Full Title

Is traditional perinatal autopsy needed after detailed fetal ultrasound and post-mortem MRI?

Short Title

Role of ultrasound and PMMR in less invasive autopsy

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Conflict of Interest

The authors have no conflicts of interest to disclose

Data Availability Statement

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

reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Bulleted Statements

What is already known about this topic?

- Prenatal ultrasound and post-mortem MRI provide good diagnostic accuracy for major congenital anomalies.

- Whilst traditional perinatal autopsy remains the reference standard investigation, many parents decline this invasive procedure.

What does this study add?

- Where prenatal ultrasound and PMMR imaging are concordant, there is little additional benefit from invasive autopsy. The highest yield from autopsy is when findings from the imaging modalities are discordant.

- Post mortem MRI may help triage cases that would benefit most from an invasive autopsy.

Abstract:

Objective

To determine the additional yield from autopsy following prenatal ultrasound and post-mortem magnetic resonance imaging (PMMR) for structural abnormalities.

Method

PMMR was performed on consecutive fetuses over a six-year period. Prenatal ultrasound and PMMR findings were categorised as concordant, partially concordant or discordant findings. The yield of new and clinically significant information from autopsy was assessed. Diagnostic accuracies for both modalities were calculated, using autopsy as reference standard.

Results

Our study consisted of 81 fetuses. PMMR and prenatal ultrasound findings were concordant in 44/81 (54.3%), partially concordant in 26/81 (32.1%) and discordant in 11/81 (13.6%) cases. In 19/81 cases (23%), autopsy provided additional information, which appeared clinically significant in 12 cases. In 10 of those 12 cases, there was discordance between PMMR and ultrasound. In only 2 of 44 cases where ultrasound and PMMR were concordant, did autopsy provide clinically significant information

Diagnostic accuracy rates for ultrasound were sensitivity of 76.8% (66.6%, 84.6%), specificity of 92.5% (88.9%, 95.0%). For PMMR the sensitivity was 79.0% (68.9%, 86.5%), specificity 97.9% (95.5%, 99.0%). PMMR had a significantly higher concordance rate with autopsy than ultrasound (89.0 vs 93.8%; p<0.001).

Conclusion

Where PMMR and ultrasound are concordant, there is little additional yield from autopsy.

Clinical Trial Registration:

ClinicalTrials.gov Identifier: NCT01417962

INTRODUCTION:

Investigation after birth of fetal anomalies detected on prenatal ultrasound is important, particularly following termination of pregnancy or fetal or perinatal loss, as there may be significant implications for genetic counselling, subsequent reproductive choices and other family members[1]. Traditionally, confirmation of prenatal findings would be obtained at perinatal autopsy which may give the underlying diagnosis. However most parents decline this invasive examination with autopsy consent rates reaching only 40%[2]. Given that significant clinical information is found in 37% of cases[3], most parents are denied this additional information.

Less invasive methods such as post-mortem imaging may provide a solution. Post mortem MRI (PMMR) has already demonstrated high diagnostic accuracy for perinatal death investigation with concordance rates (compared with autopsy) of over 90%[4,5]. A future clinical imaging pathway for perinatal death investigation could therefore involve review of prenatal ultrasound (US) findings followed by PMMR, instead of autopsy. Whilst healthcare professionals and parents are generally supportive of less invasive initiatives[6,7], a major issue concerns those of misdiagnoses and lack of certainty of findings. For example, where parents request a PMMR to confirm a prenatal diagnosis, should they be adequately reassured if both prenatal imaging and PMMR findings are concordant? If there are indeterminate or conflicting findings from both imaging modalities, would there be an additional yield from doing conventional autopsy?

Whilst family and healthcare professionals may wish to avoid invasive autopsy methods, a balance between understanding reasons for fetal anomalies or fetal demise and potential avoidance of future complications needs to be met. An evidence basis for this is currently lacking. Were it available, this information could help counsel families for non-invasive perinatal autopsy choices, aid clinicians in determining the appropriateness of referral and also pathologists in deciding whether to suggest further investigations.

Here we aim to determine the additional yield of full autopsy following detailed prenatal ultrasound imaging and PMMR examination. We also assess the diagnostic accuracy rates of both imaging modalities in the detection of major structural pathologies.

METHODS:

Ethics:

This study forms part of an ethically approved larger study investigating minimally invasive autopsy techniques and novel methods of post mortem imaging (CE13/LO/1494 and 04/Q0508/41). The full study protocol has been previously published in detail[8].

Population:

Pre-autopsy PMMR was performed in a sequential cohort of fetuses and children referred to Great Ormond Street Hospital over a six-year period, between June 2007 and 2013. This study was a retrospective review of the cases within a larger study of the diagnostic accuracy of PMMR vs autopsy (Magnetic Resonance Imaging in Autopsy study; MARIAS[5,8]) with an additional 58 patients recruited subsequent to the MARIAS cohort (unpublished data). None of the prenatal imaging data was available during the initial phase of the MARIAS study, and the information presented here has not been reported previously.

Fully informed, written parental consent for conventional autopsy and post-mortem imaging was obtained in all cases. A retrospective review of each patient's prenatal medical records was performed. Cases were excluded where the prenatal imaging findings or autopsy reports were not available for re-review.

Demographic details collected for each case included date of birth, death, gestational age, post-mortem weight, subjective degree of maceration at autopsy (based on standard criteria involving external evaluation of the fetus including skin slippage, skin discolouration and overlapping of the skull structures[9], arbitrarily scored from 0 to 3; 0 representing none, 1 mild, 2 moderate, and 3 established maceration[10]), number of days between delivery and PMMR, days between delivery and autopsy and mode of death (e.g. termination of pregnancy, stillbirth, miscarriage).

Ultrasound Imaging:

All ultrasound examinations were performed by experienced healthcare professionals trained in fetal sonography and prenatal diagnosis (i.e fetal medicine unit consultants, obstetric sonographers)

working in the UK National Health Service (NHS). Imaging was conducted according to national prenatal screening protocols offering all women at least 2 ultrasound studies between 11-14 weeks and 18-21 weeks gestation[11]. Where a severe anomaly was identified, additional ultrasound studies were performed according to local clinical practice.

Prenatal images and reports were retrospectively assessed by a fetal medicine and genetic specialist (LC) who categorised the cases for presence of abnormalities in each of five body systems (central nervous, cardiovascular, thoracic, abdominal and musculoskeletal systems). An independent adjudicator (IG), a research assistant, assisted in the data collection and ensured that consistency in data labelling and categorisation of abnormalities was followed. Where more than one ultrasound had been performed, the images were considered in their entirety to give a final diagnosis prior to termination or fetal death.

PMMR Imaging:

Bodies were stored in the mortuary at $4^{o}C$ within 24 hours of delivery and PMMR was performed during dedicated research imaging lists. All MR imaging was performed at 1.5T (Avanto, Siemens Medical Solutions, Erlangen, Germany). Body imaging included isovolumetric T1 and T2 weighted imaging for the whole body with additional isovolumetric T2 weighted constructive interface steady state (CISS) sequences covering the thorax (for cardiac anomalies) and a 2D axial T2-weighted inversion recovery sequence of the body, according to published protocols[12]. The coil used was dependent on patient size (either phase array body coil or head coil), selected to allow for best image quality.

PMMR image interpretation was reported for each of the five body systems by one of two specialist paediatric radiologists. All radiologists were accredited by the Royal College of Radiologists (London, UK) and had at least 6 years of clinical reporting experience. The imaging was reported prior to and blinded to the autopsy findings. Only a brief clinical indication regarding type of pregnancy loss and gestational age was provided at time of reporting (e.g. 19 week gestation miscarriage).

Standard Autopsy

Standard autopsy was performed by one of seven paediatric pathologists as part of routine clinical practice according to guidelines provided by the Royal College of Pathologists[13-15] and European recommendations[16]. All pathologists were accredited by the Royal College of Pathologists (London, UK) with at least 8 years autopsy experience. Pathologists were blinded to the PMMR imaging findings, but aware of the prenatal maternal and obstetric history (including ultrasound findings) as these are routinely available as part of the referral indication notes for autopsy.

Data handling and Analysis:

Our main objective was to identify the additional yield of autopsy, given the PMMR and prenatal ultrasound findings. A modification of the method described in studies by Isaken CV et al[17] and Rodriguez MA et al[18] was utilised, where a radiology research fellow (SS) (not involved in the reporting or reviewing any of the imaging cases) ascribed each patient to one of the following categories based on imaging reports:

1) Full agreement between prenatal US with PMMR (i.e. no additional finding from PMMR).
2) Partial agreement between US and PMMR (either an additional finding was reported on one modality, or there was agreement regarding the presence of an abnormality in the same body system, but not on the type of abnormality)
3) Disagreement in diagnosis between US and PMMR.

For each of the categories, autopsy results (our reference standard) was assessed to determine a) whether any additional information was provided, and b) whether this information was clinically significant. We defined clinical significance as new information which would change the overall diagnosis based on assessment by an experienced perinatal pathologist (> 20 years experience (NJS)) opinion. Descriptive statistics were used to determine the autopsy yield.

As a secondary objective, the relative diagnostic accuracies of prenatal ultrasound and PMMR in our cohort were also determined. We recorded the proportion of cases in which pathological findings were correctly depicted by each modality per body system (neurological, cardiac, thoracic, abdominal and

musculoskeletal) and for all body systems overall, irrespective of whether or not they contributed to the death. This was expressed as the proportion of undetected pathological lesions (false negative) and apparent overcalls (false positives), using autopsy as the reference standard. Exact methods were used to calculate confidence intervals. Diagnostic accuracy rates were calculated for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and concordance rates. Expected post-mortem changes on imaging and autopsy were not considered significant findings [19].

RESULTS:

Demographics:

Of the 171 fetuses recruited from the initial dataset, 140 (81.9%) had prenatal ultrasound reports and images available for re-review. One case was excluded due to non-diagnostic prenatal and PMMR imaging findings from maceration and 58/139 (41.7%) perinatal autopsy reports were unavailable. Of the remaining 81 cases 63/81 (77.8%) were terminations of pregnancy for fetal abnormalities, 7/81 (8.6%) were spontaneous miscarriages and 11/81 (13.6) still births.

Of the 81 eligible cases, there were 43/81 (54.3%) males, with median gestational age of 21 weeks (14 -41 weeks) and median post-mortem weight of 346g (16 -3480g). In 60/81 (74.1%) cases, the fetus was ≤24 weeks gestation and in 54/81 (66.7%) cases the fetus weighed ≤500g. The majority of cases (52/81, 64.2%) were described as non-macerated (score 0), 9/81 (11.1%) as early or moderately macerated (score 1 or 2), and the remainder (20/81, 24.7%) as markedly macerated (score 3). The median post-mortem interval time from death to PMMR was 6 days (0-36 days), and median time between death to autopsy was 9 days (1 – 42 days).

Case Categorisation

Overall, PMMR and ultrasound findings were concordant in 44/81 (54.3%) cases (i.e. no new information provided at PMMR), partially concordant in 26/81 (32.1%) cases, and discordant in 11/81 (13.6%) cases. A detailed breakdown of the cases are provided below and a summary flowchart is provided in **Figure 1**. New information at autopsy was found in 19/81 (23%) cases, of which 12/81 (14.8%) were clinically significant.

Category 1: Agreement between US and PMMR

Of the 44 concordant cases 32 (72.7%) were terminations of pregnancy, four (9.1%) were miscarriages, and eight (18.2%) stillbirths. In two (4.5%) cases where US and PMMR reported ventriculomegaly autopsy was non-diagnostic due to brain autolysis.

In 36/44 (81.8%) cases the autopsy did not identify any additional abnormalities. Of these 36 cases, 10/36 (27.8%) were normal on all three examinations (US, PMMR, autopsy) and 26/36 (72.2%) demonstrated significant pathological findings, all of which were diagnosed on US and PMMR, which included:

- 1 multisystem disorder (neural tube defect, pulmonary hypoplasia, abdominal cloaca)
- 8 neurological related anomalies (3 neural tube defects, 1 Dandy Walker variant, 4 absent corpus callosum)
- 6 genitourinary related anomalies (two unilateral and one bilateral renal agenesis, 3 bladder outlet obstruction
- 9 skeletal dysplasias (2 described as 'skeletal dysplasia', subtype unspecified by imaging or autopsy, requiring further genetic opinion; 1 thanatophoric dysplasia; 3 osteogenesis imperfecta; 1 lethal hypophosphatasia; 1 chondrodysplasia punctata, 1 short rib polydactyly)
- 1 arthrogryposis
- 1 complex congenital heart defect

In the remaining 6/44 (13.6%) cases, there were additional findings at autopsy, not identified at US or PMMR. The cases included the following:

- Both US and PMMR modalities identified absent corpus callosum, autopsy revealed additional cerebellar heterotopia (additional finding useful to determine underlying syndromic association);
- Both modalities reported ventriculomegaly with multiple limb contractures, autopsy revealed additional finding of VSD and malrotation (clinically significant additional findings);
- Both modalities diagnosed a skeletal dysplasia (thanatophoric dysplasia with pulmonary hypoplasia and shortened long bones), autopsy revealed additional finding of cerebral polymicrogyria (known association, therefore not clinically significant);

- Both modalities were suggestive of hydrops but no specific internal abnormalities, autopsy revealed cystic hygroma and abdominal Meckel's diverticulum (not clinically useful as cystic hygroma can be seen with hydrops and a Meckel's diverticulum is a normal anatomical variant) and

- Two cases where both modalities identified only ventriculomegaly – in one case autopsy also identified additional intraventricular haemorrhage; another case the autopsy revealed pontine calcification (neither clinically significant).

Therefore in this subset of full concordance between imaging modalities, clinically significant information was found at autopsy in only two cases (2/44; 4.5%).

Category 2: Partial Agreement between US and PMMR

A summary of these 26/81 (32.1%) cases are provided in **Table 1**. In 4/26 (15.4%) cases, the discrepant finding was neurological related and autopsy of the brain was either not performed (no consent for brain autopsy in one case) or non-diagnostic given small patient size (3 cases). For these cases, autopsy could not provide any additional information.

In 10/26 (38.5%) cases, the autopsy findings were concordant with the PMMR findings but not prenatal US, but autopsy did not yield additional clinically significant information. In 2/26 (7.7%) cases, there were significant findings on ultrasound confirmed by autopsy that were not identified by PMMR (one case of atrioventricular septal defect and one case of hydrops). In 10/26 (38.5%) cases, the autopsy revealed 'new information' (i.e. new findings in addition to the prenatal US or PMMR; or confirming absence of positive findings from the imaging).

In this subset of partial concordance between imaging modalities, 8/26 (30.1%) of autopsies provided clinically significant information, either by identifying additional findings (5/8, 62.5%) or changing the diagnosis (3/8, 37.5%) (Table 1).

Category 3: Disagreement between US and PMMR

Of the 11/81(13.6%) cases where there was disagreement between prenatal US and PMMR, in 1/11 (9%) the autopsy was non-diagnostic, in 3/11 (27.2%) the autopsy was discordant with both imaging modalities, in a further 3/11 (27.2%) the autopsy agreed with the PMMR findings, and in 4/11 (36.4%) the autopsy agreed with the US findings (**Table 2)**.

For the three cases where PMMR findings were more in keeping with autopsy results, there was ventriculomegaly on prenatal US that was not present on PMMR, indicating an apparent 'false positive' result from ultrasound.

In the 4 cases where US findings were in keeping with autopsy findings, the PMMR was non-diagnostic for one (US and autopsy were normal) and in the remaining three cases there was an unremarkable internal examination. Several overcalls (false positives) were made at PMMR including one report of dural sinus malformation, and two reports of cardiothoracic abnormalities.

Therefore in this subset of discordance between imaging modalities, only 2/11 (18.1%) autopsies provided additional clinically significant information.

Diagnostic Accuracy by Body Systems

The overall diagnostic accuracies for major pathological lesions in individual and all body systems for both imaging modalities are provided in **Table 3,** with 95% confidence intervals.

The overall diagnostic accuracy rates for prenatal ultrasound in this cohort were sensitivity of 76.8% (95% CI: 66.6%, 84.6%), specificity of 92.5% (95% CI: 88.9%, 95.0%) and concordance of 89.0% (95% CI: 85.5%, 91.8%). The sensitivity of PMMR was 79.0% (95% CI: 68.9%, 86.5%), specificity of 97.9% (95% CI: 95.5%, 99.0%) and concordance of 93.8% (95% CI: 90.8%, 95.8%). There was a statistically significant difference between specificity and concordance rate between the two imaging modalities for total body systems, although not for sensitivity rates.

For individual body systems, both prenatal ultrasound and PMMR had the highest sensitivity rates for musculoskeletal (94.7% versus 89.5% respectively), intra-abdominal (80.0% for both) and intracranial (74.2% versus 80.0%) pathologies. The lowest sensitivities for prenatal ultrasound were for thoracic pathologies (50%, versus 80% for PMMR). For PMMR the lowest sensitives were for cardiac pathologies (42.9% versus 71.4% for prenatal US).

DISCUSSION:

Our study shows that in the majority of cases, prenatal ultrasound and PMMR imaging are concordant and there was little additional benefit in performing an invasive autopsy. The highest yield from autopsy was in those cases where there was partial or complete discordance between imaging modalities, but clinically significant information was found in only a quarter of these cases (10/37; 27%).

We interpret this data to mean that where families wish to avoid invasive methods, the additional benefit of autopsy is likely to be most important where the prenatal ultrasound and PMMR findings are partially or completely discordant, and that this should be decided upon by a case by case basis, depending on likelihood of affecting future pregnancy management. Our study suggests the main caveat to this statement is ventriculomegaly, where a prenatal diagnosis was neither confirmed by PMMR nor autopsy; this apparent "false positive" imaging finding has been shown to resolve by PMMR, and may represent normal post-mortem change, unlikely to benefit from autopsy confirmation[20].

Overall, this data supports a potential change in the clinical service, such that PMMR would be offered routinely following perinatal deaths, and autopsy reserved for those in whom there is discordance between prenatal and post mortem imaging findings. This clearly has widespread economic and service delivery implications, as PMMR remains not widely available or understood, despite autopsy practice and acceptance being in decline.

Compared to other published studies, our ultrasound confirmation rate with autopsy at 42/81 (51.8%) cases is slightly lower than the 68% agreement rate reported by Rossi A et al[21] in their systematic

review of over 3500 prenatal ultrasound examinations. Nevertheless, our additional yield of new information from autopsy at 23.5% is similar to their 22.5% autopsy yield rate. These differences may be explained by small differences in our different patient demographics (wider gestational age range from 14 – 41 weeks compared to their 17 – 20 week gestation), different case mix, our relatively small population sample or differences in categorisation of anomalies.

The PMMR diagnostic accuracy rates in our study are high, and similar to independent data published by our group [22], with little difference in sensitivity rates for neurological (94%[22] versus 80% in this study), thoracic (81.8%[22] versus 80%) and abdominal (89.5%[22] versus 80%) pathologies. Cardiac (60%[22] versus 42.9%) pathologies were slightly less accurate in our study, whereas musculoskeletal pathologies (67.3%[22] versus 89.5%) were more accurate. Nevertheless these results suggest that cardiac anomalies remain difficult to diagnose on PMMR and thus results using this modality should be interpreted with caution.

Despite the strengths in this study regarding novelty of research design, unique nature of case cohort (which includes prenatal ultrasound review, PMMR and autopsy results) there were several limitations to our study. One of these relates to the timing between the ultrasound imaging and PMMR. Whilst we created a single diagnosis from all prenatal ultrasound studies, we did not examine any change in sonographic diagnoses over gestation. It is possible that sonographic findings may have changed in the timeframe between most recent ultrasound study and patient death, leading to discrepancies with PMMR results. It is possible that where additional ultrasound imaging was conducted outside of the normal imaging guidelines, different healthcare specialists may have performed such studies (e.g. sonographers versus obstetricians) introducing some differences in image quality and planes acquired for interpretation. Nevertheless this is reflective of clinical practice, and therefore we believe our results to be still valid.

Another limitation is in the interpretation and reporting of PMMR and autopsy results. In this study we did not re-review PMMR images for their findings or select our fetuses based on pre-defined demographic criteria (i.e. weight or gestational age threshold). Our PMMR reporters were blinded to prenatal imaging findings (since this was part of a larger study assessing PMMR diagnostic accuracy),

whilst the pathologists performing autopsies were not blinded and had access to all information. In addition, over half of our study sample were of smaller fetuses below 500g bodyweight in which there is a recognised reduced diagnostic accuracy rate of PMMR. This demographic skew could have affected the diagnostic accuracy of PMMR, particularly of cardiac anomalies[23,24]. One way to combat this limitation in the future may be to image fetuses using 3T MRI [25] or alternatively with microfocus computed tomography (micro-CT)[26], however these facilities were not available to us at the time of the study.

Finally, we defined 'additional information' from autopsy as any information not previously highlighted by either imaging modality. It is clear that not all new information will be clinically useful or relevant, but this is a subjective judgement and varies on a case-by-case basis. In our study, we tried to estimate clinical significance based on the opinion of an experienced perinatal pathologist, which is clearly open to interpretation, and may differ according to the population sampled and clinical indication. This is an area that requires careful parental counselling and discussion in the clinic, where the value of additional information versus the benefits of non-invasive autopsy methods should be balanced.

In this study we have shown the different accuracy rates for US, PMMR and invasive autopsy for the detection of structural anomalies in the fetus and stillbirth. However, for complete diagnosis and full clinical utility, in many cases a molecular genetic diagnosis is required to inform genetic counselling for recurrence risks and future reproductive planning and pregnancy management. For example, skeletal dysplasias and renal cystic disease may have a variety of aetiologies which can be sporadic, or inherited in an autosomal dominant or recessive fashion. Whilst molecular diagnosis may increasingly be done prenatally using exome sequencing[27-29] where parents have declined invasive testing before birth, they should be encouraged to allow storage of fetal DNA to enable further genetic investigation for definitive diagnosis.

CONCLUSION:

In conclusion post mortem MRI may be used to triage those cases which would likely most benefit from an invasive autopsy, by careful analysis of concordance with prenatal ultrasound findings.

Invasive autopsy could then be more appropriately targeted to those in whom there is a discrepancy between prenatal and post mortem findings, and is likely to generate the highest clinical yield when used in this manner, in accordance with parental wishes.

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Table 1: Category 2 Findings. Description of findings from prenatal ultrasound (US), post mortem MRI (PMMR) and resultant autopsy results for cases where the US and PMMR demonstrated partial agreement. Abbreviations: AVSD – atrioventricular septal defect, ACC – absent corpus callosum, DWV – Dandy Walker variant, CNS – central nervous system, CCHD – complex congenital heart disease, SVC – superior vena cava, CDH – congenital diaphragmatic hernia, DVA – dural venous anomaly, DSM – dural sinus malformation, CMV – cytomegalovirus, ND – non-diagnostic, VM – ventriculomegaly, US – ultrasound

Gestational Age, Gender & Mode of Death	Ultrasound Findings	PMMR Findings	Autopsy Findings	Clinically significant autopsy findings
No autopsy reference for discrepant findings				
20 weeks, Female, Termination	CNS anomaly (DWV) + talipes	CNS anomaly (DWV), no talipes	ND CNS, no talipes	None
18 weeks, Male, Termination	CCHD	CNS anomaly (intracranial haemorrhage), CCHD	Cardiac autopsy – CCHD. CNS autopsy not performed	None
16 weeks, Female, Termination	CNS - Dilated fourth ventricle, bilateral SVCs	CNS – ACC, VM	ND brain, normal body	None
21 weeks, Female, Termination	CNS – VM	CNS – ACC and VM	ND brain, normal body	None
Invasive autopsy concordant with PMMR				
22 weeks, Male, Termination	AVSD	AVSD and vertebral coronal clefting	AVSD with vertebral coronal clefting	None
34 weeks, Male, Termination	VM, intracranial haemorrhage and abnormal cerebellar cortex	VM	VM	None
21 weeks, Male, Termination	Bilateral dysplastic kidneys	Absent right kidney, cystic/dilated left kidney	Pulmonary hypoplasia, right renal agenesis, large cystic	None

			left kidney	
35 weeks, Female, Termination	Intracranial haemorrhage with VM	Intracranial haemorrhage, no VM	Intracranial haemorrhage, no VM	None
32 weeks, Female, Termination	ACC, posterior fossa cyst, VM	ACC, no VM	ACC, no VM	None
21 weeks, Female, Termination	Marked VM	Absent corpus callosum, no VM	Absent corpus callosum, no VM, mild intracranial haemorrhage	None
34 weeks, Male, Termination	Marked VM and abnormal cerebellum	VM, intracranial haemorrhage	VM, intraventricular haemorrhage	None
20 weeks, Female, Termination	Facial dysmorphism, micrognathia, arthrogryposis	Normal brain appearances, arthrogryposis	No facial dysmorphism, arthrogryposis	None
26 weeks, Male, Termination	VM, ACC, AVSD, left renal agenesis	VM, schizencephaly, left renal agenesis	VM, schizencephaly, left renal agenesis	None
23 weeks, Female, Termination	Talipes, hemivertebrae and abnormal head shape	Talipes, no brain/head anomalies.	Bilateral talipes, normal brain/head	None
New information from invasive autopsy				
20 weeks, Female, Termination	CNS – partial ACC	CNS – partial ACC, vermis hypoplasia	Normal brain, CCHD	Changed diagnosis; normal CNS, abnormal cardiovascular system
23 weeks, Female, Termination	Pulmonary hypoplasia, echogenic kidneys, short limbs	Pulmonary hypoplasia, short limbs, normal abdomen.	Pulmonary hypoplasia, dysplastic kidneys and intestinal malrotation.	Autopsy identifies intestinal malrotation and further characterises renal issues.
20 weeks, Male, Termination	VM, interhemispheric cyst.	VM, pulmonary hypoplasia, renal agenesis, vertebral and rib anomalies	VM, caudal regression, renal agenesis, pulmonary hypoplasia, imperforate anus, VSD, vertebral and rib anomalies	Autopsy provides additional information on spinal and cardiac issues.
22 weeks, Male, Termination	Bladder outlet obstruction, absent	ACC, bladder outlet obstruction	Bladder outlet obstruction	Autopsy clarifies the lack of intracranial, cardiac

	stomach bubble, dilated cardiac chambers			pathology.
27 weeks, Male Termination	Dilated anterior horns of the lateral ventricles	Left sided cerebral polymicrogyria	Focal cortical malformation	Autopsy changes intracranial diagnosis
21 weeks, Male, Termination	VM, hypoplastic cerebellum, semilobar holoprosencephaly	VM, hypoplastic cerebellum	Lissencephaly	Autopsy changes intracranial diagnosis.
32 weeks, Female, Intrauterine Death	Cystic space on right cerebral hemisphere	Right hemimegalencephaly	Cortical malformation (right lobe) right DVA, necrosis of pituitary	Autopsy clarifies the intracranial appearances.
23 weeks, Male, Termination	Cardiomegaly, ascites, calcified liver,	VM, periventricular calcification, hydropic, renal cortical necrosis, calcified fibrotic liver, ascites,	Normal brain (ventricular size not assessed due to autolysis), pulmonary CMV infection and hypoplasia, renal infarction, splenomegaly, calcific liver, extramedullary haematopoiesis.	Autopsy provides additional intra-abdominal findings
20 weeks, Female, Termination	Severe VM, small cerebellum, tetralogy of Fallot	VM with white matter change. No cardiac findings.	Small VSD (2mm) and VM	None
32 weeks, Male, Intrauterine Death	CDH, echogenic kidneys, short limbs	ND brain & cardiac imaging. CDH.	CDH, posterior fossa cyst	None
Prenatal US detected features not identifiable on PMMR				
15 weeks, Female, Termination	Cystic hygroma, pulmonary hypoplasia, hydropic	ND cardiac and brain imaging. Pulmonary hypoplasia.	Cystic hygroma and marked pulmonary hypoplasia	None
22 weeks, Male, Termination	VM, AVSD, polydactyly	ACC, ND cardiac imaging, polydactyly	ND brain appearances, AVSD, post axial polydactyly	None

Table 2: Category 3 Findings. Description of findings from prenatal ultrasound (US), post mortem MRI (PMMR) and resultant autopsy results for cases where the US and PMMR showed complete disagreement. Abbreviations: ACC – absent corpus callosum, DSM – dural sinus malformation, VM – ventriculomegaly

Gestation, Gender & Mode of Death	Ultrasound Findings	PMMR Findings	Autopsy Results	Clinically significant autopsy findings
Invasive Autopsy Discordant with US and PMMR				
18 weeks, Female, Termination	Heart not identified.	Neural tube defect.	External features typical of holoprosencephaly with proboscis, body too macerated for adequate assessment	Non-contributory for internal findings.
25 weeks, Male, Termination	VM	Normal	Subtle neuronal migration anomalies (dentate dysplasia, periventricular nodular heterotopias, cerebellar heterotopias)	Identifies additional neuronal migration anomalies.
23 weeks, Male, Termination	Partial ACC with posterior fossa arachnoid cyst	Normal	Probable cortical malformation on medial aspect of occipital lobe.	Identifies additional finding of cortical malformation
Invasive Autopsy Concordant with US				
17 weeks, Male, Miscarriage	Normal	Non-diagnostic	Normal	None
24 weeks, Male, Intrauterine death	Echogenic bowel (uncertain clinical significance) with fetal growth restriction	Dural sinus malformation, DSM	Normal internal examination, severe fetal growth restriction	None
20 weeks, Male, Miscarriage	Normal	Small VSD	Normal	None
33 weeks, Female,	Normal	Anomalous pulmonary	Normal	None

Intra-uterine death		venous drainage		
Invasive Autopsy Concordant with PMMR				
25 weeks, Male, Termination	Moderate VM	Normal	Normal	None
25 weeks, Male, Termination	Moderate VM	Normal	Normal	None
24 weeks, Female, Termination	Severe VM	Normal	Normal	None
Invasive Autopsy Non-Diagnostic				
20 weeks, Female, Termination	Arachnoid cyst and VM	Normal	Non-diagnostic neuropathology, normal body appearances.	None

Table 3: Table of prenatal ultrasound (US) and post-mortem MRI (PMMR) diagnostic accuracy rates for both individual and overall summated body system findings for major pathological diagnoses. 95% confidence intervals are provided in squared brackets. TP – true positive, FP – false positive, FN – false negative, TN – true negative, NE – not examined at autopsy, AL – autolysed at autopsy, ND – non-diagnostic imaging, PPV – positive predictive value, NPV – negative predictive value, CNS – central nervous system, MSK – musculoskeletal. * - denotes significantly different accuracy rates

|	TP / FP	FN / TN	NE/ AL / ND	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Concordance (%)
CNS US (n=81)	23 / 4	8 / 33	4 / 9 / 0	74.2 [56.8, 86.3]	89.2 [75.3, 95.6]	85.2 [67.5, 94.1]	80.5 [66.0, 89.8]	82.4 [71.6, 89.6]
CNS PMMR (n=81)	24 / 4	6 / 32	4 / 9 / 2	80.0 [62.7, 90.5]	88.9 [74.7, 95.6]	85.7 [68.5, 94.3]	84.2 [69.6, 92.6]	84.8 [74.3, 91.6]
Cardiac US (n=81)	5 / 3	2 / 68	1 / 1 / 1	71.4 [35.9, 91.8]	95.8 [88.3, 98.6]	62.5 [30.6, 86.3]	97.1 [90.2, 99.2]	93.6 [85.9, 97.2]
Cardiac PMMR (n=81)	3 / 2	4 / 63	1 / 1 / 7	42.9 [15.8, 75.0]	96.9 [89.5, 99.2]	60.0 [23.1, 88.2]	94.0 [85.6, 97.7]	91.7 [83.0, 96.1]
Thoracic US (n=81)	5 / 2	5 / 65	1 / 1 / 2	50.0 [23.7, 76.3]	97.0 [89.8, 99.2]	71.4 [35.9, 91.8]	92.0 [84.3, 96.9]	90.9 [82.4, 95.5]
Thoracic PMMR (n=81)	8 / 0	2 / 68	1 / 1 / 1	80.0 [49.0, 94.3]	100 [94.7, 100]	100 [67.6, 100]	97.1 [90.2, 99.2]	97.4 [91.1, 99.3]
Abdominal US (n=81)	12 / 4	3 / 59	1 / 2 / 0	80.0 [54.8, 93.0]	93.7 [84.8, 97.5]	75.0 [50.5, 89.8]	95.2 [86.7, 98.3]	91.0 [82.6, 95.6]
Abdominal PMMR (n=81)	12 / 0	3 / 62	1 / 2 / 1	80.0 [54.8, 93.0]	100 [94.2, 100]	100 [75.8, 100]	95.4 [87.3, 98.4]	96.1 [89.2, 98.7]
MSK US (n=81)	18 / 9	1 / 45	2 / 1 / 5	94.7 [75.4, 99.1]	83.3 [71.3, 91.0]	66.7 [47.8, 81.4]	97.8 [88.7, 99.6]	86.3 [76.6, 92.4]
MSK PMMR (n=81)	17 / 0	2 / 57	2 / 1 / 2	89.5 [68.6, 97.1]	**100*** **[93.7, 100]**	**100*** **[81.6, 100]**	96.6 [88.5, 99.1]	**97.4*** **[90.9, 99.3]**
Total Body Systems US (n = 405)	63 / 22	19 / 270	9 / 14 / 8	76.8 [66.6, 84.6]	92.5 [88.9, 95.0]	74.1 [63.9, 82.2]	93.4 [90.0, 95.8]	89.0 [85.5, 91.8]
Total Body Systems PMMR (n = 405)	64 / 6	17 / 282	9 / 14/ 13	79.0 [68.9, 86.5]	**97.9*** **[95.5, 99.0]**	**91.4*** **[82.5, 96.0]**	94.3 [91.1, 96.4]	**93.8*** **[90.8, 95.8]**
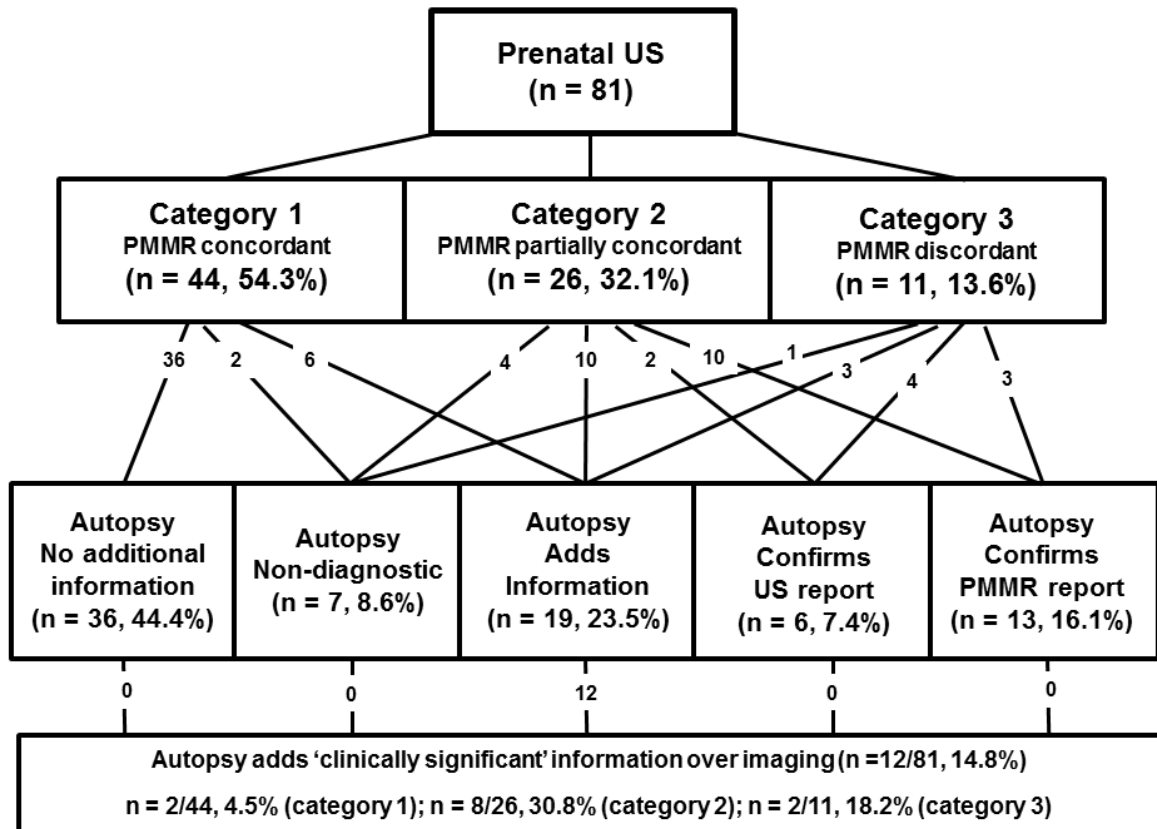
Figure 1: Flowchart demonstrating the numbers of cases with full, partial concordance and discordance between prenatal ultrasound (US) and perinatal post-mortem MRI (PMMR). The numbers of cases where there was additional new and clinically significant information found at autopsy are demonstrated in the bottom rows of the flowchart, showing the relative contributions from each of the imaging group categories.