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Prenatal Diagnosis of Arachnoid Cysts Without Extra-Central Nervous System Anomalies in the Korean Population: A Multi-Center Retrospective Study on Postnatal Diagnosis and Clinical Outcomes

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ABSTRACT

Background: The aim of our study was to investigate the clinical characteristics, discrepancies in postnatal diagnosis, and outcomes of prenatally diagnosed arachnoid cysts without extra-CNS anomalies.

Methods: This study was a multi-center retrospective cohort study from 16 participating university hospitals in South Korea, with patient data pooled from January 2010 to December 2019. This study focused on cases with prenatally diagnosed arachnoid cysts and analyzed postnatal diagnoses related to CNS anomalies, the need for surgery, and clinical outcomes.

Results: Thirty-seven fetuses with fetal arachnoid cysts were ultimately included in our analysis. These included 27 supratentorial cysts and 10 posterior fossa cysts, with 11 cases (29.7%) presenting associated CNS anomalies. The most common associated anomalies were ventriculomegaly (18.9%) and callosal abnormalities (10.8%). No chromosomal abnormalities were detected during antenatal care. Postnatal regression was observed in 14.8% of supratentorial cysts and 10.0% of posterior fossa cysts. Neurologic

Mi-Young Lee and Hyun Sun Ko contributed equally to this work.

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complications, present in 21.6% of all cases, were more prevalent in cases with associated CNS anomalies compared to isolated arachnoid cysts.

Conclusion: In cases diagnosed with prenatal arachnoid cysts, ventriculomegaly and callosal anomalies are the most commonly associated CNS anomalies. The presence of additional CNS anomalies is the most critical factor affecting neurologic outcomes.

1 | Introduction

During the fetal period, intracranial cysts can be classified based on their location: extra-axial, intraparenchymal, or intraventricular (Society for Maternal-Fetal Medicine (SMFM) et al. 2020). Among extra-axial cysts, arachnoid cysts are the most common, with an incidence of 0.2% to 1.1% (Hong et al. 2023). Although it is difficult to differentiate between these types of intracranial cysts during the fetal period, the presence of anechoic cysts in the extra parenchymal region on ultrasound often raises suspicion of an arachnoid cyst (Pierre-Kahn and Sonigo 2003).

When encountering fetuses with arachnoid cysts, ultrasound or magnetic resonance imaging (MRI) is used to assess extra-central nervous system (CNS) or associated CNS anomalies. Examinations for chromosomal abnormalities or viral infections can also be helpful in evaluating the developmental prognosis. Isolated fetal arachnoid cysts generally have good developmental outcomes (Yin et al. 2018; Pierre-Kahn et al. 2000).

The extant research in this area is subject to several limitations. To begin, many studies are limited to single-center case series, which has resulted in a lack of large-scale investigations (De Keersmaecker et al. 2015; Beresford et al. 2020; Bannister et al. 1999). In addition, existing studies often report cases with various accompanying anomalies beyond the CNS, thus contributing to confusion in prognosis interpretation (Yin et al. 2018; Bannister et al. 1999; Chen 2007; Grossman et al. 2022). There is also a lack of research targeting prenatal arachnoid cysts in South Korea in particular.

Therefore, our study aimed to investigate the clinical characteristics and outcomes of fetuses diagnosed with arachnoid cysts without extra-CNS anomalies.

2 | Method

2.1 | Ethical Compliance

The present study was approved by the Institutional Review Board (IRB) of each of The Catholic University of Korea (approval number: KC20RCDI0305), Asan Medical Center (approval number: 2020-0654), Seoul National University (approval number: 2020-2164), Kyung Hee University School of Medicine (approval number: KHNMC 2020-04-019), Kangwon National University Medicine (approval number: A-2020-04-013), Korea University College of Medicine (approval number: 2020AN0428), Samsung Medical Center, Sungkyunkwan University School of Medicine (approval number: 2020-05-014), Inha University College of Medicine (approval number: INHA2020-04-050), Ewha Womans University (approval number: 2021-06-027-006), Kyungpook National University (approval number: KNUH 2020-06-008), and Konkuk University Medical Center (approval number: KUMC2022-04-061).

2.2 | Study Design

This study utilized data from a multicenter retrospective cohort study that was conducted to evaluate the prognosis of fetal isolated CNS anomalies. The original cohort study collected data from 16 university hospitals in South Korea from 2010 to 2019, while focusing solely on cases with CNS anomalies and excluding cases with multiple anomalies. The collected types of brain anomalies included dysgenesis of the corpus callosum, ventriculomegaly, mega cisterna magna, intracranial cysts, and other types of brain malformations. Each institution conducted a retrospective review by extracting prenatal ultrasound reports from the medical records or searching for patients who had been assigned a fetal brain anomaly diagnosis using the International Classification of Diseases-10 (ICD-10) code O350. Additionally, cases with unknown postnatal outcomes or prenatally detected concomitant anomalies were excluded. The present study focused on prenatally diagnosed arachnoid cysts, aiming to investigate their postnatal diagnosis, associated CNS anomalies, clinical outcomes, and the need for surgery.

2.3 | Data Collection

Maternal characteristics such as age, parity, body mass index (BMI), and delivery information including gestational age at delivery, cesarean section, fetal sex, and birth weight were collected. The following information reflecting various characteristics at the time of brain lesion diagnosis were also collected: gestational age at diagnosis, cyst size, maximum cyst size, number of cysts, cyst location, accompanying CNS anomalies, and chromosomal abnormalities.

Data on the final diagnosis after birth were collected, and various outcomes were investigated, including common neonatal adverse outcomes such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and neonatal death. The neurological outcomes were also examined for developmental delays, visual and hearing impairments, seizures, and cerebral palsy. For cases necessitating surgical intervention, information regarding the specific surgical procedures were also collected.

2.4 | Statistical Analysis

The data are expressed as medians with interquartile ranges and numbers with percentages. For comparative analysis, the Mann–Whitney U test was employed for continuous variables

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between two groups, while the Kruskal-Wallis test was performed for three-group comparisons. Fisher's exact test was used for categorical variables. All statistical analyses were conducted using IBM SPSS Statistics version 25.0 software (IBM Inc., Armonk, NY).

3 | Result

Information on 796 patients with isolated brain malformations was collected from 16 university hospitals. Among them, 37 cases were prenatally diagnosed as arachnoid cysts (Figure 1). Of these 37 arachnoid cysts, 27 cases were supratentorial cysts, while 10 cases were infratentorial cysts. Table 1 lists the maternal and clinical characteristics according to the locations of the cysts. Arachnoid cysts were detected at a median of 30 weeks of gestation with a median size of 19 mm. Additionally, 30% of the cases with arachnoid cysts were associated with other CNS anomalies. Prenatal MRI examinations were performed in 5.4% of cases, whereas postnatal MRI examinations were performed in 83.8% of cases. All 37 cases underwent postnatal MRI or ultrasound, with 29 cases (78.4%) undergoing both, 6 cases (16.2%) having only ultrasound, and 2 cases (5.4%) having only MRI. About half of the deliveries were performed by cesarean section, occurring at an average gestational age of 38.4 weeks.

Out of the 37 cases that were prenatally suspected to be arachnoid cysts, 23 (62%) were persistently observed as arachnoid cysts postnatally (Figure 1). The prenatal and postnatal diagnoses are summarized in Table 2. Among the supratentorial cysts, 17 cases were prenatally diagnosed as isolated arachnoid cysts, and 4 of these were resolved after birth. Conversely, four other cases that were initially prenatally diagnosed as isolated arachnoid cysts were identified postnatally as having porencephaly, schizencephaly, or intracranial hemorrhage (ICH). The accompanying CNS anomalies identified prenatally were ACC and ventriculomegaly, accounting for 10 cases (37%) of supratentorial cysts. Among these, five cases consistently showed associated malformations postnatally, while

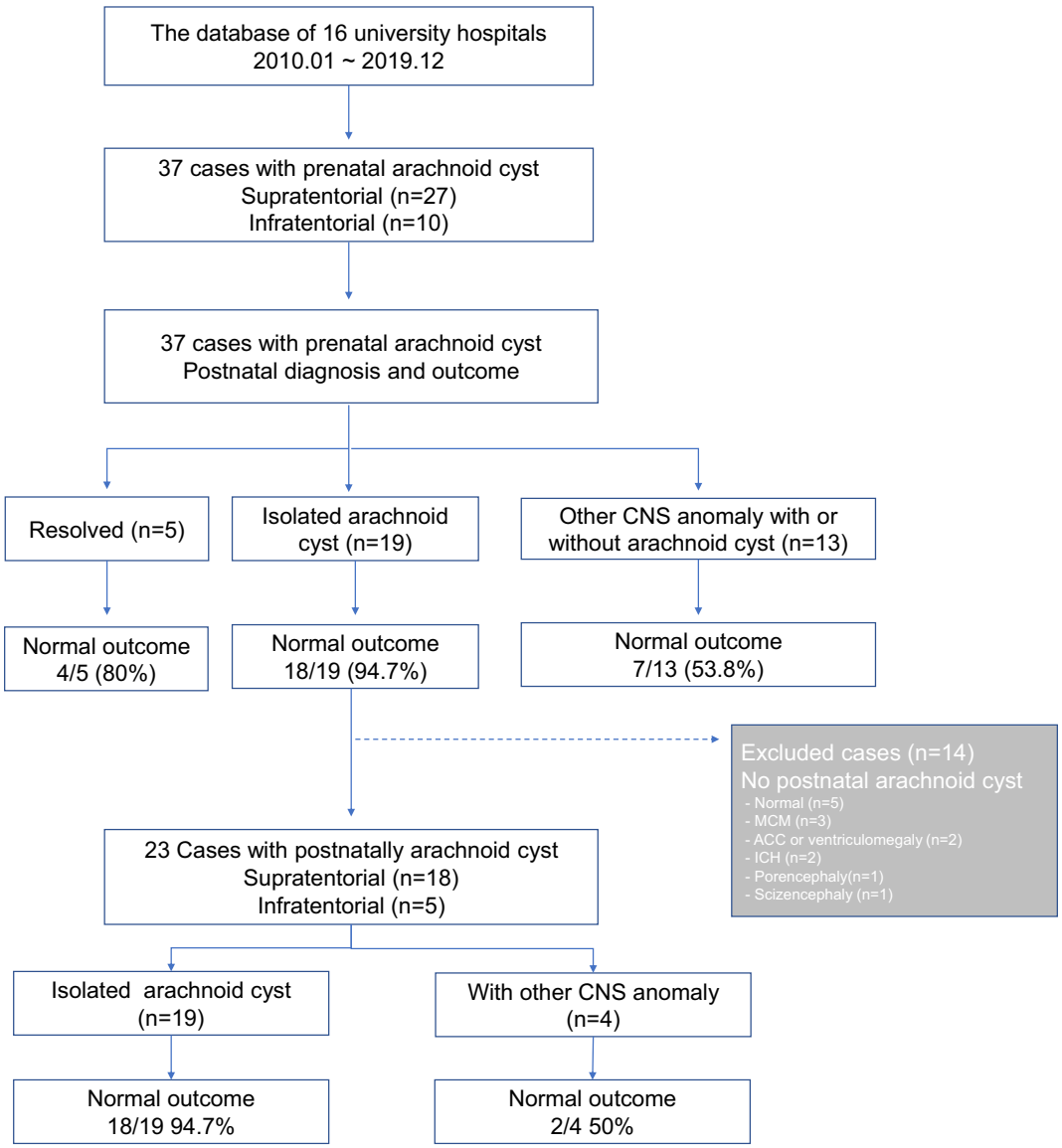

FIGURE 1 | Developmental outcomes of prenatal or postnatal arachnoid cysts according to the absence or presence of associated CNS anomalies.

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TABLE 1 | Maternal and clinical characteristics of study population.

	Total ($n = 37$)	Supratentorial cysts ($n = 27$)	Infratentorial cysts ($n = 10$)
Maternal age (years)	33 (32–37)	34 (32–37)	32 (29–34)
Nulliparity	19 (51.4%)	13 (48.1%)	6 (60.0%)
Pre-pregnancy BMI (kg/m^2)	21.0 (19.5–23.4)	21.1 (19.4–23.5)	21.0 (20.0–23.3)
GA at diagnosis (weeks)	29.9 (22.7–33.1)	30.1 (24.0–34.6)	25.1 (21.7–31.0)
Size at diagnosis (mm)	19.0 (10.3–27.9)	18.3 (10.0–24.0)	27.9 (11.8–38.7)
Prenatal MRI performed	2 (5.4%)	1 (3.7%)	1 (10.0%)
Postnatal MRI performed	31 (83.8%)	21 (77.8%)	10 (100%)
Extra-CNS anomaly	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prenatal associated CNS anomaly	11 (29.7%)	10 (37.0%)	1 (10.0%)
Chromosome abnormality	0 (0.0%)	0 (0.0%)	0 (0.0%)
GA at delivery (weeks)	38.4 (38.1–39.4)	38.5 (38.1–39.0)	38.9 (38.0–40.2)
Cesarean section	18 (48.6%)	14 (51.9%)	4 (40.0%)
Male fetus	24 (64.9%)	16 (59.3%)	8 (80.0%)
Birth weight (kg)	3.06 (2.87–3.69)	3.06 (2.91–3.62)	3.09 (2.85–4.07)

Note: Data are presented as median and interquartile range for continuous variables, and numbers and percentage for categorical variables.
Abbreviations: BMI, body mass index; CNS, central nervous system; GA, gestational age; MRI, Magnetic resonance imaging.

four, initially suspected to have accompanying anomalies prenatally, were confirmed as isolated arachnoid cysts after birth. Among the infratentorial cysts, one case was resolved post-delivery, and three cases were identified as mega cisterna magna postnatally.

Table 3 lists a comparison of maternal characteristics and prenatal ultrasound findings based on the postnatal diagnosis. Three groups were established according to the postnatal diagnosis: those with arachnoid cysts that resolved after birth, those with an isolated arachnoid cyst, and those with other CNS anomalies. These groups showed significant differences in terms of the cyst's size at the time of diagnosis, its maximum size reached, and the presence of prenatal associated CNS anomalies (Table 3). In cases that resolved after delivery, the cysts were initially the smallest, with a median size of 5.0 mm. Those cysts did not increase in size during pregnancy, and there were no accompanying prenatal CNS anomalies. Conversely, in cases with other CNS anomalies, the cysts were largest at diagnosis, with a median size of 27.0 mm, and exhibited a pattern of growth during pregnancy. Moreover, the prevalence of prenatal CNS anomalies in this group was 50%.

These findings were further categorized into those for supratentorial and infratentorial cysts and presented in Tables S1 and S2, respectively. Supratentorial cysts showed differences in terms of the time of diagnosis, maximum size, and presence of CNS anomalies among the groups. Similar to the overall data, the resolved group had the smallest cyst size and no associated CNS anomalies. In cases with other CNS anomalies, the diagnoses were made earlier, the cysts were larger, and there was a higher rate of prenatal other CNS anomalies. Infratentorial cysts showed a similar pattern. However, due to the smaller sample size of these cysts, no significant differences were found in the maternal characteristics and ultrasound findings among the groups.

Table 4 presents a comparison of neonatal adverse outcomes based on postnatal diagnoses. While there were no differences in terms of gestational age at delivery and birth weight among the groups, significant differences were observed in the frequency of adverse neurological outcomes. Notably, there were differences in the incidence of developmental delay, visual abnormalities, and seizures. Cases with other CNS anomalies had the worst neurological outcomes; approximately half of them exhibited developmental delay, 23% had visual abnormalities, and 31% had seizures. In contrast, only one case in both the normal group and the isolated arachnoid cyst group showed an adverse neurological outcome. Table S3 details the prognosis of cases with arachnoid cysts, excluding those where cysts disappeared and CNS anomalies unrelated to arachnoid cysts. When assessing developmental outcomes of simple arachnoid cysts versus arachnoid cysts with CNS anomalies, 50% of the latter group exhibited poor neurological outcomes. However, the difference between these two groups was not statistically significant due to the small sample size. There were no visual abnormalities or seizures in any cases of isolated arachnoid cysts, whereas such symptoms were observed in two out of four cases of arachnoid cysts with CNS anomalies, indicating a higher frequency of these complications with statistical significance.

Among the 37 cases of prenatal arachnoid cysts, six (16.2%) required surgery after childbirth (Table 5). In case 3, which had the largest cyst size and was diagnosed late, developmental delay sequelae remained. Otherwise, the majority of cases showed good progress without developmental disorders.

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TABLE 2 | Prenatal and postnatal diagnosis of arachnoid cyst.

Prenatal diagnosis	Postnatal diagnosis	*N*
Supratentorial arachnoid cyst		27 (100%)
Isolated		17 (63.0%)
	Resolved	4 (14.8%)
	Isolated arachnoid cyst	10 (37.0%)
	Porencephaly	1 (3.7%)
	ACC with schizencephaly	1 (3.7%)
	Intracranial hemorrhage	1 (3.7%)
Associated with CNS anomaly (ventriculomegaly or ACC)		10 (37.0%)
	Isolated arachnoid cyst	4 (14.8%)
	Ventriculomegaly	1 (3.7%)
	ACC	1 (3.7%)
	ACC with arachnoid cyst	3 (11.1%)
	Intracranial hemorrhage	1 (3.7%)
Infratentorial cyst		10 (100%)
Isolated		9 (90.0%)
	Resolved	1 (10.0%)
	Isolated arachnoid cyst	5 (50.0%)
	Mega cisterna magna	3 (30.0%)
Associated with CNS anomaly (ventriculomegaly)		1 (10.0%)
	Hydrocephalus with arachnoid cyst	1 (10.0%)

Note: Data are presented as numbers and percentage.
Abbreviations: ACC, agenesis of the corpus callosum; CNS, central nervous system.

4 | Discussion

Our study analyzed data from cases with isolated brain anomalies, collected over a 10-year period from 16 university hospitals. Out of the 796 cases with isolated brain anomalies, we identified 37 individuals (4.6%) with arachnoid cysts, suggesting that these are an infrequent type of brain anomaly. The prenatal prevalence of arachnoid cysts has been reported to range from 0.2% to 1.1% (Grossman et al. 2022; Yahal et al. 2019), with an increased prevalence of 1.3% to 2.6% observed during childhood (Al-Holou et al. 2010; Kim et al. 2002). Although the precise locations of the cysts could not be determined in our study, the majority were located in the central portion of the brain. It has been reported that the most common location of arachnoid cysts in the prenatal period is the interhemispheric space, while in childhood, they are more frequently found in the middle cranial fossa (Hong et al. 2023; Grossman et al. 2022; Al-Holou et al. 2010).

Arachnoid cysts are relatively rare conditions, and their rarity complicates the diagnosis and prognosis of fetal brain cysts. Our study showed four cases initially diagnosed with arachnoid cysts were postnatally confirmed to be other conditions such as porencephaly, schizencephaly, or ICH. Due to their cystic appearance in the brain, arachnoid cysts can be confused with lesions with poor prognoses, such as porencephaly or schizencephaly. In prenatal ultrasound, when a cystic lesion is observed in the brain, the absence of mass effect is a crucial diagnostic criterion for porencephaly (Abergel et al. 2017). Schizencephaly is discernible by the presence of gray matter-lined clefts (Denis et al. 2001). When the diagnosis is uncertain, additional MRI can be considered. Although MRI was only conducted in 5% of cases in our study, fetal MRI can play a pivotal role in ascertaining the presence of associated CNS or extra-CNS anomalies. A prior study showed that approximately 10% of cases initially diagnosed with arachnoid cysts through ultrasound were subsequently revised to a different anomalies following MRI evaluation (Yin et al. 2018). Therefore, MRI is recommended to ensure a more accurate diagnosis and can be valuable in detecting additional anomalies, regardless of the fetal position or maternal obesity levels.

In our cohort, postnatal resolution of cysts was noted in five cases, comprising 13.5% of the cohort. This rate is consistent with frequencies reported in similar studies (De Keersmaecker et al. 2015; Yahal et al. 2019). The cases where cysts resolved postnatally or those involving isolated arachnoid cysts typically presented smaller cyst sizes at prenatal diagnosis and a lower frequency of concurrent CNS anomalies (Table 3). These cases tended to have favorable prognoses, thus indicating that fetuses presenting with small cysts or without concurrent CNS anomalies may have good outcomes. Consistent with other studies, isolated arachnoid cysts were associated with normal neurodevelopmental outcomes in approximately 90% of cases (Yin et al. 2018; Pierre-Kahn et al. 2000).

In cases where other CNS anomalies were diagnosed postnatally, the initial cyst size was generally larger, and the presence of concurrent CNS anomalies was more common. Notably, in nearly half of these cases, CNS anomalies were not detected prenatally, highlighting the need for clinicians to be aware of the potential for associated abnormalities. Particularly, cases that were diagnosed postnatally with other CNS anomalies, as compared to those with isolated arachnoid cysts, tended to have poorer neurodevelopmental prognoses. This was especially evident in cases accompanied by ventriculomegaly or ACC, which were correlated with increased incidence of visual impairments and seizures. Ventriculomegaly can occur due to the obstruction of cerebrospinal fluid caused by arachnoid cysts (Martínez-Lage et al. 2011). It is also suggested that ACC might disrupt the development of the corpus callosum, especially in cases involving midportion cysts (Mankotia et al. 2016). ACC is particularly associated with

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TABLE 3 | Maternal characteristics and prenatal ultrasound findings by postnatal diagnosis.

	Resolved ($n=5$)	Isolated arachnoid cyst ($n=19$)	Other CNS anomaly ($n=13$)	p
Maternal age (years)	34 (30–35)	33 (32–37)	32 (27–37)	0.675
Nulliparity	3 (60.0%)	10 (52.6%)	6 (46.2%)	0.860
Pre-pregnancy BMI (kg/m^2)	19.5 (17.5–20.9)	20.9 (19.1–23.4)	22.6 (20.6–24.5)	0.128
GA at diagnosis (weeks)	21.9 (21.3–34.2)	30.6 (25.0–35.6)	27.1 (20.5–32.4)	0.121
Size at diagnosis (mm)	5.0 (3.8–16.0)	19.0 (10.2–25.0)	27.0 (16.7–36.9)	0.024
Maximum size (mm)	5.0 (3.8–16.0)	24.0 (18.0–37.0)	33.1 (20.5–54.7)	0.006
Prenatal associated CNS anomaly	0 (0.0%)	4 (21.1%)	7 (53.8%)	0.040
Multiple cysts	0 (0.0%)	0 (0.0%)	1 (7.7%)	0.387

Note: Data are presented as median and interquartile range for continuous variables, and numbers and percentage for categorical variables.
Abbreviations: BMI, body mass index; CNS, central nervous system; GA, gestational age.

TABLE 4 | Neonatal adverse outcomes based on postnatal diagnosis.

	Resolved ($n=5$)	Isolated arachnoid cyst ($n=19$)	Other CNS anomaly ($n=13$)	p
GA at delivery (weeks)	39 (33.6–40.1)	38.6 (38.1–40.0)	38.4 (37.7–38.7)	0.188
Birthweight (kg)	3.33 (2.10–4.20)	3.11 (2.87–3.62)	3.00 (2.84–3.74)	0.663
Neonatal adverse outcomes[a]	1 (20.0%)	0 (0.0%)	2 (15.4%)	0.170
Adverse neurological outcomes	1 (20.0%)	1 (5.3%)	6 (46.2%)	0.022
Developmental delay	0 (0%)	1 (5.3%)	6 (46.2%)	0.008
Visual abnormalities	0 (0%)	0 (0%)	3 (23.1%)	0.049
Auditory Abnormality	0 (0%)	0 (0%)	0 (0%)	—
Seizure	1 (20.0%)	0 (0.0%)	4 (30.8%)	0.040
Cerebral palsy	0 (0%)	0 (0%)	1 (7.7%)	0.387

Note: Data are presented as median and interquartile range for continuous variables, and numbers and percentage for categorical variables.
Abbreviations: CNS, central nervous system; GA, gestational age.
[a]Neonatal adverse outcomes included respiratory distress syndrome, bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and neonatal death.

visual impairments, and the diagnosis of such accompanying anomalies is crucial for prognosis assessment.

Concurrent CNS anomalies were identified in about 30% of cases (11 cases), yet none exhibited chromosomal abnormalities. According to a recent systematic review, arachnoid cysts were accompanied by CNS anomalies in 74% of cases and extra-CNS anomalies in 14% (Youssef et al. 2016). It should be noted that chromosomal abnormalities are generally not reported in most cases of isolated arachnoid cysts, and when they are present, they are associated with multiple structural anomalies. Our study, which focused solely on isolated brain malformations, did not encounter any cases with extra-CNS anomalies, thus explaining the absence of chromosomal anomalies. It is also important to note that neurodevelopmental outcomes are more significantly influenced by genetic factors and the presence of CNS or extra-CNS abnormalities than by factors such as gestational age at diagnosis, cyst size or location, or the necessity for surgical intervention (Pierre-Kahn and Sonigo 2003; Beresford et al. 2020).

Out of the 37 cases of arachnoid cysts, six (16.2%) necessitated surgical intervention, employing a variety of techniques such as cisternostomy, fenestration, and shunting. While our study did not investigate the specific reasons for surgery, other studies suggest that the main reasons include ventriculomegaly or hydrocephalus (47%), cyst expansion (15%), and the presence of mass effect or elevated intracranial pressure (ICP) (Beresford et al. 2020). Surgical intervention is typically recommended for children exhibiting neurological deficits attributed to cysts and increased ICP.

The major strength of our research is the multicenter, university-hospital-based data collection approach. Considering that the majority of anomaly diagnoses in South Korea are referred to university hospitals, our cohort can be considered representative of pregnant women in South Korea carrying fetuses with anomalies. Our study therefore holds considerable significance, as it encompasses a substantial number of cases of fetal brain cysts in South Korean pregnant women. It provides comprehensive data on prenatal

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TABLE 5 | Cases involving surgical treatment of arachnoid cysts.

	Location	GA at diagnosis (weeks)	Size (mm)	Postnatal size (mm)	Prenatal diagnosis	Postnatal diagnosis	Associated with CNS anomaly	Surgical management	Developmental delay	Cerebral palsy
1	Supratentorial	32.2	18	36	Arachnoid cyst	Arachnoid cyst	No	Endoscopic cysto-ventriculo-cisternostomy	No	No
2	Supratentorial	23.3	15	56	Arachnoid cyst	Arachnoid cyst	No	Endoscopic fenestration	No	No
3	Supratentorial	35.4	77	75	Arachnoid cyst	Arachnoid cyst	No	Shunt placement	Yes	No
4	Supratentorial	29.6	19	34	Arachnoid cyst	Arachnoid cyst	No	Craniotomy	No	No
5	Infratentorial	21.1	8	36	Arachnoid cyst	Arachnoid cyst	No	Shunt placement	No	No
6	Infratentorial	23.0	12	40	Arachnoid cyst	Arachnoid cyst	No	Shunt placement	No	No

Abbreviations: CNS, central nervous system; GA, gestational age.

characteristics, postnatal diagnoses, and neurological outcomes, which until now has been limited in terms of South Korea-specific data.

However, our research has several limitations. The retrospective nature of our data collection implies the possibility of missing cases and information. Moreover, the assessment of developmental outcomes would be enhanced with extended follow-up periods. Further, developmental outcomes were assessed based on pediatric outpatient follow-up, with a median follow-up duration of about 6 months. This relatively short follow-up period represents a limitation in terms of providing a comprehensive assessment of developmental progress.

5 | Conclusion

Our findings indicate that cysts that are initially small, exhibit no size progression, and are not accompanied by other CNS abnormalities are highly likely to either resolve spontaneously or persist as isolated arachnoid cysts. Conversely, the presence of additional CNS anomalies may indicate a less favorable neurologic prognosis. The CNS anomalies most frequently associated with arachnoid cysts are ventriculomegaly and callosal anomalies. In general, a favorable prognosis is anticipated when the cyst either regresses or remain as an isolated arachnoid cyst after birth.

Author Contributions

S.H., H.S.K., and J.K.J. designed the study; S.H., Y.M.J., H.-J.S., S.N., J.G.B., K.H.A., M.-Y.L., H.K., J.-H.S., S.R.C., S.C.K., K.A.L., H.S.K., M.J.K., J.E.S., H.S.H., S.Y.K., H.S.W., J.K.J., and H.S.K. conceptualized and acquired the data; S.H., H.S.K., M.-Y.L. and J.K.J. analyzed and interpreted the data; H.S. and H.S.K. drafted the manuscript; H.S.K. and M.-Y.L. revised the manuscript; and all authors critically revised the manuscript. All authors approved the final version.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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