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Detecting Fetal Central Nervous System Anomalies Using Magnetic Resonance Imaging and Ultrasound

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ABSTRACT

Background: Most fetal abnormalities can be detected on ultrasound, the evaluation of fetal CNS abnormalities can be limited by various factors, including obesity, polyhydramnios, multiple pregnancies, and increased cranial ossification during the third trimester. **Objective:** This study aimed to evaluate the ability to detect fetal central nervous system (CNS) anomalies using *in utero* magnetic resonance imaging (iuMRI) and ultrasound (US) techniques. **Methods:** This prospective study was approved by the institutional review board (Ref: 2968/QĐ-ĐHYHN dated 11 July 2019), and the requirement to obtain the informed consent of patients was waived. This study included 66 fetuses with diagnosed or suspected CNS abnormalities based on the results of a prenatal screening US performed at the antenatal diagnosis center of the Central Obstetrics and Gynecology Hospital. All pregnant women with a suspected diagnosis of abnormal fetal CNS on US underwent 1.5-Tesla iuMRI within 14 days of the US at Hanoi Medical University Hospital between June 2019 and June 2020. Cohen's kappa coefficient (κ) was used to determine the agreement between US and iuMRI findings. **Results:** A total of 66 pregnant women were examined, including 66 fetuses, for which 79 abnormalities were detected by US and 98 abnormalities were detected by iuMRI. The average gestational age was 29 weeks and 6 days. The comparison of iuMRI and US findings revealed similar diagnoses for 71 abnormalities (67%) and different diagnoses for 35 abnormalities (33%). The level of agreement between US and iuMRI was almost perfect for ventriculomegaly and cystic lesions, with κ values 0.87 and 0.84, respectively. The level of agreement between US and iuMRI was the weakest for hemorrhage, with a κ value 0 (no agreement), and cortical abnormalities, with a κ value of 0.46 (weak agreement). **Conclusion**: The level of agreement between US and iuMRI diagnoses was almost perfect for the detection of ventriculomegaly and was weakest for the detection of hemorrhage and cortical abnormalities, which were abnormalities detected by iuMRI but not by ultrasound.

Keywords: MRI fetus, Prenatal diagnosis, Central nervous system abnormalities.

1. BACKGROUND

Fetal central nervous system (CNS) abnormalities are among the most commonly encountered congenital abnormalities (1). Many different methods can be used to obtain prenatal diagnoses, including ultrasound (US), which is one of the most commonly used methods (2). Although most fetal abnormalities can be detected on ultrasound (3), the evaluation of fetal CNS abnormalities can be limited by various factors, including obesity, polyhydramnios, multiple pregnancies, and increased cranial ossification during the third trimester (4).

In utero magnetic resonance imaging (iuMRI), which was first performed in 1983 and is increasingly being used worldwide (5), has been demonstrated in multiple studies to be a very useful technique for the assessment of fetal abnormalities in most organs, especially those in the CNS (6-9). In Vietnam, during recent years, iuMRI has been implemented in some hospitals to supplement US during the assessment of fetal CNS abnormalities; however, no studies have compared the detection capabilities of CNS abnormalities between iuMRI and US.

Some children with CNS abnormalities die after birth (10), and those who survive may suffer from psychomotor developmental abnormalities. A study by Shirasaka *et al,* examining the causes of epilepsy in children treated at Bach Mai Hospital from 2002 to 2004, reported that congenital CNS abnor-

malities accounted for 12% of cases (11). The early and accurate detection of CNS abnormalities can provide clinicians with the necessary information to make a prognosis, perform prenatal counseling, and determine the most appropriate treatment after birth.

2. OBJECTIVE

Therefore, in this study, we aimed to evaluate the abilities of iuMRI and US to detect fetal CNS abnormalities.

3. METHODS

Study group

A prospective study was performed on 66 fetuses carried by 66 pregnant women, who were each diagnosed or suspected of CNS abnormalities based on the findings of a prenatal screening US at the antenatal diagnosis center of the Central Obstetrics and Gynecology Hospital. These women underwent iuMRI within 14 days of the US examination, using a 1.5-Tesla MRI scanner at Hanoi Medical University Hospital between June 2019 and June 2020. This study was approved by the institutional review board (Ref: 2968/QĐ-ĐHYHN dated 11 July 2019), and the requirement to obtain the informed consent of patients was waived.

Definition of anomalies

Each fetus was assessed using the obtained images for the following categories of brain malformations: a) ventriculomegaly, b) midline developmental abnormalities, c) posterior fossa malformations, d) cortical developmental abnormalities, e) cyst, f) destructive lesions, and g) vascular malformations.

Ventriculomegaly is defined as an atrial width equal to or greater than 10 mm. The measurement was performed in the axial plane at the atria of the lateral ventricle and glomus of the choroid plexus (12).

Midline developmental abnormalities include a heterogeneous group of conditions, such as agenesis of the septum pellucidum and agenesis of the corpus callosum (13). Agenesis of the corpus callosum can include both the complete and partial absence of the corpus callosum.

The evaluated posterior fossa malformations included large cisterna magna, vermian hypoplasia, cerebellar malformations (cerebellar hypoplasia and cerebellar dysplasia), Dandy–Walker malformation, and Joubert syndrome. Large cisterna magna was defined as cisterna magna larger than 10 mm (14). Vermian hypoplasia was defined as the partial absence of the inferior portion of the cerebellar vermis with normal cerebellar hemispheres (15). Dandy–Walker malformation was diagnosed when all of the following features were identified: 1) a large median posterior fossa cyst that widely communicates with the fourth ventricle, 2) a small, rotated, raised cerebellar vermis, 3) an upwardly displaced tentorium, 4) an enlarged posterior fossa, 5) anterolaterally displaced but apparently normal cerebellar hemispheres, and 6) a normal brain stem (16). Joubert syndrome was diagnosed when molar tooth sign (MTS) was detected on the axial plane (reflected by thickened superior cerebellar peduncles), combined with cerebellar vermis hypoplasia and a deepened interpeduncular fossa (17).

Cortical development abnormalities were assessed across the following categories: polymicrogyria, periventricular nodular heterotopia, and hemimegalencephaly. Polymicrogyria was characterized by the appearance of too many infoldings for gestational age (18). Periventricular nodular heterotopia was characterized by gray matter nodules lining the lateral walls of the ventricles (18). Hemimegalencephaly was characterized by the enlargement of all or part of one cerebral hemisphere (19). Cystic malformations were evaluated by the evaluations of intracranial cysts on US or iuMRI. Destructive lesions included hemorrhage and ischemia. The intracranial hemorrhage findings on US included ventriculomegaly, hyperechoic acute clot, hyperechoic nodular choroid plexus, avascular intracranial mass, increased periventricular white matter echogenicity in the acute phase, or porencephaly and hydranencephaly in the chronic phase (20, 21). Cerebral hemorrhage lesions appeared hypointense on T2*-weighted gradient-echo, and T2-weighted (T2W) single-shot fast spin-echo (SSFSE) and hypertense on T1-weighted (T1W) imaging in the acute phase (20,21). The later phase can appear hypointense on T2*-weighted gradient-echo, revealing porencephaly cysts and hydranencephaly (20). Ischemia is nonspecific on US and may present ventriculomegaly, parenchymal atrophy, porencephaly, or hydranencephaly (22). On iuMRI, ischemia can present similar lesions as those observed on US or appear hyperintense on diffusion imaging (acute ischemia) (21).

Pregnancy ultrasound and iuMRI

All US images and measurements were obtained using a four-dimensional (4D) US scanner (Voluson S10, GE Healthcare, New York, USA) equipped with a convex 2–5 MHz 4D probe.

All iuMRI examinations were conducted on a 1.5-Tesla Signa HD (GE Healthcare, Wisconsin, USA), with a GE 8-channel cardiac coil. The scanning protocol included the following sequences: (1) T2W imaging, using SSFSE on axial, sagittal, and coronal planes; (2) axial T1W; (3) axial diffusion-weighted image; and (4) T2*-weighted gradient-echo. No contrast agent was administered in any cases. Images were transferred to a picture archiving and communication system (PACS) workstation (Carestream PACS; Carestream Health, Eemnes, Netherlands). All images were analyzed by a single observer with over 15 years of practical experience diagnosing images in the fields of obstetrics and gynecology.

Statistical analysis

Our data included fetal age and detected fetal CNS abnormalities, which were divided into groups of abnormalities. SPSS version 20 was utilized for data analysis (IBM Corp, New York, USA). Categorical variables are displayed as numbers and percentages. The values of Cohen's kappa (κ) were evaluated as follows: values ≤ 0 indicated no agreement; 0.01−-0.20 indicated no-to-slight agreement; 0.21−0.40 indicated fair agreement, 0.41−0.60 indicated moderate agreement, 0.61−0.80 indicated substantial agreement, and 0.81−1.00 indicated almost perfect agreement (23). A significance level of p < 0.05 was adopted.

	US n (%)	iuMRI n (%)
Ventriculomegaly	42 (53.2)	44 (44.9)
Midline developmental abnormalities	18 (22.8)	18 (18.37)
Posterior fossa malformations	9 (11.4)	12 (12.25)
Cortical developmental abnormalities	3 (3.8)	9 (9.18)
Cyst	6 (7.6)	8 (8.16)
Destructive lesions (Hemorrhage)	0 (0)	6 (6.12)
Vascular malformations	1 (1.30)	1 (1.02)
Total	79 (100)	98 (100)

Table 1. Rate of fetal central nervous system abnormalities on ultrasound (US) and in utero magnetic resonance imaging (iuMRI)

	iuMRI and US similar diagnoses n	iuMRI and US different diagnoses n
Ventriculomegaly	41	4
Midline developmental abnormalities	14	8
Posterior fossa malformations	7	7
Cortical developmental abnormalities	3	6
Cyst	6	2
Destructive lesions (Hemorrhage)	0	6
Vascular malformations	0	2
Total	71 (67%)	35 (33%)

Table 2. Comparing the results of ultrasound (US) and in utero magnetic resonance imaging (iuMRI) for the detection of fetal central nervous system abnormalities.

		Yes	No	Kappa	p
Ventriculomegaly	Yes	41	1	0.87	< 0.01
	No	3	21		
Midline developmental abnormalities	Yes	14	4	0.69	< 0.01
	No	4	44		
Posterior fossa malformations	Yes	7	2	0.62	< 0.01
	No	5	52		
Cortical developmental abnormalities	Yes	3	0	0.46	< 0.01
	No	6	57		
Cyst	Yes	6	0	0.84	< 0.01
	No	2	58		
Destructive lesions (Hemorrhage)	Yes	0	0	0	1
	No	6	60		

Table 3. The level of agreement between the ultrasound (US) and in utero magnetic resonance imaging (iuMRI) for the diagnosis of fetal central nervous system abnormalities.
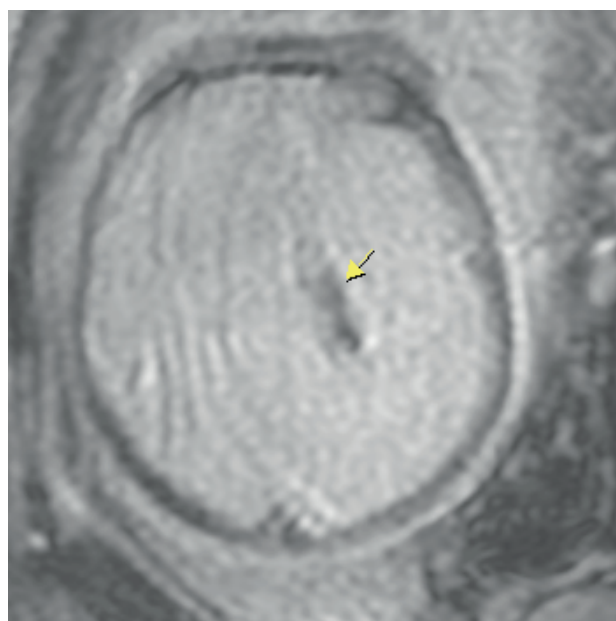
Figure 1. Axial in utero magnetic resonance image of a fetus, showing left cerebral parenchymal hemorrhage at 34 weeks gestational age. Axial T2* sequence shows an area of low signal intensity (arrow) in the left parenchyma, suggestive of a hemorrhagic lesion.

4. RESULTS

General items

Among the 66 pregnant women carrying 66 fetuses who were evaluated, the mean age was 28.5 ± 5.5 years (range 17–44 years). The mean gestational age was 29 weeks and 6 days (range 20–37 weeks).

Abnormalities

The total number of abnormalities detected by US and iuMRI are presented in Table 1. The most common primary diagnosis on both US and iuMRI was ventriculomegaly (53.2% and 44.9%, respectively), followed by midline abnormalities (22.8% and 18.37%), and posterior fossa malformations (11.4% and 12.25%), whereas other abnormalities accounted for smaller proportions.

The performance of iuMRI, using various sequences and multiplanar visualization, allows doctors to directly examine the cerebral parenchyma, facilitating the detailed evaluation of the CNS anatomy (18). An example

of a hemorrhage lesion detected on iuMRI, showing an area of low signal intensity (arrow) in the left cerebral parenchyma on T2*-weighted gradient-echo, is shown in Figure 1. Cortical abnormalities were primarily detected on the T2W pulse series in multiplanar sequences, such as polymicrogyria, which was detected in the bilateral parietal lobe, showing the delayed development of the sulci relative to gestational age in Figure 2.

Comparison between ultrasound and magnetic resonance imaging

As presented in Table 2, the similarities and differences between US and iuMRI diagnoses were 67% and 33%, respectively. Among CNS abnormalities, the two most commonly identified differential abnormalities between US and iuMRI were midline developmental abnormality and posterior fossa malformations. The following abnormalities were hemorrhage and cortical development.
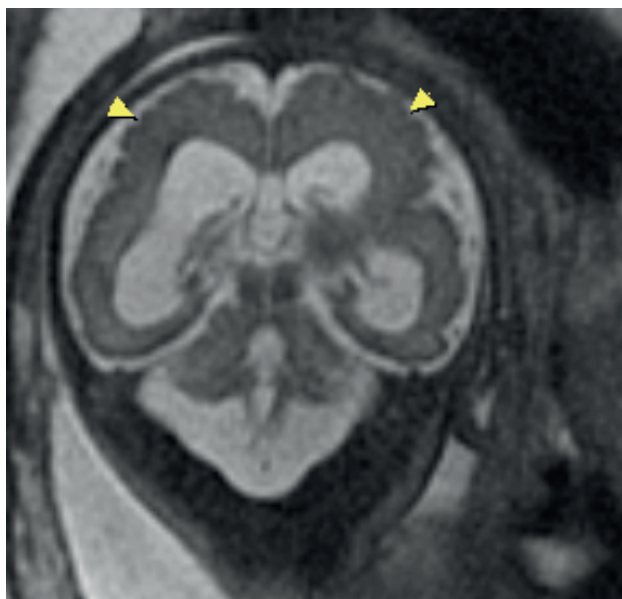
Figure 2. Coronal in utero magnetic resonance imaging in a fetus at 34 weeks 2 days, diagnosed with ventriculomegaly on ultrasound. Axial T2-weighted single-shot fast spin-echo shows ventriculomegaly and polymicrogyria on the bilateral parietal lobe (arrowhead) and delayed sulci development relative to gestational age.

As presented in Table 3, the lowest level of agreement between US and iuMRI was calculated for cerebral parenchymal damage abnormalities (in our study, cerebral hemorrhage), which had a κ of 0 (p = 1). Cortical abnormalities had a moderate level of agreement, with a κ of 0.46 (p < 0.01). Ventriculomegaly and cysts had perfect agreement, with κ values of 0.87 (p < 0.01) and 0.84 (p < 0.01), respectively.

5. DISCUSSION

Fetal CNS abnormalities are the most commonly detected congenital abnormalities (1). Most fetuses with CNS abnormalities die *in utero*, some die after birth, and the remainder survive but may encounter psychomotor developmental abnormalities (9, 24). Therefore, early detection, prognosis, and patient counseling are essential. Around the world, several studies have demonstrated that iuMRI can detect additional CNS abnormalities that may be suspected on US, which can alter the diagnosis, prognosis, and pregnancy management strategies (9, 25).

In our study, the mean gestational age was 29 weeks and 6 days, and most cases were older than 24 weeks of gestation (92%). On iuMRI, in addition to the ventriculomegaly abnormality, the most commonly identified abnormalities were midline abnormalities (18.37%), followed by posterior fossa malformations and cortical developmental anomalies. In Griffith *et al*'s study examining suspected fetal CNS abnormalities using US at many centers in the UK, the majority of gestational ages were below 24 weeks (64.73%) (9). This difference is likely due to differences in the pregnancy management model among countries, the frequency of follow-up visits that pregnant women attend, professional qualifications, and the availability of equipment and facilities.

The most common primary diagnosis identified on US was ventriculomegaly (53.2%), with other abnormalities accounting for smaller proportions, which were similar to the findings reported by Griffith *et al* (9).

When comparing the two methods, our study showed similar diagnoses for 67% of abnormalities and differential diagnoses for 33% of abnormalities. The most differentially diagnosed abnormalities between iuMRI and US were the midline developmental abnormalities, which represented in 22.8% of cases with differential diagnoses (8/35 anomalies), and posterior fossa malformations, which represented 20% of cases with differential diagnoses (7/35 anomalies). Hemorrhage and cortical abnormalities each represented 17% (6/35 anomalies) of differential diagnoses. Previous studies showed variable results. Griffith *et al* (9) reporting differences between US and iuMRI ranging from 23% to 29%. Rossi *et al* (25) reported that irMRI differed from US in 30% of fetuses, especially for midline anomalies. Paladini *et al* (26) reported that US and iuMRI were concordant in 86.5% of cases. Our study, Griffith *et al* (9), Paladini *et al* (26), and Rossi *et al* (25) found that iuMRI was able to detect additional lesions that were either suspected or overlooked on US. Therefore, iuMRI can contribute additional information to clinicians.

Among fetal CNS abnormalities, the most commonly shared abnormalities, which were identified by both US and iuMRI, included ventriculomegaly and cystic lesions, which had perfect agreement (κ values of 0.87 and 0.84, respectively; p < 0.01). This result was consistent with those reported by Rossi *et al* (25). The lowest levels of agreement were identified for destructive lesions (hemorrhage in our study) and cortical abnormalities, which had κ values of 0 (p = 1) and 0.46 (p < 0.01), respectively. iuMRI was able to detect these abnormalities, which were largely missed on US. In our study, cerebral hemorrhage lesions were small, in the late stage, and hypointense on T2*-weighted gradient-echo. However, these lesions were not detected on US. The hypointense lesions on T2*-weighted gradient-echo must differ from calcification associated with fetal infections (21). However, intracranial calcifications associated with fetal infections are more common in the periventricular region and basal ganglia (27), and punctate calcifications may be difficult to detect on iuMRI (28). In addition to intracranial calcifications, fetal infections can present other abnormalities, such as intraventricular synechiae and extra-CNS symptoms, such as hepatomegaly, splenomegaly, and effusions (pericardial, pleural, and ascites) (27). Therefore, iuMRI can be used to make a correct diagnosis of intracranial hemorrhage. T2W SSFS, performed on three planes with high-resolution and multiplanar visualization of the cerebral parenchyma, allows for the detection of small and discrete lesions, particularly cortical abnormalities, such as polymicrogyria and gray matter heterotopia (18). In addition, iuMRI is not limited by fetal position, amniotic fluid, or skull ossification, which can prevent the visualization of some issues on US (29).

This study still presents some limitations. First, the study analyzed a small sample size from only one imaging center, which may reduce the representative value of this study and limit the ability to generalize the findings. Second, due to the lack of sedatives approved for maternal use, combined with long scanning times, fetal movements can affect image quality. Third, this study did not perform the gold standards of autopsy, or postnatal MRI or US to confirm any findings, which limits the reliability of the study. Future studies should be performed on larger sample sizes and conduct follow-up after birth to validate the prenatal findings and compare these against our current results.

6. CONCLUSION

The results showed that US and iuMRI had the highest agreement for the detection of ventriculomegaly and the lowest agreement for cerebral hemorrhage and cortical abnormalities, which were abnormalities detected by iuMRI but not by US. In the future, more studies should be conducted using larger samples, and postnatal examinations should be performed to increase the reliability of these findings. Providing additional information to clinicians will improve prenatal prognosis and facilitate the delivery of appropriate counseling to pregnant women carrying fetuses with CNS abnormalities.

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