outcome
22	28	34+1	34+4	0	CS	2.64	None	4	Bilateral	NP	CP, epilepsy, and VPS
23	44	18+4	22+5	0	VD	0.40		2	Bilateral		IUFD and PDHA1 mutation
24	37	30+0	34+4	1	CS	2.21	None	4	Bilateral	Confirmative	Epilepsy and developmental delay
25	32	21+6		1				2	Bilateral		FL
26	39	21+2		0				4	Bilateral		FL
27	32	27+0	35+1	0	CS	1.89	None	3	Bilateral		VPS and neurologic impairment

MRI, magnetic resonance imaging; ICH, intracranial hemorrhage; GA, gestational age; US, ultrasonography; CS, cesarean section; DCDA, dichorionic diamniotic twin; IUGR, intrauterine growth restriction; IUFD, intrauterine fetal death; NP, not performed; CP, cerebral palsy; FL, follow-up loss; VD, vaginal delivery; AGC, advanced gastric cancer; R/O G-TCP, rule out gestational thrombocytopenia; SAH, subarachnoid hemorrhage; VPS, ventriculoperitoneal shunt; SDH, subdural hemorrhage; CENPJ, centromere protein J; COL4A1, collagen type IV alpha 1 chain; ATR, anthrax toxin receptor; ARFGEF2, adenosine diphosphate-ribosylation factor guanine nucleotide-exchange factor-2; EOMES, eomesodermin transcript; Lt., left; HSV IgM/G, herpes simplex virus immunoglobulin M, and immunoglobulin G; parvovirus IgM/G, parvovirus B19 immunoglobulin M, and immunoglobulin G; PDHA1, pyruvate dehydrogenase alpha 1.

surgery, were identified. The liveborn infant who underwent surgery underwent grid insertion and left occipital lobectomy. Motor impairment, including cerebral palsy, was present in 13 infants (81.2%), while six showed neurologic impairment. Developmental delay, assessed using the Bayley's test, was observed in nine infants. Eleven infants (68.7%) had epilepsy. Characteristics of the individual data are presented in Table 3.

Discussion

Determining the etiology of fetal ICH has been reported to be an arduous task [6,9,11,16-18]. Maternal and fetal risk factors are also associated with fetal ICH. Maternal risk factors include vitamin K deficiency [19-21], history of trauma during pregnancy, drug exposure, especially aspirin and anticoagulation, infection, placental abruption, preeclampsia, and immune thrombocytopenia [7,14]. Fetal risk factors include fetal alloimmune thrombocytopenia, fetal thrombophilia, twin-to-twin transfusion syndrome, demise of a co-twin in monochorionic twins, and single gene mutations associated with specific genes. Mutation of the collagen type IV alpha 1 chain (COL4A1) gene is reportedly the most common cause of single gene mutation in fetal ICH or IVH [22,23]. In the present study, a case of COL4A1 gene mutation was identified. When a specific genetic factor is identified, clinicians must provide appropriate genetic counseling to parents for subsequent pregnancies through a trio test. If fetal and neonatal alloimmune thrombocytopenia is suspected, intravenous immunoglobulins can be considered [24]. However, some studies have suggested that intrauterine growth restriction may play a role in fetal ICH or IVH [1]; this was confirmed in only one fetus in our study. Specific factors could not be identified in 70% of the fetuses in this study. However, they were identified in four fetuses, which included fetal protein C deficiency, COL4A1, pyruvate dehydrogenase alpha 1, and centromere protein J single gene mutations, and single fetal death in monochorionic diamniotic twins.

Prenatal ultrasonography findings of fetal ICH can be diverse [5,7], and we systematically analyzed them across four categories: progressive ventriculomegaly, increased periventricular echogenicity, echogenic intraventricular clot, and irregular choroid plexus. Initially, fetal ICH manifests as a homogeneous echogenic zone without posterior shadowing in the ventricles or brain parenchyma, which is distinct from the

choroid plexus. As the blood clot lyses, the ultrasonographic appearance becomes more heterogeneous, with the mass developing into an internal sonolucent core and an external echogenic rim. Blood clots often obstruct the cerebral aqueduct, which is a narrow channel that allows cerebrospinal fluid to flow between the third and fourth ventricles, resulting in bilateral ventriculomegaly [7,10]. Consequently, our study demonstrated that ventriculomegaly was the most common finding, with bilateral ventriculomegaly present in 75% of fetuses with high-grade (grade 3 and 4) ICH. Over time, blood within the ventricles increases echogenicity along the ventricular borders, facilitating the identification of progressive ventriculomegaly [7]. However, if the hemorrhagic lesion is too small or too recent, identifying fetal ICH or IVH in <4 hours may be challenging. This difficulty was evident in the 13th case in our study, which was the only mismatched case between prenatal ultrasonography and postnatal MRI because of its small size.

Fetal ICH was predominantly diagnosed in the third trimester in our study, which is consistent with the findings of previous studies [1,10,11,16,25]. Consequently, even if detailed sonography performed during the second trimester (between 18-22 weeks of gestation) is normal, clinicians should carefully monitor ultrasonography findings in the third trimester to avoid potential misdiagnosis of fetal IVH. Given the critical nature and need for long-term treatment of the neurological sequelae of fetal IVH, it is crucial to ensure that no neurological impairment occurs in the newborn during the delivery procedure, thereby preventing unwarranted blame on clinicians by parents [1].

Many researchers have attempted to introduce additional diagnostic modalities to detect fetal ICH at an early stage and more accurately. Magnetic resonance imaging exhibits high accuracy in detecting minor foci of germinal matrix hemorrhage [3,26-28] and could be beneficial in workups and prenatal counseling [7,10,11,14,18]. The European Neurosonography Working Group demonstrated that fetal MRI exhibited 5.4% more power than multiplanar neurosonography in identifying structural anomalies in the fetal brain [27]. However, MRI cannot serve as the primary imaging method for all pregnant women during first-line screening radiography, replacing ultrasonography to detect brain abnormalities, owing to cost factors. In our study, only four mothers underwent prenatal MRI, and the results did not differ from those obtained using ultrasonography. Additionally, it is questionable whether the outcomes would be affected, even if they were performed to influence the decisions of pregnant women and clinicians, given that abnormalities are often found at an advanced stage during ultrasonography.

With regard to postnatal outcomes (Table 2), all cases of neurosurgical intervention, motor impairment, neurological impairment, developmental delay, and epilepsy were observed in high-grade fetal ICH. Previous studies have reported a significant association between the grade and location of the hemorrhage and occurrence of severe neurologic complications [8,9,11,16,29,30]. Gupta et al. [25] showed that normal neurodevelopmental outcomes decreased in infants with higher grades of both unilateral and bilateral IVH, particularly in those with parenchymal involvement. Moreover, they demonstrated a better postnatal prognosis than our results, as their cases were evenly distributed across grades 1-4 in 37 liveborn infants [25]. Eldad et al. [31] revealed that groups with parenchymal hemorrhages exhibited a significantly higher incidence of severe neurological outcomes or neonatal death than those with non-parenchymal hemorrhages. However, our study did not observe a significant difference, owing to its small sample size.

Regarding the timing of diagnosis, the likelihood of requiring a ventriculoperitoneal shunt increased after 32 weeks of gestation, coinciding with the disappearance of the germinal matrix, as post-hemorrhagic dilatation persisted even after delivery [16]. Our study showed similar results: six of nine patients (66.7%) who required a ventriculoperitoneal shunt were diagnosed after 32 weeks of gestation. To improve our ability to prenatally predict postnatal neurological outcomes, we need to study various clinical prognostic factors and ultrasound findings and develop predictive markers.

Hemorrhagic lesions can undergo intrauterine progression or regression. Ghi et al. [8] reported that 72% of grade 1 and 2 hemorrhages were neurologically normal, whereas only 41% of grade 3 and 4 hemorrhages were considered normal. They asserted that complete regression of grade 1 and 2 hemorrhages in fetuses is possible, citing two cases of grade 2, where normal neonatal neurosonography was observed in 11 liveborn infants [8]. Conversely, previous studies have shown that intrauterine progression of hemorrhage from a lower to a higher grade is associated with worse neurodevelopmental outcomes [2,8,32]. Our findings revealed that only one of the 16 infants showed normal development (6.2%). Most liveborn infants exhibit high-grade IVH with

intrauterine progression. We did not observe intrauterine regression in high-grade ICH cases; however, it was more common in low-grade ICH. Therefore, small transient hemorrhage cases in which regression might not be detected during antenatal ultrasonography are difficult to identify in our data.

Currently, in the context of low-grade fetal IVH, it has been reported that Cesarean section does not improve prognosis, and vaginal delivery does not worsen hemorrhage [6]. However, in high-grade cases, most pregnant women prefer Cesarean delivery because of the fear of worsening fetal brain damage during labor. Furthermore, in cases where delivery is necessitated by findings, such as progressive ventriculomegaly, a Cesarean section can be safely performed with the involvement of a pediatric neurosurgeon and neonatologist.

This study has several strengths. First, we compared prenatal and postnatal images and analyzed long-term follow-up outcomes (an average of 40.1 months) at a large single center in South Korea. Other studies reported an average infant/child developmental assessment age of 11.6 months [8] and 21.6 months [25]. Second, we used an extensive clinical database of all patients, including detailed genetic and hematological evaluations. Third, neurodevelopmental delay was quantitatively assessed using the Bayley scale along with clinical follow-ups at pediatric neurology and rehabilitation clinics. However, this study had a few limitations that should be considered. Low-grade cases have a low detection rate on ultrasonography; therefore, recruiting more low-grade samples is necessary. There may have been data collection bias, as only high grades were included. As this was a single-center study with a limited sample size of 27 participants, it is necessary to conduct further investigations to determine whether the results are significant after collecting data from additional patient groups. Furthermore, among the live births, preterm births accounted for more than half of the infants (10 [62.5%]), and preterm birth itself was a confounding factor for poor prognosis. However, most of the fetuses were delivered at late preterm, and given that brain maturity was almost complete at this time, the effect was considered small. Additionally, the rate of induced abortions could not be accurately estimated; therefore, the results may differ from those of other countries. Therefore, multicenter studies with larger sample sizes are warranted.

In conclusion, fetal ICH is a rare complication diagnosed during pregnancy, with subsequent fetal neurological sequelae or perinatal death. Fetal ICH is mainly diagnosed based on the findings of progressive ventriculomegaly on prenatal ultrasonography, and it tends to be identified as a higher grade. In most fetal ICH cases, the underlying etiology is unknown and the prognosis is usually poor, especially for fetuses with higher grades. Our study showed that fetuses diagnosed with prenatal ICH, especially those affected by a higher grade, may be at an increased risk of long-term neurodevelopmental sequelae. Comprehensive counseling should be provided to parents with fetal ICH to ensure that they receive appropriate antenatal counseling to make informed decisions and optimal postnatal care.

Conflicts of interest

None.

Ethical approval

This study was approved by the Institutional Review Board (YUHS 4-2023-1011) and performed in accordance with the tenets of the Declaration of Helsinki.

Patient consent

Written informed consent and the use of patient images were not required for publication.

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