Accuracy and clinical utility of standard postmortem radiological imaging after early second trimester termination of pregnancy

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ABSTRACT

Objective: This study aims to assess accuracy and clinical utility of postmortem radiological exams [Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Radiography (XR)] after termination of pregnancy at <23 weeks' gestation for congenital fetal malformations in comparison to autopsy.
Study design: This a prospective single-center study on fetuses underwent termination of pregnancy for fetal defects. Overall concordance between any radiological exam and autopsy was evaluated. For postmortem MRI only, the following subgroups were analyzed: 1) total agreement; 2) agreement for main findings; 3) agreement for main findings but major relevant additional findings at autopsy; 4) total disagreement.
Results: 174 cases were collected. The overall concordance with autopsy for main findings was 71% (115/163) for postmortem MRI and 99% (173/174) for prenatal ultrasound (US). Postmortem MRI detection rate was high for central nervous system (CNS) defects (98%), gastrointestinal, genitourinary and respiratory defects (100%), while it was poor for cardiovascular and musculoskeletal defects (25% and 42%, respectively). For musculoskeletal abnormalities, the performance of postmortem XR and postmortem CT exams improved the detection rate from 42% for postmortem MRI alone to 92%.
Conclusions: Postmortem MRI has a good overall concordance for fetal defects after termination of pregnancy performed at <23 weeks. Along with autopsy, postmortem MRI may be offered for all cases of CNS defects in order to prevent inconclusive exams due to autolysis of the brain tissue, while postmortem CT and postmortem XR are indicated for musculoskeletal defects. In the presence of multiple abnormalities or cardiac defects the couple should be counseled on the poor performance of radiological investigations.

Introduction

In case of termination of pregnancy for fetal abnormalities, postmortem investigations are of fundamental importance to verify the prenatal diagnosis and/or add clinical information useful for parental counseling [1–6].

Although autopsy represents the reference standard, the steady decline in parental consent has increased the use of less invasive diagnostic techniques [7–11]. Postmortem magnetic resonance imaging (MRI) is the alternative technique of choice because of its high-contrast tissue resolution, while the field of application for post-mortem computed tomography (CT) or radiography (XR) is restricted to musculoskeletal anomalies and vascular brain lesions [12–14].

The largest prospective study on postmortem MRI, the MARIAS study, report a detection rate of 95% when performed together with ancillary investigations in the so-called "minimally invasive autopsy" [15]. However, if performed alone, postmortem MRI accuracy dropped to 43% with a non-diagnostic rate of 35% for gestational ages < 24 weeks, while it increased to 63% with a non-diagnostic rate of 4% for gestational ages > 24 weeks [15]. Such low performance of postmortem

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MRI for fetuses < 24 weeks may be of concern for those countries where the legal bound to perform termination of pregnancy is set at earlier gestational epochs (i.e. 23 weeks), especially if autopsy is declined.

The aim of this study was to assess the accuracy and clinical utility of radiological exams, including fetal postmortem MRI, CT and XR in comparison to autopsy, in a selected population of fetuses that underwent termination of pregnancy before 23 weeks' gestation for congenital anomalies.

Material and methods

This is a prospective single-center trial with collection of cases over a twelve-year period, from 2007 to 2019. Inclusion criteria were: i) medical termination of pregnancy following a ultrasound diagnosis of congenital fetal anomalies; ii) gestational age between >16 weeks and <23 weeks of gestation; iii) performance of postmortem radiological investigations; iv) parental consent to autopsy. Requested postmortem radiological investigations were driven by the prenatal diagnosis and, thus, did not always include all techniques. Exclusion criteria were: i) termination of pregnancy performed for different reasons other than fetal defects; ii) no radiological investigations and/or autopsy; iii) termination of pregnancy performed in a different hospital. The study was approved by our Internal Review Board (Prot. CE/V-104, RC 21/09) and a informed consent form was collected in all cases. All prenatal scans were performed by clinicians with more than 5 years of experience in fetal medicine. Ultrasonography and neurosonography included both 2D and 3D technology with Voluson E10 and Voluson E8 US machines (General Electrics, USA) equipped with a 5–9 MHz volumetric transvaginal transducer, a 4–8 MHz volumetric convex 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. The transvaginal approach was chosen for the 2D/3D evaluation of the fetal brain in case of cephalic presentation to achieve additional information. Scans were performed according to national and international guidelines (SIEOG [Società Italiana di Ecografia Ostetrica e Ginecologica] and ISUOG [International Society of Ultrasound in Obstetrics and Gynecology]) [16–18]. The fetus was kept refrigerated at 4 °C after termination of pregnancy for 24–48 h. The radiologists, with more than 5 years of experience, were aware of the prenatal diagnosis. Postmortem MRI studies were performed with a Philips Ingenia 1.5 T system (equipped with a eight-channel dS Ped. Head Spine coil; Philips Healthcare, Andover, MA, USA), using TSE sequences to produce T2-weighted images (echo time (TE), 200 ms; slice thickness, 3 mm) and TSE sequences to obtain T1-weighted images (echo time TE, 20 ms; slice thickness, 3 mm). The time of the examination was 50 to 80 min long, depending on the fetal size. Postmortem CT was performed using a TC Philips "Brilliance" (Eindhoven-Netherland); 40-layer, 80 Kv and 40 to 65 mA, 0.9 mm slices (HR) and 1 mm reconstruction, Kernel convolution standard (B) and detailed (D); in some cases, a 3D reconstruction in volume and skeletal mode was performed. Three-planes reconstruction was obtained with 2–3 mm slices thickness and volume-rendering (VR), and dedicated bones and soft tissues window. Postmortem XR was performed using the XR DR polyfunctional Adora with digital system (sagittal and coronal planes). Immediately after the radiological exam was performed, the fetus was put in formalin solution or under vacuum and sent for autopsy, performed by a single with more than 10 years of experience.

Concordance between postmortem radiological examinations and conventional autopsy findings was investigated [19,20]. Autopsy was considered the gold standard technique. Concordance (yes or no) was defined by the proportion of cases in which the prenatal ultrasound or the postmortem imaging identified correctly the primary fetal anomaly found at autopsy that led to termination of pregnancy. For fetuses with multiple anomalies, concordance was defined as "present" if at least two of the major abnormalities identified at autopsy were also seen at US or postmortem exams. Next, the cases were classified into the following groups for ultrasound and postmortem MRI only:

Table 1
Main indications for termination of pregnancy categorized by system and defect.

System (N)	Fetal defect	N
Central nervous system (54)	Corpus callosal dysmorphism	15
	Neural tubal abnormalities	13
	Posterior fossa abnormalities	9
	Hydrocephaly	7
	Complex CNS anomaly	5
	Holoprosencephaly	3
	Intracranial tumor	1
	Septo-optic dysplasia	1
Multiple abnormalities (50)	Normal karyotype	27
	Abnormal karyotype	13
	Syndromes	10
Cardiovascular (26)	Tetralogy of Fallot	4
	Complex CHD	2
	Severe coarctation of aorta	2
	Transposition of great arteries	3
	Univentricular heart	5
	Arteriovenous malformation	1
	Conotruncal defect	1
	Ebstein anomaly	2
	Pulmonary atresia	1
	Valvular abnormalities	1
	Eterotaxy	1
Genitourinary (14)	Bilateral renal agenesis	5
	Bilateral dysplastic kidneys	6
	Dysplastic kidney + renal agenesis	2
	Bladder estrophy	1
Musculoskeletal (13)	Skeletal dysplasia	9
	Arthrogryposis	3
	Fibular emimelia	1
Respiratory (6)	Congenital diaphragmatic hernia	3
	Congenital cystic adenomatoid malformation	2
	Pulmonary hypoplasia	1
Gastrointestinal (2)	Hyperechogenic bowel (CMV infection)	1
	Gastroschisis	1
Face and neck (2)	Bilateral anophthalmia	1
	Bilateral cleft lip	1
Others (7)	Severe IUGR	6
	Amniotic band syndrome	1

N, number; CNS, central nervous system; CHD, congenital heart defect; IUGR, intrauterine growth restriction.

1. Group1: full agreement between postmortem MRI or ultrasound findings and autopsy;
2. Group 2: agreement for main findings but minor additional anomalies found at autopsy;
3. Group 3: agreement for main findings but major relevant additional findings found at autopsy;
4. Group 4: total disagreement.

Two authors primarily classified the cases according to the final diagnosis provided at the time of the examination. For Group 3, those defects whose diagnosis is known to be feasibile at both ultrasound or postmortem MRI where labeled as "missed findings", while those defects not diagnosable at either ultrasound or postmortem MRI were labeled as "expected discrepancy". "Total disagreement" was present if the diagnosis at autopsy was not concordant with ultrasound or postmortem MRI, including the spectrum of "non-diagnostic" exam.

Verification of the data homogeneity was performed. Due to the small sample size and heterogeneity of the population (unbalanced rate of true positive versus true negative cases) a non-parametric descriptive analysis of the sample was chosen. Data were presented as frequencies and percentages, or as median values and interquartile ranges (IQR), as appropriate. The Fisher exact two-tailed test was used to determine the significance of the association in 2x2 contingency tables. Concordance, sensibility and specificity were also calculated on 2x2 contingency tables when appropriate. Confidence intervals (95% CIs) were calculated on the percentages of concordance. The concordance between pmMR and autopsy, and between US and autopsy was evaluated with the

Table 2
Overall concordance for ultrasound, postmortem magnetic resonance, radiography and computed tomography.

pmMR vs. conventional autopsy	*Se*	*Sp*	*Concordance*	*CI 95%*	*k Cohen*
Total number, 163	70%	100%	71%	64–78%	0.69
pmMR/pmXR/pmTC vs. conventional autopsy	***Se***	***Sp***	***Concordance***	***CI 95%***	***k Cohen***
Total number, 174	74%	100%	75%	68–81%	0.73
US vs. conventional autopsy	***Se***	***Sp***	***Concordance***	***CI 95%***	***k Cohen***
Total number, 174	99%	100%	99%	98–100%	0.98

MRI, Magnetic Resonance Imaging; Se, sensibility; Sp, specificity; CI, confidence interval.

Cohen's K (scores of 0.00 indicate absence of concordance; from 0.01 to 0.20, concordance is weak; from 0.21 to 0.40, concordance is acceptable; from 0.41 to 0.60, concordance is regular; from 0.61 to 0.80, concordance is good; from 0.81 to 0.99, concordance is excellent and 1.00 indicates perfect concordance).

All statistical analyses were carried out with Stata/IC 14.2 (College Station, USA).

Results

During the study period, 196 pregnancies underwent termination of pregnancy due to ultrasound findings of single or multiple fetal congenital anomalies. Of these, 22 cases were excluded from the analysis because of: deny consent to fetal autopsy (6 cases); no postmortem radiological investigation (13 cases); autolysis of the brain tissue at autopsy (3 cases). This led to 174 eligible cases. Postmortem MRI, either alone or in combination with other radiological investigations, was performed in 163 cases. The median gestational age at diagnosis and at the time of termination of pregnancy was 20.9 weeks (IQR 19.0 – 21.6) and 20.9 weeks (IQR 19.4 – 21.6), respectively. The median maternal age was 33 years (IQR 28–38). The main indications for termination of pregnancy are listed in Table 1. Central nervous system anomalies (n = 54), and multiple congenital abnormalities (n = 50) were the most

Table 3
Postmortem magnetic resonance *vs.* autopsy concordance for primary diagnosis by anatomical district/system.

pmMR vs. autopsy	N	Se	Sp	Concordance	CI (95%)	k Cohen
CNS	52	98%	100%	99%	98–100%	0.99
Multiple abnormalities	44	61%	99.2%	89%	84–94%	0.68
Cardiovascular	24	25%	100%	89%	84–94%	0.36
Genitourinary	14	100%	100%	100%	100–100%	1.00
Musculoskeletal	12	41%	100%	96%	93–99%	0.57
Gastrointestinal	2	100%	100%	100%	100–100%	1.00
Respiratory	6	100%	100%	100%	100–100%	1.00
Face and neck	2	50%	100%	99%	98–100%	0.66
Others	7	38%	100%	97%	94–100%	0.53

pmMR, postmortem magnetic resonance; N, number; Se, sensibility; Sp, specificity; CI, confidence interval; CNS, central nervous system.

Table 4
Subgroup analysis by anatomical district/system for postmortem magnetic resonance imaging.

System	Group 1*(N)	%	Group 2** (N)	%	Group 3# (N)	%	Group 4¶ (N)	%
All system	63/163	**39**	37/163	**22**	12/163	**7**	51/163	**31**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	12/163	7	–	–
CNS	37/52	**71**	11/52	**21**	3/52	**6**	1/52	**2**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	3/52	**6**	–	–
Multiple abnormalities	4/44	**9**	17/44	**39**	5/44	**11**	18/44	**41**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	5/44	**11**	–	–
Cardiovascular	0	**0**	4/24	**17**	2/24	**8**	18/24	**75**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	2/24	**8**	–	–
Genitourinary	11/14	**79**	2/14	**14**	1/14	**7**	0	**0**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	1/14	**7**	–	–
Musculoskeletal	3/12	**25**	0	**0**	1/12	**8**	8/12	**67**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	1/12	**8**	–	–
Gastrointestinal	1/2	**50**	0	**0**	0	**0**	1/2	**50**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	–	–	–	–
Respiratory	5/6	**83**	1/6	**17**	0	**0**	0	**0**
-expected discrepancy	–	–	–	–	–	–	–	–
-missed diagnosis	–	–	–	–	–	–	–	–
Face and neck	1/2	**50**	0	**0**	0	**0**	1/2	**50**
-expected discrepancy	–	–	–	–	–	–	–	–
Others	–	–	–	–	–	–	–	–
-expected discrepancy	1/7	**14**	2/7	**29**	0	**0**	4/7	**57**
-missed diagnosis	–	–	–	–	–	–	–	–

CNS, central nervous system; N, number.
* Group 1: total agreement.
** Group 2: agreement for main findings.
# Group 3: agreement for main findings but major relevant additional findings at autopsy.
¶ Group 4: total disagreement.

represented indications.

Overall detection rate and concordance by technique

The overall detection rate for postmortem MRI alone or in combination with postmortem CT and postmortem XR was 70% (95% CI 64–78%) and 74% (95% CI 68–81%), respectively. The concordance with autopsy was good in both cases (k Cohen of 0.69 and 0.73, respectively). The overall detection rate for prenatal ultrasound was 99% (95%CI 98–100%) and the concordance with autopsy was excellent (k = 0.98) (Table 2). The detection rate of postmortem MRI according to the anatomical system was high for CNS, genitourinary, gastrointestinal and respiratory system; moderate for musculoskeletal and face and neck system; low for the cardiovascular system and the group "others" (Table 3). The detection rate obtained when also postmortem CT and postmortem XR were taken into account was similar for all defects, apart from the musculoskeletal system where it improved from 42% to 92% (Table S1, online supplementary material). The detection rate by anatomical district/system for ultrasound examination reached 100% in all groups apart from the cardiovascular system, where it was 96% (Table S2, online supplementary material). In this case, termination of pregnancy was performed because of a severe form of early fetal growth restriction plus the suspicion of a major cardiac defect; the study of the cardiac anatomy could not be performed because of oligohydramnios and unfavorable fetal position. The autopsy detected the presence of transposition of the great arteries with pulmonary stenosis.

Postmortem MRI and ultrasound subgroup analysis

Group 1. The overall agreement between autopsy and postmortem MRI was 39% (63/163) (Table 4). The systems where postmortem MRI performed better were the respiratory, genitourinary and CNS (83%, 79% and 71%, respectively), while performance was poor for musculoskeletal, multiple abnormalities and "others" (25%, 9% and 14%, respectively) and 0% for the cardiovascular system.

Group 2. An agreement for main findings with minor additional defects at autopsy was present in 37 cases (37/163; 23%), mainly in the multiple congenital abnormalities group (17/44; 39%). The additional findings mostly reported at autopsy were in the spectrum of limbs defects (syndactyly, polydactyly, clinodactyly, abnormal position of the limbs) and orofacial defects (micrognathia, retrognathia, micro- and macrophthalmia, hyper- and hypotelorism, low-set ears, short neck).

Group 3. In 7% (12/163) of cases, there was agreement for main findings at postmortem MRI, but autopsy added major relevant findings. No case was registered in the subgroup of "expected discrepancy", while all 12 were "missed diagnoses" as follows: two cases of cardiovascular defects; five cases of multiple congenital abnormalities; one case in the genitourinary system; three cases in the CNS system.

Group 4. In 31% (51/163) of cases, there was a total disagreement between postmortem MRI and autopsy. In 96% (49/51) of cases, postmortem MRI was non-diagnostic since it did not report the presence of any abnormality: the most represented groups were cardiovascular (n = 18), multiple congenital anomalies (n = 16) and musculoskeletal (n = 8). In the remaining 4% (2/51), pmMR findings were horseshoe kidney and agenesis of the corpus callosum, not confirmed at autopsy. The false-positive rate of postmortem MRI was 8% (n = 9/116) with 4 cases of "overcalled" agenesis of the corpus callosum, all in the group of multiple abnormalities.

Ultrasound subgroup analysis is shown in Table S3 (online supplementary material).

Discussion

This study shows that postmortem radiological investigations, and postmortem MRI in particular, have a good accuracy for congenital fetal anomalies in fetuses that underwent medical termination of pregnancy at <23 weeks, with an overall detection rate of 70%. Postmortem MRI might be considered an alternative to autopsy for CNS, genitourinary, gastrointestinal and respiratory defects due to the high contrast tissue resolution that increases the accuracy of the test (Fig. 1S, Fig. 2S, Fig.3S, online supplementary material). The addition of postmortem XR and/or postmortem CT improves the accuracy for musculoskeletal defects from 42 to 92%, suggesting they should be added in these cases (Fig.4S, Fig.5S, online supplementary materia). The 70% concordance with autopsy reported in our data is higher than the 43% reported by the MARIAS groups [15]. However, in a secondary analysis, both ultrasound and postmortem MRI findings were reviewed retrospectively by specialists in fetal medicine and pediatric radiologists in a subgroup of 81 fetuses and, similarly to our results, postmortem MRI accuracy rose to 79% [21]. The authors found that autopsy provided an incremental yield mainly when there is partial concordance or total discordance between ultrasound and postmortem MRI concluding that autopsy should always be recommended in these cases, irrespectively of the involved district/system. In our cohort, we confirm that autopsy is particularly useful for cases with partial or no agreement. However, this approach implies that all termination of pregnancy should have a postmortem MRI but this is not feasible in all prenatal units at the moment and may not be cost-effective. Based on our findings, we believe that parents should be counseled on the optimal postmortem examination depending on the anatomical system involved rather than on the presence of discordance between ultrasound and postmortem MRI.

Despite the overall concordance between ultrasound and autopsy was 99%, proving a high detection rate when ultrasound is performed by experienced physicians, autopsy could still add major relevant findings in 11% of cases: the majority were anomalies of the brain cortical development, like cortical abnormalities or nodular heterotopia, not easily detectable in the early mid-trimester (Fig.6S, online supplementary materia) [22]. Within this group, postmortem MRI identified additional defects in all except one case confirming the high accuracy of postmortem MRI for brain defects (Table 5) [23]. Furthermore, in three cases excluded from the analysis because of CNS autolysis, postmortem MRI confirmed the ultrasound prenatal diagnosis, adding clinically relevant information in one. Taken together, for gestational ages < 23 weeks and in the presence of CNS defects, postmortem MRI after termination of pregnancy may be routinely considered to prevent inconclusive autopsy exams.

Table 5
Additional relevant clinical findings at postmortem magnetic resonance imaging *vs.* ultrasound.

Case	GA at TOP	US findings	pmMR additional findings confirmed at autopsy
1	20	Suspicion of holoprosencephaly	Semilobar holoprosencephaly
2	21	Hydrocephaly+periventricular hyperechogenicity	Hydrocephaly + nodular cortical heterotopia
3	22	Holoprosencephaly	Holoprosencephaly + intraabdominal mass
4	22	CC agenesis; interhemispheric cyst; right microphtalmia	CC agenesis + abnormal right cortical sulcation
5	22	CC agenesis	CC agenesis + right occipital pole agenesis
6	21	Bilateral ventriculomegaly	Bilateral ventriculomegaly + germinal matrix asymmetry
7	21	CC agenesis	CC + right pachygyria
8	21	Cerebellar hypoplasia, thinned parieto-occipital cortex, periventricular hyperechogenicity	Cerebellar hypoplasia, thinned parieto-occipital cortex + periventricular nodular heterotopia

pmMR, postmortem magnetic resonance; US, ultrasound; GA, gestational age; TOP, termination of pregnancy; CC, corpus callosum.

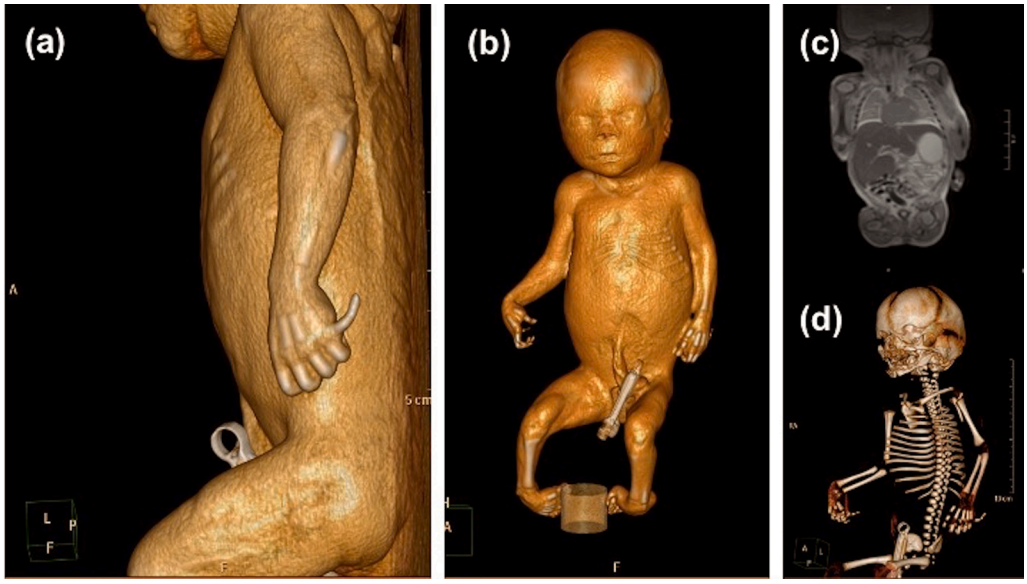

Fig. 1. A case of Simpson Golabi Behmel syndrome: in (a) and (b) volume reconstruction using 3D CT scan showing postaxial polydactyly, abnormal position of the hands and bilateral talipes; in (c) the MRI image showing hepatomegaly and stomach ectasia; in (d) CT scan in 3D skeletal mode showing bilateral postaxial polydactyly.

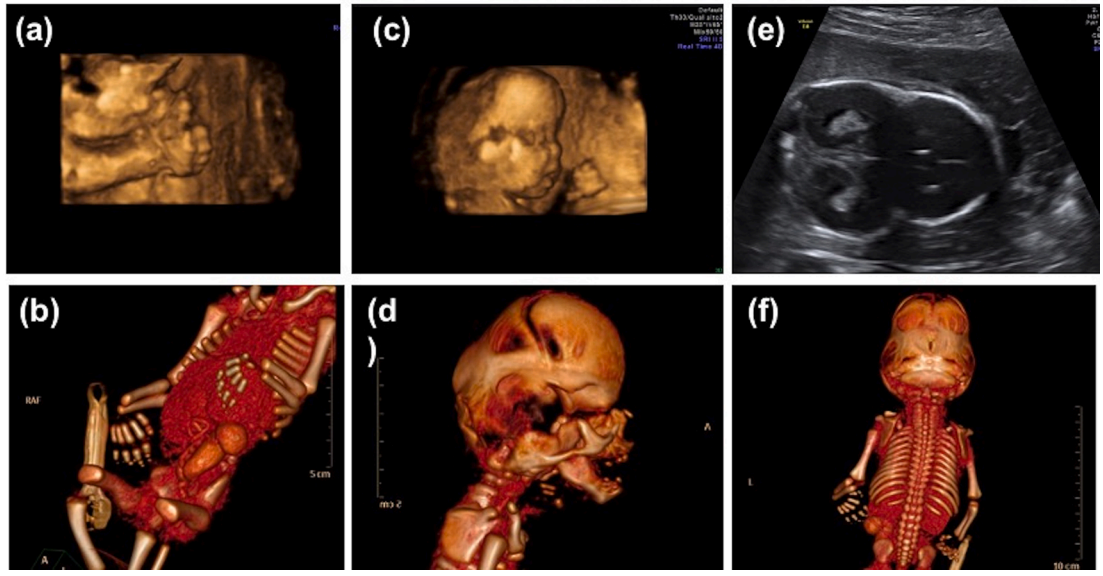

Fig. 2. A case of Pfeiffer syndrome type II: abnormal position of the hands at ultrasound 3D reconstruction in (a) and CT scan reconstruction in skeletal mode (b); abnormal profile with high, broad forehead, midface hypoplasia and prominent lower jaw at ultrasound 3D reconstruction in (c) and 3D computed tomography scan reconstruction (d); cloverleaf skull secondary to severe craniosynostosis at 2D ultrasound (e) and 3D computed tomography scan reconstruction (f).

The opposite is true for termination of pregnancy performed because of multiple congenital anomalies. Our cohort is the largest series evaluating the detection rate of postmortem MRI in fetuses with multiple congenital anomalies: total agreement was achieved in only 9% of cases while autopsy added additional findings in 50%. These results are in line with a recent study by Hellkvist *et al.* on 34 cases of termination of pregnancy for fetal defects: only 11 were multiple defects and the detection rate for main diagnosis was 27% [24]. The assessment of these subgroups of fetal defects is particularly important since fetuses with multiple abnormalities carry the highest risk of genetic syndromes and recurrence for the couple [3]. Postmortem MRI is characterized by low accuracy and high risk of false positive diagnosis, therefore it is not the best diagnostic tools. Even though in some cases the use of a CT scan with reconstruction in 3D volume and skeletal mode may contribute to the diagnosis of some genetic syndromes, as shown in Fig. 1 and in Fig. 2, autopsy should always be recommended to achieve the highest precision in diagnosis. If parents decline autopsy, a careful external examination by a clinical geneticist or a pathologist and/or CT scan with 3D reconstruction is indicated.

The main limitation of the study is that radiologists were not blinded to the ultrasound diagnosis. Moreover, the use of a 1.5 postmortem MRI field may have lowered the accuracy for certain fetal defects, especially cardiac abnormalities, as shown in some studies with high-field MRI scanner (3.0 T/9.4 T) [25,26]. The strength is the homogeneity of the population and, to our knowledge, this is the largest study reporting on the performance of postmortem investigations in fetuses < 23 weeks after TOP, including a variety of fetal defects such as gastrointestinal, renal, pulmonary defects and multiple abnormalities usually less

investigated in previous reports [27,28].

Conclusion

Postmortem MRI has a good overall concordance with autopsy for fetal defects after termination of pregnancy performed at <23 weeks. When feasible, postmortem MRI should always be performed in cases of CNS defects to prevent inconclusive exams due to autolysis of the brain tissue.

For other districts/anomalies, conventional postmortem MRI adds overall little in terms of diagnostic yield and autopsy remains the gold standard to identify additional findings helpful for the post-procedure counseling. In case autopsy is declined, postmortem MRI can be considered as an alternative for respiratory, genitourinary and gastrointestinal defects, while postmortem CT and postmortem XR are indicated only for musculoskeletal anomalies. Parents should be made aware of the low performance of postmortem radiological investigations for cardiac defects and multiple abnormalities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.04.023.

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