Intrauterine *versus* post-mortem magnetic resonance in second trimester termination of pregnancy for central nervous system abnormalities

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ABSTRACT

Objective: To evaluate if limiting factors of intrauterine magnetic resonance imaging (iuMRI) performed in the early second trimester of pregnancy (19–23 weeks) affect its accuracy in comparison to post-mortem MRI (pmMRI) in fetuses that underwent termination of pregnancy (TOP) for central nervous system (CNS) defects.
Study design: This is a secondary analysis of a 10 years prospective observational study. Cases of TOP < 23 weeks for CNS malformation that had undergone neurosonography (NSG), iuMRI, pmMRI and autopsy were included. The agreement between iuMRI and pmMRI was calculated. The autopsy represented the gold-standard.
Results: Overall, 143 TOPs for fetal congenital anomaly underwent the post-mortem diagnostic protocol. Of these, 31 cases underwent iuMRI and pmMRI for CNS abnormality. Three cases were excluded due to brain autolysis at autopsy. Corpus callosum defects were the most represented (16/28; 57 %). In only one case of posterior fossa defect, pmMRI identified the presence of vermian hypoplasia not diagnosed at iuMRI. In 2 cases (7%), iuMRI added clinically relevant additional findings to NSG, that were posteriorly confirmed by pmMRI.
Conclusions: The study shows that, at 19–23 weeks and for CNS defects, limiting factors that might influence the performance of iuMRI have little influence on iuMRI accuracy. This finding is particularly important for professionals who work in countries with legal bound for TOP in the early second trimester.

Introduction

Intrauterine magnetic resonance imaging (iuMRI) is a complementary exam to neurosonography (NSG), as it improves the prenatal detection of central nervous system (CNS) defects [1–5].

Gestational age is of crucial importance when assessing the fetal brain since, at early stages, the development of some of the brain structures is not yet completed. However, iuMRI has limitations that may affect its performance, especially at earlier stages, such as small fetal size, maternal breathing, fetal movements and lower resolution of the images [6,7]. For all these reasons, iuMRI is best performed at 26–32 weeks when it is more likely to be of added value to NSG diagnosis and counseling in case of CNS defects. However, such aspect poses a diagnostic challenge in those countries where the legal bound for termination of pregnancy (TOP) is set before 23 weeks [8].

The largest trial on the accuracy of iuMRI for fetal brain defects, the MERIDIAN study, reported a 93 % accuracy for iuMRI with a 7 % margin of error, regardless of gestational age, with a 50 % increase in diagnostic information when compared to ultrasound [9,10].

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More recently, this finding has been questioned by subsequent studies which suggested that the additional diagnostic yield of iuMRI, when performed in the setting of a dedicated neurosonography (NSG) by an experienced operator, ranges between 5% and 10 % [11–13].

Moreover, in the MERIDIAN study, incorrect iuMRI diagnosis were considered to have an impact on prenatal counseling in 55 % of cases [10]. Therefore, even if the role of iuMRI seems to be strictly related to the performance of a standardized NSG, the diagnosis needs to be corroborated by post-mortem analysis in order to provide the patients a certain diagnosis and, where possible, counseling about the recurrence risk in future pregnancies.

Postmortem magnetic resonance (pmMRI) does not have the limitations of iuMRI and has been increasingly used, mainly because of reduced rate of autopsy due to low parents' acceptance [14].

Despite the fact that several studies have been published on the diagnostic accuracy of iuMRI and pmMRI in relation to autopsy, few have directly compared the performance of both in relation to each other in a specific subset of patients. In this study, we aim to evaluate the performance of iuMRI and pmMRI in cases of TOP in the early second trimester (19–23 weeks) for CNS malformation, in order to address the possible impact of technical limiting factors on the performance of iuMRI.

Materials and methods

This is a secondary analysis of a 10 years prospective observational study of a diagnostic protocol after TOP for fetal congenital malformation at a single center, the Institute for Maternal and Child Health – IRCCS Burlo Garofolo, Trieste, Italy (tertiary referral hospital and research center). Briefly, the diagnostic protocol after TOP for fetal congenital malformation included: 1) radiologic examinations (pmMRI, computerized tomography (CT) and X-ray); 2) genetic evaluation and genetic examinations such as karyotype and Array, if not performed during the prenatal period; 4) serology screening for maternal infection (TORCH) has been performed in all cases of ventriculomegaly; and 3) autopsy. Patients' consent was obtained for postmortem diagnostic examinations. For the purposes of this study we included only cases with CNS malformation that had undergone both iuMRI and pmMRI in a short time interval.

All prenatal ultrasound examinations were performed at the Fetal Medicine and Prenatal Diagnosis Unit two experts in prenatal diagnosis and NSG (G.D'O. and T.S.) in women referred for the suspicion of fetal anomaly on routine ultrasonography (US). Gestational age (GA) was calculated from the crown-rump length. Prenatal US were performed with Voluson E10 and Voluson E8 machines (General Electrics, USA) equipped with a 5–9 MHz volumetric transvaginal transducer, a 4–8 MHz volumetric convex transducer and a 1–6 MHz curved matrix electronic 4D probe, and with a 6–12 MHz volumetric transvaginal transducer and a 4–8 MHz volumetric convex transducer, respectively. The transvaginal approach was chosen for the 2D/3D evaluation of the fetal brain in case of cephalic presentation. The scans were performed according to national and international guidelines [SIEOG (*Società Italiana di Ecografia Ostetrica e Ginecologica*) and ISUOG] [15,16]. Guidelines from the ISUOG were applied to perform NSG: a multiplanar assessment of the fetal head (axial, coronal and sagittal planes) was used to visualize the midline structures, lateral ventricles, corpus callosum, cerebellar body and vermis, third and fourth ventricles [17]. The iuMRI was performed on the request of the clinician that performed prenatal NSG.

For the iuMRI study, the mother was lying in a left lateral decubitus or supine, without holding breath. Fetal iuMRI imaging was performed with single-shot fast spin-echo (SE) T2-weighted imaging in axial, sagittal, and coronal planes (echo-time (TE) 90–250 ms) on a 1.5 T unit (Philips Ingenia, Eindhoven, Netherland), by using a torso phased-array coil. Single-shot fast SE T2-weighted images of 3–4 mm were acquired.

Fetal pmMRI studies were performed with a Philips Ingenia 1.5 T open-bore system. "Single-shot T2" (SSH TSE and TSE T2 HR) and T1 TSE sequences were taken in the three planes, using "body" and "brain" dedicated studies. Duration of examination was 50–80 min, depending on the size of the body and fetal movements. Two expert radiologists (F.Z. and M.G.), with knowledge of the US diagnosis, performed both the intrauterine and the postmortem radiological investigations.

In order to perform the postmortem radiological investigations, the fetus was kept refrigerated at 4–6 °C after TOP. Immediately after the radiological exam, the fetus was kept in formalin solution or under vacuum and sent for autopsy. A single operator (R.B.), with extensive experience in fetal and perinatal pathology, performed all autopsies. Concordance (yes or no), defined by the proportion of cases in which iuMRI and pmMRI correctly identified the primary fetal abnormality provided by autopsy, irrespective of any additional finding, was calculated. The concordance with prenatal NSG was also evaluated. The rate of additional clinically relevant findings provided by iuMRI and pmMRI in comparison to prenatal NSG is also reported. Quantitative variables are expressed as medians and interquartile ranges (IQR). Descriptive statistics were used to compare the findings between iuMRI, pmMRI, NSG and autopsy. The study protocol was approved by the institute's ethics committee on human research.

Results

Overall, there were 143 TOPs for fetal congenital anomaly that underwent postmortem diagnostic protocol. Of these, 31 fetuses with a CNS congenital malformation that had undergone both iuMRI and pmMRI are included in this study. Three cases (3/31, 10 %) were excluded from further analyses due to autolysis of the brain tissue at autopsy.

The median maternal age was 33 years (IQR 28–37). The median gestational age at diagnosis and at iuMRI were 20.9 weeks (IQR 19.0–21.6) and 21.0 weeks (IQR 20.7–21.5), respectively. The median gestational age at the time of TOP was 20.9 weeks (IQR 19.4–21.6). The median interval in days between prenatal US and iuMRI was 0 (IQR 0–1), between TOP and pmMRI was 0 (IQR 0–1), and between TOP and autopsy was 16 (IQR 10–27), respectively (Table 1).

The list of CNS abnormalities is reported in Table 2. Abnormalities of the corpus callosum were the most represented defects (n = 16). Second in frequency were posterior fossa abnormalities followed by ventriculomegaly. The detailed list of abnormalities, with NSG, iuMRI, pmMRI and autopsy findings, is shown in the Appendix (Table S1). Serology screening for maternal infection was negative in all cases of ventriculomegaly. An abnormal karyotype

Table 1
Demographic and clinical characteristics of the studied population.

Demographic characteristics	Median	IQR
Maternal age	33	28–37
GA at US diagnosis	20.9	19.0–21.6
GA at iuMRI	21.0	20.7–21.5
GA at TOP	20.9	19.4 - 21.6
Time-lapse US-iuMRI (days)	0	0–1
Time-lapse TOP-pmMRI (days)	0	0–1
Time-lapse TOP-autopsy (days)	16	10–27

IQR, interquartile range; GA, gestational age; US, ultrasonography; iuMRI, intrauterine magnetic resonance imaging; TOP, termination of pregnancy; pmMRI, post-mortem magnetic resonance imaging.

Table 2
List of central nervous system defects.

Fetal CNS defects	N
Isolated corpus callosum abnormality	10
Non-isolated corpus callosum abnormality	6
Posterior fossa abnormalities	6
Ventriculomegaly	3
Complex CNS defect	1
Semilobar holoprosencephaly	1
Spina bifida occulta	1
Total	28

CNS, central nervous system; N, number.

was found in four cases (4/28; 14.3 %), and results are shown in the Appendix (Table S1).

The primary diagnosis agreement rates between iuMRI and autopsy, and pmMRI and autopsy were 96.4 % (27/28) and 100 %, respectively: in one case the differential diagnosis between a Blake's pouch cyst and inferior vermian hypoplasia could not be made by iuMRI, while pmMRI reported the presence of vermian hypoplasia, confirmed at autopsy.

With regard to additional main findings, pmMRI was superior to iuMRI in providing the correct diagnosis in one case: both NSG and iuMRI described the presence of agenesis of the corpus callosum associated to interhemispheric cysts, while abnormalities of the right cortex gyration and homolateral hemisphere hypoplasia, later defined as right pachygyria at autopsy, were identified at pmMRI. Both, iuMRI and pmMRI correctly identified additional findings in two cases not seen at NSG (Table 3): in one case, iuMRI and pmMRI reported the presence of hemisphere asymmetry and abnormal right gyration in addition to the NSG diagnosis of agenesis of the corpus callosum and multiple supratentorial cysts; in the second, iuMRI and pmMRI added the presence of sinus thrombosis and right polymicrogyria to a complex CNS defect of agenesis of the vermis and cerebellar hypoplasia associated to partial agenesis of the corpus callosum and right microphthalmia at NSG. In three cases iuMRI was requested to clarify a diagnostic query arisen from NSG evaluation (Table 4): in two cases, the presence of periventricular calcifications associated with ventriculomegaly were diagnosed as nodular cortical heterotopia at iuMRI (Fig. 1); in one case NSG evaluation could not provide a definitive diagnosis regarding the type of holoprosencephaly because of increased maternal body mass index (BMI 38 Kg/m^2), while iuMRI confirmed the presence of semilobar holoprosencephaly. There was one false-positive additional finding where both iuMRI and pmMRI reported the presence of abnormalities of gyration of the right cortex, not confirmed at autopsy, in addition to the findings of agenesis of the corpus callosum, interhemispheric septate cyst and right microphthalmia on NSG.

In one of three cases in which autopsy could not be performed because of autolysis of the brain tissue, both iuMRI and pmMRI identified the presence of corpus callosum agenesis and dysplastic cerebellum concordant with prenatal NSG, while in the remaining two cases, autolysis also affected pmMRI imaging.

Discussion

The main finding of this study is that intrinsic technical limiting factors of iuMRI do not impact significantly this diagnostic method before 23 weeks, compared to the same technique after removing these limiting factors. Concordance between iuMRI and autopsy was 96.4 % and in no case the post-mortem examination, either by pmMRI or autopsy, changed the primary prenatal diagnosis, provided by NSG and iuMRI.

To date, there are only two other similar studies aiming to compare the performance of iuMRI and pmMRI for fetal brain defects [18,19]. The study by *Whitby et al.* included 12 fetuses at higher gestational age (mean 25 weeks), with 10 available autoptic examinations. [18] The study by *Izzo et al.* included a larger cohort of fetuses (n = 53), at similar ages to our cohort (mean 21.8 weeks) [19]. However, in this retrospective study, the autopsy was not available in all cases and did not represent the gold-standard. Instead, the reference standard was the combination of iuMRI and pmMRI reviewed together by two expert neuroradiologists. Thus, our study represents the largest cohort of fetuses with available iuMRI and pmMRI before 23 weeks in which the autopsy was available and the examination was performed prospectively in a scenario of clinical setting.

Whitby et al. reported a total concordance between iuMRI and pmMRI [18]. In the study by *Izzo et al.* the "correctness ratios", defined as the percentage of iuMRI and pmMRI correct examinations in relation to the reference standard represented by iuMRI and pmMRI, were 79 % and 45 %, respectively [19]. The low accuracy of pmMRI was explained mainly by the large amount of false negative exams in the group of cerebrospinal fluid defects, such as ventriculomegaly or increased cisterna magna where iuMRI diagnosis was assumed to be correct. Conversely, less cases were reported as negative at the iuMRI review and these were mainly in the group of cortical anomalies, where pmMRI was assumed to be correct. Therefore, although the study by *Izzo et al.* showed that the combination of iuMRI and pmMRI findings can improve the overall performance as compared to each exam taken separately, in our opinion autopsy should be still considered the gold-standard technique to evaluate the true detection rate of the radiological investigations, even more so when there is a discrepancy in the diagnosis between the two methods.

In our cohort, iuMRI showed a good performance for cortical development malformations with a detection rate of 85.7 % and we would expect it to be equal or even higher if iuMRI is performed at later gestational ages due to the physiological process of fetal brain development [13]. In line with *Izzo* et al., iuMRI also had a good performance for defects such as periventricular nodular heterotopia (PVNH), characterized by a low sensitivity (56 %) when iuMRI is performed before 24 weeks probably due to smaller dimensions of the lesions and similar appearance to the normal germinal matrix [20]. In our experience, in two cases NSG reported the presence of hyperechoic ventricular walls associated to ventriculomegaly, raising the suspicion of PVNH, which was confirmed at iuMRI and post-mortem investigations. The appearance of such lesions at iuMRI was, indeed, very subtle compared to pmMRI, underlining the importance of a combined approach based on NSG

Table 3
Clinically relevant additional findings of intrauterine MRI and post-mortem MRI compared to neurosonography.

Case	US diagnosis	GA US	iuMRI and pmMRI diagnosis	GA iuMRI
1	Posterior fossa abnormalities + partial agenesis of corpus callosum + midline cyst + right microphtalmia	20 + 3	US findings + sinus thrombosis+abnormal right gyration	20 + 3
3	Corpus callosum agenesis + multiple interhemispheric cysts	20 + 5	US findings+hemisphere asymmetry + abnormal right sulcation	21 + 0

iuMRI, intrauterine magnetic resonance imaging; pmMRI, post-mortem magnetic resonance imaging; NSG, neurosonography; US, ultrasound; GA, gestational age.

Table 4
Clinical contribution of intrauterine magnetic resonance to neurosonography.

Case	US diagnosis	GA US	iuMRI diagnosis	GA iuMRI
17	Hydrocephaly + periventricular calcification	21 + 0	US findings+ventricular nodular heterotopia	21 + 0
18	Hydrocephaly + periventricular calcifications	20 + 2	US findings+ventricular nodular heterotopia	20 + 3
20	Suspicion of holoprosencephaly	20 + 0	Semilobar holoprosencephaly	20 + 1

iuMRI, intrauterine magnetic resonance imaging; NSG, neurosonography; US, ultrasound; GA, gestational age.

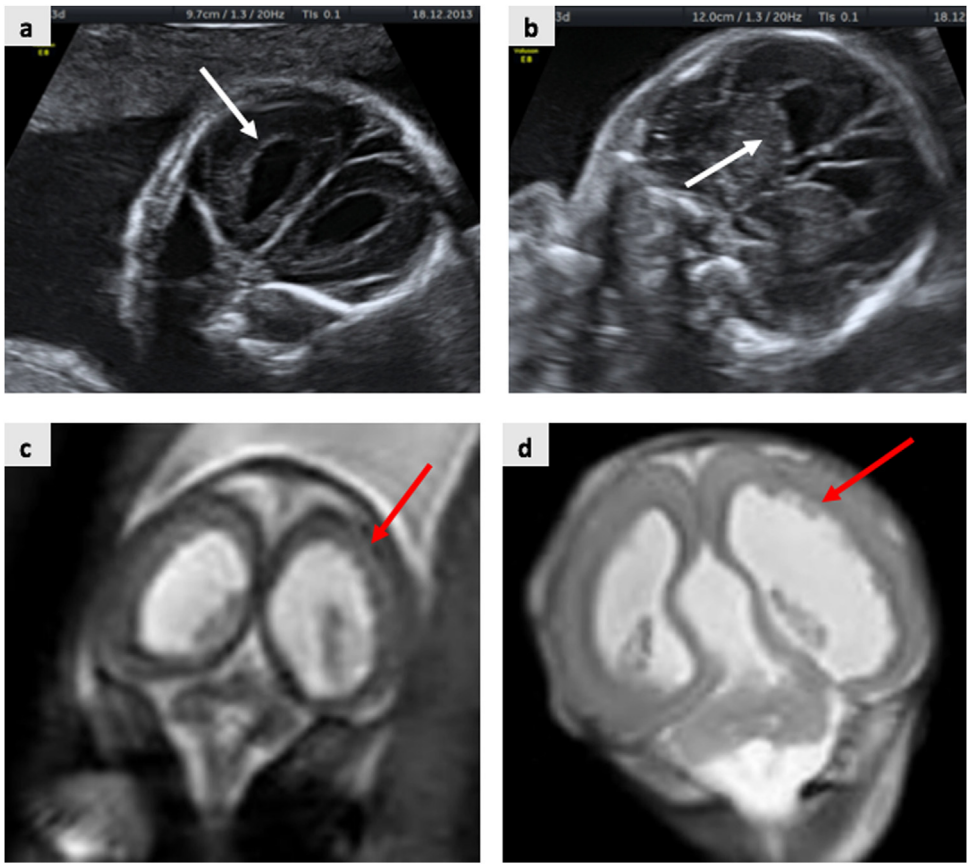

Fig. 1. Hydrocephaly and periventricular nodulat heterotopia (PVNH). The white arrows in (a) and (b) indicate the hyperechoic appearance of the periventricular wall at neurosonography; the red arrow in (c) shows the presence of nodularity of the ventricular walls seen at iuMRI compatible with PVNH and the same findings can be seen in (d) at pmMRI. Of note, the better definition of the periventricular lesions at pmMRI than at iuMRI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

and iuMRI in order to achieve the best possible diagnostic performance at such early stages.

One area still open to debate is the study of the posterior fossa that may be affected by a spectrum of defects, where differential diagnosis is extremely important for the prognosis and counseling [21]. The diagnostic performance of iuMRI for posterior fossa defects appears to be worse than for other CNS defects, especially for abnormalities of the cerebellar vermis [11,22].The prenatal assessment of the cerebellar vermis is challenging in the early mid-trimester because of its incomplete development until 20 weeks [23,24]. All these aspects play an important role when it comes to the diagnosis of subtle abnormalities such as inferior vermian hypoplasia (iiVH) where the missing part is the caudal portion of the vermis: the consequence is a high rate of overcalls with a reported false-positive rate as high as 32 % with profound impact on prenatal counseling and parents' decision [25]. In our cohort, we had an overall good performance of iuMRI alone and a good concordance between NSG, iuMRI, pmMRI and autopsy in the diagnosis of defects of the cerebellar vermis but we acknowledge that our numbers may be too few to draw a definitive conclusion. Therefore, both clinicians and parents need to be aware of the diagnostic technique limitations at early stages of pregnancy, and this aspect should be extensively discussed during counseling.

A comparative analysis between NSG and iuMRI was not our primary aim. However, in our cohort, iuMRI identified additional defects in only two cases providing a diagnostic yield of 7 %, mainly in the group of malformation of cortical development. This finding is in line with previous studies that reported a rate of additional information at iuMRI in the range of 5–10 % when NSG was performed by experienced operators [11–13,26], These data support the concept that iuMRI should be performed after a thoughtful and systematic examination of the fetal brain with a multiplanar approach.

The strength of this study is the homogeneity of the included population. To our knowledge, this is the first study comparing prenatal iuMRI and pmMRI for the evaluation of CNS fetal defects at <23 weeks after NSG and corroborated by autopsy in all cases. Another important factor is the short time interval elapsed between NSG, iuMRI and pmMRI, with the majority of iuMRI done within two days from the NSG. This is of particular

importance for CNS defects, since the brain grows and develops very rapidly in the second trimester and longer time intervals between NSG and iuMRI could falsely improve the performance of the latter. Likewise, the time-lapse between TOP and pmMRI is critical for the occurrence of autolysis of the brain tissue, which could affect up to 50 % of post-mortem examinations [27,28]. Our median interval was 0 days, meaning that the exam was performed within 24 h in the majority of cases, while in two cases where autolysis occurred, pmMRI was done two to three days after TOP. Therefore, our data suggest that, for CNS defects, it is of extreme importance to perform pmMRI within the first 24 h after TOP to avoid autolysis occurrence at autopsy. Finally, the experience of the physician performing the iuMRI may have reduced the possibility of error as also reported by *Batty et al* who showed a higher error rate for less experienced operators [10]. The main limitation of the study is the small number of cases, due to the current practice in our Unit to request iuMRI only for diagnostic queries after NSG or for CNS defects at risk of associated anomalies, as per the ISUOG guidelines on fetal MRI [8]. Moreover, we acknowledge that, despite the growing body of evidence supporting the use of iuMRI at earlier gestational ages, its accuracy for certain fetal CNS defects, like hemorrhage or malformation of cortical development, is still an open debate. Further prospective studies on NSG and iuMRI performed by experienced operators with larger samples are needed to corroborate our findings.

Conclusion

Our data suggest that the limiting factors such as fetal and maternal movements, in womb location and others, have little impact on iuMRI accuracy, within the diagnostic potential of the technique itself, at gestational age <23 weeks in case of CNS malformations. In this setting, the iuMRI is useful in identifying additional relevant findings. Although iuMRI is more accurate and recommended in the late second trimester or in the third trimester, the findings of our study might be particularly useful for those professionals who work in countries with a legal bound for TOP in the early second trimester.

Declaration of Competing Interest

None.

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