Original Investigation

Fetal intracranial hemorrhage: prenatal sonographic diagnosis criteria and postnatal outcomes

Gedik Özköse et al. Fetal intracranial hemorrhage

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DOI: 10.4274/jtgga.galenos.2021.2021-0042

Received: 11 March, 2021 **Accepted:** 29 July, 2021

Abstract

Objective: This study aimed to provide sufficient knowledge of prenatally diagnosed fetal intracranial hemorrhage (ICH) defining the ultrasound (US) examination results, the contribution of fetal magnetic resonance imagination (MRI) to the diagnosis, and the pregnancy outcomes from our series of fetal ICH cases.

Material and methods: This retrospective observational study included eleven fetuses who were diagnosed as having ICH from April 2016 to August 2020. The data regarding the medical records, prenatal US and MRI findings, treatments applied, and prognosis of fetal ICH cases were collected from the hospital database and analyzed.

Results: Fetal ICHs were grade 3 in 6 cases, and grade 4 in the remaining 5 cases. The mean gestational age at diagnosis was 30.2 weeks. Nine (81.8%) of the cases were diagnosed in the third trimester and two (18.2%) were diagnosed in the second trimester. Fetal cranial MRI was performed in 7/11 cases following ultrasonographic diagnosis. The fetal MRI confirmed the fetal ICH diagnosis and previous US findings regarding location and grade in all cases. Five patients (45.5%) diagnosed with grade 3 (n=1) and grade 4 (n=4) ICH underwent pregnancy termination. Of the remaining 6 cases, one case (9.1%) diagnosed with grade 3 fetal ICH resulted in an IUFD. Four cases classified as grade 3 fetal ICH and one case with grade 4 fetal ICH were born alive at term.

Conclusion: The clinical manifestations of fetal ICH are diverse and have a wide spectrum of severity and prognostic implications. Fetal ICH cases were mainly detected in the third trimester, with a minority detected in the second trimester. These cases can be safely diagnosed and graded with US examination, but the underlying etiology frequently cannot be determined. Fetal cranial MRI might aid in the diagnosis confirmation and combined use with the US provide appropriate counseling to the parents.

Keywords: Fetal intracranial hemorrhage, prenatal diagnosis, ultrasound

Introduction

Neonatal intracranial hemorrhage (ICH) is a common postnatal complication in low birth weight premature infants in the postnatal period. However, it rarely occurs in the prenatal period, affects approximately 0.5-0.9 per 1000 pregnancies [1]. Fetal ICH is mostly diagnosed in the later stages of gestation as an incidental ultrasound (US) finding following a normal US examination in the second trimester [2]. Prenatal diagnosis of fetal ICH has been increasingly reported in recent years because of the advances in either US examination and magnetic resonance imaging (MRI) technologies [3]. However, the exact incidence of fetal ICH is still unclear due to the difficulties by the ultrasonographic diagnosis and some fetal ICHs are still missed [4].

In most cases, the cause of fetal ICH can not be identified. Possible predisposing factors for this complication include maternal trauma, thrombocytopenia, maternal use of anticoagulants crossing the placenta, fetal coagulation disorders, non-immune hydrops fetalis, twin to twin transfusion syndrome (TTTS), fetal infections, and severe fetal hypoxia [5,6,7].

There is a wide variation in the ultrasonographic appearance of fetal ICH as it is difficult to identify and differentiate from other intracranial lesions [5]. The prognosis of fetal ICH is closely associated with the grade of hemorrhage and the severity of associated brain injury [3]. Previous studies reported that prenatally diagnosed ICHs experience a poor outcome; approximately 40% of fetuses die either during the course of gestation or within the first month following birth and less than half of the survivors show a healthy neurologic development [8]. Therefore, diagnosis in the early stages is crucial.

In recent years, with the advancement of US technologies, and the utilization of fetal MRI as a diagnostic tool for fetal cerebral pathologies, the number of diagnosed patients has increased and the predictive ability of the prognosis of this complication has improved. Knowledge of diagnostic criteria, early identification, clinical importance, and the prognosis of fetal ICH is essential to provide accurate prenatal parental counseling and pregnancy management [7,9]. This study aimed to provide a sufficient knowledge of prenatally diagnosed fetal ICH defining the US examination results, the contribution of fetal MRI to the diagnosis, and the pregnancy outcomes from our series of 11 fetuses with ICH.

Material and Methods

We performed this retrospective observational study on patients admitted to the Perinatology Unit of the XXX Training and Research Hospital from April 2016 to August 2020. Eleven fetuses who were diagnosed as having ICH were included in this study. The study protocol was approved by the institution's Ethics Committee (2020.12.226). A written informed consent form was obtained from all parents.

The data regarding the medical records, prenatal two-dimensional (2D) US and MRI findings, treatments applied, and prognosis of these 11 fetal ICH cases were collected from the hospital database and analyzed. All ultrasonographic fetal cranial examinations were performed and analyzed by expert sonographers with advanced training in prenatal diagnosis, transabdominally and also transvaginally when the fetus is in cephalic presentation, using high-resolution ultrasound devices (Voluson 730 Expert and Voluson E6) with a convex probe (3.5-5 MHz for transabdominal examinations, 5-6.5 MHz for transvaginal examinations).

We performed the central nervous system (CNS) examination according to the ISUOG practice guidelines [10]. This examination included evaluation of the cisterna magna, lateral ventricles, choroid plexus, thalamus, and cavum septum pellucidum in the transcerebellar,

transventricular, and transthalamic planes. Also, the umbilical cord and its insertion, all four extremities, intraabdominal organs, heart and great vessels, spine, and face were evaluated to determine any associated abnormalities. We performed serial 2D US examinations (every 2-4 weeks) to detect the lesion progression, fetal biometry, and fetal wellbeing. In cases where fetal intrauterine growth restriction (IUGR) was suspected, we conducted a Doppler US examination of the fetal umbilical arteries [11].

We diagnosed the fetal ICH based on the presence of one or more of the following characteristics: intraventricular hyperechogenic foci suggesting clots, hyperechogenic and intended ventricular walls, ventriculomegaly with irregular bulky choroid plexus, parenchymal hyperechogenic avascular mass, increased echogenicity in periventricular white matter, and porencephalic cyst formation. We assessed the location, size, and appearance of all the lesions. The intraventricular hemorrhage was classified as grade 1 when the hemorrhage was limited to the subependymal germinal matrix; grade 2, when the blood clots inside the lateral ventricle without ventriculomegaly or ventriculomegaly <15 mm at the level of lateral ventricular atria; grade 3, when the clots affected one or two lateral ventricles with ventriculomegaly greater than 15 mm at the level of the lateral ventricular atria; and grade 4, when grade 1 to 3 hemorrhages accompanied with hemorrhage in a large part of the periventricular parenchyma [3,9].

Antenatal work-up to determine the underlying cause of fetal ICH included a history of previous pregnancy characteristics, maternal trauma, history of drug exposure (especially acetylsalicylic acid and anticoagulant therapy), assays for alloimmune and isoimmune thrombocytopenia, coagulation tests (platelet count, prothrombin time, activated partial thromboplastin time), and maternal serological testing for parvovirus B19, toxoplasmosis, rubella, and cytomegalovirus infections [6].

We offered fetal cranial MRI to all patients to confirm the ICH diagnosis and to evaluate the hydrocephaly irrespective of the degree of ventriculomegaly [2]. Standard MRI scanning procedures were conducted using a 1.5 T MRI scanner. The mothers experienced the MRI scanning after a 4 h of fasting, in the empty bladder condition, and the supine position without sedation.

Pediatric neurologists performed the postnatal evaluation and cranial brain imaging in all living newborns. Pediatric hematologists evaluated all living newborns regarding congenital bleeding diseases. Pregnancy outcomes, fetal and postnatal morbidity, and mortality were analyzed.

Statistical analysis

IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used for statistical evaluation of our research data. We performed a descriptive analysis of the records following the completion of the audit. Continuous variables were presented as mean±standard deviation or median (minimum-maximum). Categorical variables were presented as frequencies and percentages.

Results

During the study period, a total of 11 cases with fetal ICH were identified in our tertiary referral hospital. We summarized the demographic characteristics, US and MRI findings, and outcomes of the cases in Table 1. Fetal ICHs were grade 3 in 6 cases, and grade 4 in the remaining 5 cases. No cases with grade 1 and 2 hemorrhage were detected. ICH was observed as bilateral in all cases (n=11, 100%). The mean gestational age at diagnosis was 30.2 weeks (ranging from 22 weeks to 36 weeks). Nine (81.8%) of the cases were diagnosed in the third trimester and two (18.2%) were diagnosed in the second trimester. One of the cases diagnosed at the second trimester was grade 3 fetal ICH and the other was grade 4 fetal ICH. Serological testing was performed in 8 cases, while hematological and coagulation tests were performed

in all cases. All of these tests were normal and underlying etiology could not be identified in any case.

We presented some of our cases' US findings in figure 1a, 1b, 1c, and 1d. Figure 1a demonstrates echogenic, irregular and nodular lateral ventricular borders. Figure 1b shows intraventricular hyperechogenic foci suggesting clots with unilateral and bilateral ventriculomegaly. Figure 1c represents periventricular hypoechoic nodules. Figure 1d illustrates periventricular leukomalacia.

When we analyzed the outcomes of 6 grade 3 fetal ICH cases, one of them underwent pregnancy termination. One case resulted in an intrauterine fetal demise (IUFD) at 25 weeks of gestation. In one case, ventricular width showed progression at follow-up. This case underwent a ventriculoperitoneal shunt placement after the birth and died at 6th months of age. In two cases, ventriculomegaly showed regression during the postnatal follow-up. However, epilepsy and hemiparesis were observed in these cases. A ventriculoperitoneal shunt placement was performed in one case in the postnatal period. In this case, whose follow-up continued, no complications or neurological handicaps were observed regarding the fetal ICH and shunt placement.

When we evaluated the 5 cases with initial diagnosis of grade 4 fetal ICH, periventricular leukomalacia was observed in three of them, and both periventricular leukomalacia and porencephalic cysts were observed in two them (Figure 2). Four of these pregnancies were terminated. One live birth infant lost to follow-up during the postnatal period.

Fetal cranial MRI was performed in 7/11 cases following ultrasonographic diagnosis. The fetal MRI confirmed the fetal ICH diagnosis and previous US findings regarding location and grade in all cases.

In our series of 11 cases, 5 patients (45.5%) diagnosed with grade 3 (n=1) and grade 4 (n=4) fetal ICH underwent pregnancy termination. Of the remaining 6 cases, one case (9.1%) diagnosed with grade 3 fetal ICH resulted in an IUFD. Four cases classified as grade 3 fetal ICH and one case with grade 4 fetal ICH were born alive at term. Live born infants were followed-up for a median duration of 18 months (ranging from 7 months to 36 months).

Discussion

In our series of fetal ICH cases, similar to the previous reports, US findings are observed in various clinical presentations from hyperechogenic and intended ventricular walls to complete liquefaction with a cystic hypoechoic mass. Different US signs of fetal ICH have been identified as a consequence of alterations in extension, location and amount of bleeding, and internal echo pattern depending on the blood clot formation and lysis, and thus, prenatal diagnosis is frequently challenging. Also, the ultrasonographic characteristics of fetal ICH changes over time in an orderly manner [12]. The US finding of a recent hemorrhage, irrespective of location, is a brightly echogenic mass without dorsal shadowing. Early on, a fetal ICH seems like a homogeneous echogenic zone within the brain parenchyma or ventricles that are separated from the choroid plexus. In the process of time, as the blood clot dissolves, the US presentation becomes more heterogeneous, and the mass reveals an internal sonolucent core and an external echogenic rim [2]. Fetal ICH is commonly related to ventricular dilatation as a consequence of cerebral aqueduct obstruction by the blood clot. Also, the blood within the ventricles ended in an echogenic border lining the ventricle or nodular structures [5]. Involvement of the brain cortex can be identified by the demonstration of the echogenic collection extension to the surrounding periventricular parenchyma in the early stages [8]. Retraction, lysis, and resorption of the surrounding parenchyma and blood clot ended in a porencephalic cyst formation, a solid mass-like structure composed of the infarcted brain and blood clot [3]. This cyst becomes evident commonly about two weeks after the initiation of hemorrhage [8].

Fetal and maternal risk factors were found to be related to fetal ICH. Predisposing fetal risk factors include fetal alloimmune thrombocytopenia, umbilical cord entanglement, umbilical cord thrombosis, fetal thrombophilia, the demise of a co-twin in monochorionic placentation, TTTS, severe hypoxia, and severe IUGR. Maternal risk factors for fetal ICH include vitamin K deficiency, pregnancy complications (placental abruption, preeclampsia), infections, immune thrombocytopenia, coagulation disorders, seizures, trauma, medications (warfarin), and drugs [3,7,13]. However, previous studies reported that in the majority of cases no identifiable risk factor was detected. Fetal and maternal diseases that might have caused fetal ICH only in 20-45% of cases [6,8,13,14]. In this study, no identifiable etiologic factor was detected in any of the cases. However, we performed maternal serological testing in 8/11 cases. The lack of serologic testing in the remaining 3 cases may be considered to be a limitation of our study.

The mean gestational age at the time of diagnosis in this study cohort was 30.2 weeks. This finding was consistent with previous studies [6,7,8,13,14]. All cases were suffered from bilateral fetal ICH, similarly with the literature [7,13]. All of our cases were grade 3 and 4, and consistent with those of previous studies, which had a reported range from 70% to 100% [7,12,13]. Grade 1 fetal ICH was rarely reported since the findings are subtle and are easily missed in the standard axial planes used on US examination.

The neurodevelopmental outcomes of the fetuses complicated with this condition are still unclear due to the paucity of data in the literature. Also, the variety of pregnancy termination rates and the heterogeneousness of the etiology of fetal ICH or concomitant co-morbidities make it difficult to evaluate the results. Previous studies reported that there was a significant association between the grade and location of the hemorrhage and the occurrence of severe neurologic complications [15,16]. Cases with grade 2 ICH are related to better outcomes with a survival rate of 100% and only 10% of these cases suffer from mild neurologic sequelae. Also, in lower grades of hemorrhage, complete disappearance of abnormal US findings may be observed with better postnatal neurologic consequences [3,8,13]. However, the experience with grade 1 and 2 fetal ICHs was limited in the literature. In our study cohort, no cases with grade 1 and 2 hemorrhages were observed. Grade 3 and 4 hemorrhages are associated with poorer neonatal outcomes than the lower grade fetal ICHs. Ghi et al. reported that no losses were reported were detected in fetuses with grade 1 and 2 hemorrhages and 72% of these infants showed healthy neurologic development. However, 41% of infants staged as grade 3 and 4 were considered neurodevelopmentally normal [8]. A recent study reported that 2/3 of infants with grade 3 fetal ICH suffer from adverse neurologic outcomes [3]. In our study cohort, of the infants with grade 3 and 4 ICH, 45.5% (5/11) were born alive at term, with no postnatal deaths. Of them, two cases were suffering from epilepsy and hemiparesis and three cases (60%) were reported to be a healthy neurologic development.

In most fetal ICH cases, the sonographic signs were detected between 28 and 33 weeks of pregnancy. However, Anderson et al. stated that fetal ICH may be identified between 18-20 weeks of gestation [17]. Previous studies demonstrated that US examination provides an accurate diagnosis with no false-positive results [6,8,13]. However, blood clots may undergo complete resolution and disappear, ventriculomegaly resolves and it may be observed as a healthy brain appearance in the US examination. These US features make the prenatal diagnosis challenging [12]. Therefore, fetal ICH should be considered in the differential diagnosis of ventriculomegaly cases in the prenatal period.

The role of fetal MRI in the diagnosis, grading, and evaluation of fetal ICH is still controversial and dependent on the clinicians' experience [6,8]. Previous studies postulated that fetal MRI is a beneficial adjunct to US examination in the examination of fetal ICH or ischemic lesions and provides information differing from other imaging techniques. Ghi et al. reported that the US examination was always diagnostic in fetal ICH cases, and MRI, when

performed, proved accurate but did not add further information about the case. They stated that MRI has a role at least in those patients where the US examination is inconclusive [8]. Kutuk et al. demonstrated that MRI confirmed the diagnosis made by the US and defined the hematoma dimension, bleeding zone, and eliminated other intracranial abnormalities, particularly in fetuses with grade 3 and 4 ICHs [6]. In the case series of Adiego et al., MRI accurately detect the location and grade of the ICH, provided additional information concerning the etiology of ICH in one case [3]. In this cohort, fetal cranial MRI was performed in 7 cases. In these cases, MRI proved the diagnosis, bleeding region and grade of the hemorrhage detected by US examination. However, fetal MRI did not provide to us additional information about the fetal ICH cases. This might be due to the fact that our study cohort consisted of fetuses with grade 3 and 4 hemorrhage. Also, we performed fetal MRI within the 7 days of US evaluation, eliminating the probability of up-grading of fetal ICH between to imaging modalities. It seems reasonable to combine MRI with US to the evaluation of the fetuses with low-grade ICH and identifying the predisposing factors of the hemorrhage.

There are some limitations to this study, including its retrospective design, and an absence of autopsy information. Also, the lack of grade 1 and 2 fetal ICH cases may lead to biased outcomes due to the high termination of pregnancy rates in grade 4 cases. The absence of serologic testing in 3 cases may be considered to be another limitation of this study. Moreover, we did not perform three-dimensional (3D) sonography in the assessment of ICH. However, Pooh et al. demonstrated that a 3D US scan is superior to an MRI in the evaluation of normal and abnormal CNS findings. Further studies are needed that evaluate the ICH cases with 3D US scan and compare the outcomes of 3D sonography with MRI.

Conclusion

The clinical manifestations of fetal ICH are diverse and have a wide spectrum of severity and prognostic implications. Fetal ICH cases were mainly detected in the third trimester, with a minority detected in the second trimester. These cases can be safely diagnosed and graded with US examination, but the underlying etiology frequently cannot be determined. Fetal cranial MRI might aid in the diagnosis confirmation and combined use with the US provide appropriate counseling to the parents.

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Table 1. Demographic characteristics, US and MRI findings, and outcomes of the cases

Case	Age	Gestational week at diagnosis	Grade of ICH	Ultrasonographic Findings	MRI Findings	Outcome	Gestational week at delivery	Type of delivery
1	20	36	Gr 3	- Ventriculomegaly (39/33 mm) - Intraventricular hyperechogenic foci suggesting clots	- Ventriculomegaly (32/35 mm) - Bilateral intraventricular hyperechogenic foci suggesting clots	- Pregnancy termination	37	Vaginal delivery
2	20	25	Gr3	- Ventriculomegaly (15/22 mm)	-	- IUFD	25	Vaginal delivery
3	25	31+2	Gr3	- Ventriculomegaly (19/21 mm) - Echogenic and irregular lateral ventricle borders - Intraventricular hyperechogenic foci suggesting clots	-	- Died at postnatal 6th months	38	Vaginal delivery
4	26	32+5	Gr 3	- Ventriculomegaly (33/20 mm) - Intraventricular hyperechogenic foci suggesting clots	- Ventriculomegaly (37/25 mm) - Intraventricular hyperechogenic foci suggesting clots (More prominent in the left ventricle)	- Hemiparesis and epilepsy	37	Cesarean Delivery
5	19	30+1	Gr4	- Ventriculomegaly (12/22 mm) - Porencephalic cyst	- Ventriculomegaly (11/21 mm)	- Pregnancy termination	32	Vaginal delivery

					- Intraventricular hyperechogenic foci suggesting clots - Porencephalic and encephalomalastic cysts in periventricular white matter			
6	29	32+6	Gr 4	- Ventriculomegaly (19/14 mm) - Echogenic and irregular lateral ventricle borders - Ventricular leukomalacia	-	- Lost to follow-up	36	Vaginal delivery
7	19	22+1	Gr 4	- Ventriculomegaly (19/20 mm) - Diffuse liquefication in the parenchyma	-	- Pregnancy termination	23	Vaginal delivery
8	30	28+6	Gr 4	- Ventriculomegaly (13/15 mm) - Echogenic and irregular lateral ventricle borders - Parenchymal hemorrhage	- Ventriculomegaly (16/14 mm) - Parenchymal hemorrhage - Cystic-encephalomalastic changes	- Pregnancy termination	30+5	Vaginal delivery
9	20	35	Gr 3	- Ventriculomegaly (28/28 mm) - Echogenic and irregular lateral ventricle borders	- Ventriculomegaly (32/35 mm) - Intraventricular hyperechogenic foci	- Ventriculoperitoneal shunt placement	38+2	Cesarean Delivery

					suggesting clots			
10	21	28	Gr 3	- Ventriculomegaly (14/13 mm) - Echogenic and irregular lateral ventricle borders	- Ventriculomegaly (17/17 mm) - Irregular lateral ventricle borders - Intraventricular hyperechogenic foci suggesting clots	- Hemiparesis and epilepsy	36+3	Vaginal delivery
11	18	32	Gr4	- Ventriculomegaly (26/35 mm) - Echogenic lateral ventricle borders - Parenchyma is liquefied	- Ventriculomegaly (26/35 mm) - Parenchyma is liquefied	- Pregnancy termination	32+3	Vaginal delivery

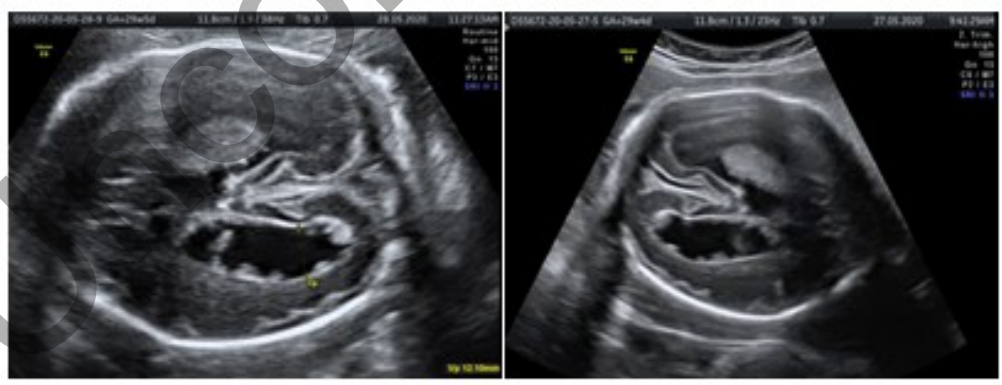

Figure 1a. Echogenic, irregular and nodular lateral ventricle borders

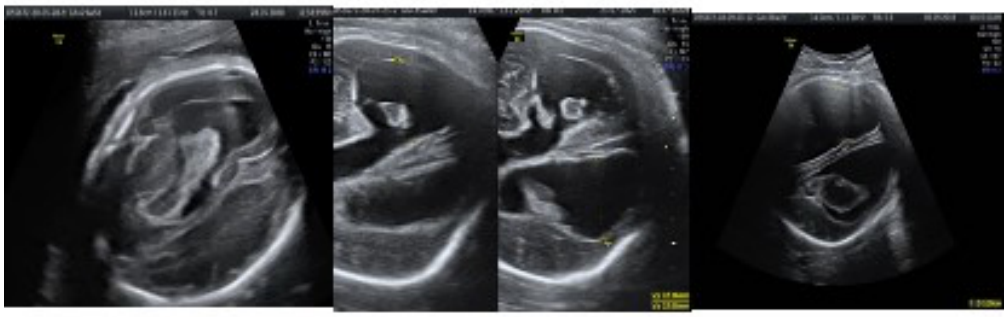

Figure 1b. Intraventricular hyperechogenic foci suggesting clots with unilateral and bilateral ventriculomegaly (arrow)

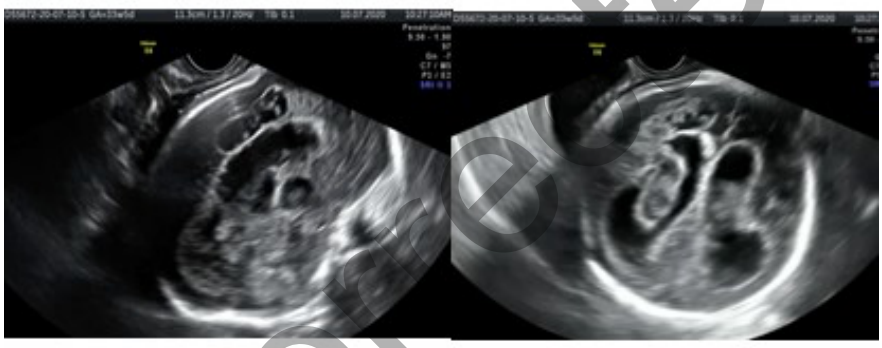

Figure 1c. Periventricular hypoechoic nodules (arrow)

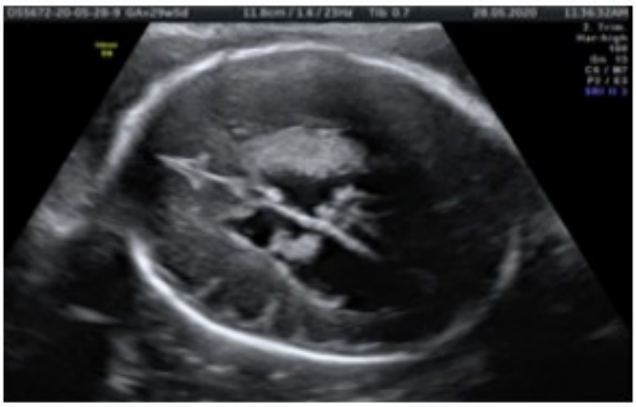

Figure 1d. Periventricular leukomalacia (arrow)

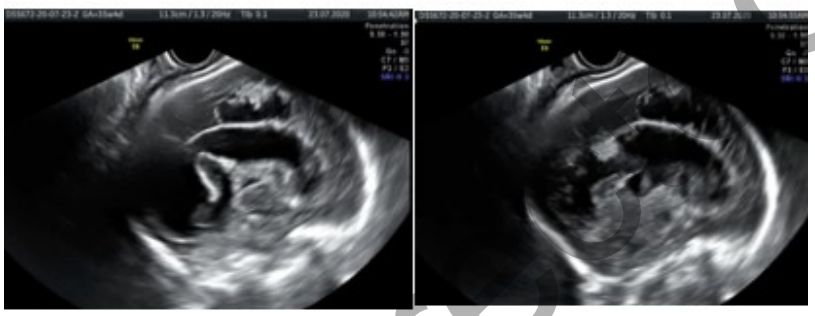

Figure 2: Porencephalic cyst (arrow)