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Post-mortem Magnetic Resonance (PMMR) Imaging Appearances of Feticide in Perinatal Deaths

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Abstract:

Introduction: The aim of this study was to characterise imaging features seen in fetuses having undergone feticide by intra-cardiac potassium chloride injection (KCl) compared to non-terminated fetuses at post-mortem magnetic resonance imaging (PMMR).

Method: A case control study was performed comparing PMMR findings between two groups of patients - those having undergone feticide were matched to a control group of miscarried/stillborn fetuses. The groups were matched according to gestational ages, weight and time since death. Two independent readers reviewed the PMMR for thoracic, abdominal and musculoskeletal imaging features. Fishers exact test was conducted for differences between the patient groups.

Results: 26 cases of feticide (mean gestation 25 weeks (20 – 36)) and 75 non-terminated fetuses (mean gestation 26.7 weeks (19 – 36)) were compared. There was a higher proportion of feticide cases demonstrating pneumothoraces (23.1% vs 1.3%, p= 0.001), haemothoraces (42.3% vs 4%, p = 0.001), pneumopericardium (30.8% vs 5.3%, p = 0.002) and a haemopericardium (34.6% vs 0%, p = 0.0001). Intracardiac gas and intra-abdominal findings were higher in the feticide group, but the differences were not statistically significant.

Conclusion: Characteristic PMMR features of feticide can help improve reporter confidence in differentiating iatrogenic from physioloigcal/pathological processes

Keywords:

Post-mortem, MRI, Perinatal, Paediatric, Feticide, Termination

Abbreviations:

(PM)MR – (post-mortem) magnetic resonance imaging

PMI – post-mortem interval

TOP – termination of pregnancy

GA – gestational age

KCl – Potassium Chloride

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Introduction:

Advances in antenatal imaging assessments have resulted in earlier diagnosis of potentially debilitating congenital conditions and a rise in number of terminations of pregnancy (TOP) [1,2]. The agreement between the antenatal ultrasound and autopsy findings have shown to be high (>60% [3]) however a detailed fetal autopsy can provide additional information in almost 40% of cases [4], and refine genetic counselling in approximately a third of cases [5,6]. Nevertheless, the declining rates of parental consent for autopsy (recently estimated at 38% for perinatal deaths [2]), prohibits the discovery of this information. Post mortem MRI (PMMR) in perinatal deaths have shown high rates of concordance when compared to standard autopsy findings, when performed in a specialist centre (up to 90% overall [7]), especially when interpreted by trained readers and may provide a suitable alternative or adjunct to the traditional methods of autopsy, with benefit of being non-invasive and more acceptable to parents [8].

The interpretation of perinatal PMMR differs considerably to live paediatric imaging in several crucial ways. Physiological post-mortem changes, including decomposition and autolysis must be accurately differentiated from pathological features, with additional complications in perinatal imaging of maceration-related and iatrogenic changes (i.e. feticide)[9]. This is of particular importance when a full clinical history may be incomplete or unavailable, and an awareness of the typical ‘non-pathological’ findings can prevent inappropriate over-diagnoses.

The aim of this study was therefore to identify any PMMR imaging differences between fetuses who underwent iatrogenic termination of pregnancy via feticide by intra-cardiac potassium chloride injection (KCl) in line with Royal College of Obstetricians and Gynaecologists (RCOG) guidelines [10]

to non-terminated fetuses of a similar gestational ages and size. Common features across these two groups are likely to relate to physiological post mortem changes, whereas differences which could be attributable to feticide would aid in correct interpretation of future PMMR studies.

Methods:

Study Cohort

A retrospective review of our institution's radiology information system was conducted for all post-mortem MRIs performed over a 5.5 year period (January 2012 – July 2017) and cases were divided into two groups according to the clinical history. Written informed consent was obtained from all parents for clinical pre-autopsy PMMR, which includes usage of data for audit, research and education, as part of our institution's post-mortem imaging protocol. Ethical approval was not required for this study as it was performed as part of a retrospective audit on data imaging quality and imaging features of post mortem MRI.

The 'feticide' cohort included cases with a known history of termination of pregnancy (TOP) from intra-cardiac injection where a stated date of procedure was given. Cases where the clinical notes or indication for imaging included feticide or termination of pregnancy but without information on the stated method or date of the intervention were excluded. The 'control' group included miscarried or stillborn fetuses, without a history of TOP, over the same time period. Cases with a similar demographic profile for range of gestational ages, post-mortem weights and time from death to imaging were included. Non-diagnostic imaging cases or those with gross pathology that may interfere with interpretation were excluded. Cases were excluded from both cohorts where imaging was incomplete or non-diagnostic, or clinical data was insufficient to be able to determine the mode of delivery.

Demographic details obtained from the post-mortem and imaging reports for each patient included date of birth, death, gestational age, post-mortem weight, maceration score at clinical autopsy (0 to 3 - 0 representing none and 3 representing late/established maceration) and intra-uterine retention (time between feticide and delivery where appropriate / available). As accurate estimation of the intra-uterine retention time in non-terminated fetuses is challenging, this was determined to be the date of

confirmed absence of the fetal heart beat at antenatal sonography, or time the mother first noticed the absence of fetal movements, whichever was recorded earlier. Where neither of these details could be elicited from the notes, the intra-uterine retention time was left as 'unknown'. The cause of death in the non-terminated group at autopsy, and the indication for termination of pregnancy in the feticide group, were recorded.

Magnetic Resonance Imaging

All MR imaging was performed at 1.5T (Avanto, Siemens Medical Solutions, Erlangen, Germany) with a conventional phase array body coil. Our body imaging protocols include and have been previously published [11], and this study primarily examined 3D volumetric whole body T1-weighted (FOV 360mm; slice thickness 1.4mm; TR 5.9ms, TE 2.4ms) and T2-weighted sequences (FOV 360mm, slice thickness 1.4mm; TR 3500ms, TE 173ms) of the thorax and abdomen. The bodies were stored in the mortuary at 4^{o}C and PMMR was performed during dedicated research imaging lists to prevent any disruption to usual clinical services.

Image Analysis

Imaging datasets for both groups were provided to two independent readers in a randomised order, blinded to the patient's antenatal details including any history of feticide. Each reader assessed all cases for the presence of gas, fluid or blood within the pericardial, pleural and peritoneal cavities, as well as the presence of intracardiac gas, and soft tissue oedema and surgical emphysema along the chest and abdominal walls. The laterality of an abnormality (i.e. left or right) was defined as location with respect to the sternum. Following independent assessment, a consensus agreement between two readers was reached, with a third reader adjudicating in the event of non-consensus. All readers were board certified radiologists with 6, 7 and 11 years of radiology experience respectively.

Statistical Analysis

The frequencies and percentages of the variables scored were calculated. Differences in proportions were compared using Fisher's exact test. A p value of <0.05 was considered statistically significant between the two groups.

Diagnostic accuracy rates (i.e. sensitivity, specificity, positive and negative predictive values and concordance) were calculated for any radiological features that were significantly associated with the feticide group.

Results:

A total of 305 PMMRs were acquired for all childhood deaths over our study time period, with 118 (38.6%) referred with a history of TOP. Of these, 90 (76.3%) cases were excluded - 10/118 (8.4%) were due to medical terminations and 80/118 (67.7%) referrals either did not provide details for type of termination or the date of intracardiac injection. In 28/118 (23.7%) there was a stated history and date of intra-cardial KCl injection, however 2 of these were excluded due to a non-diagonstic PMMR. Therefore, 26 remaining cases formed our 'feticide group' and were matched with 75 'non-feticide' control cases in a ratio of 1:3 (Table 1).

Clinical indications for termination of pregnancy included 12 (46.1%) neurological, 2 (7.7%) cardiac, 2 (7.7%) abdominal, 3 (11.5%) renal, 3 (11.5%) musculoskeletal and 4 (15.5%) multisystem disorders. Within the control group, the cause of death at autopsy was unexplained in 34 (45.3%) cases (in keeping with large observational studies [12]), due to placental abnormalities in 30 (40%) cases and fetal anomalies in 11 (14.6%) cases. Placental causes of death included ascending genital infection (15/30, 50%), placental abruption (4/30, 13.3%) and those relating to placental vascular perfusion (11/30, 36.7%). Abnormal fetal findings at autopsy included intracranial haemorrhage (1/11, 9.1%), skeletal dysplasia (2/11, 18.2%), intestinal atresia (1/11, 9.1%), neonatal haemochromatosis (1/11, 9.1%), fetal alloimmune disease (1/11, 9.1%), VACTERL spectrum (1/11, 9.1%), holoprosencephaly (1/11, 9.1%), genetic copy number loss (1/11, 9.1%) and congenital cardiac disease (2/11, 18.2%).

Imaging findings:

A consensus agreement was reached for all cases. The frequency of PMMR findings in both populations are outlined in **Table 2.**

The commonest radiological findings irrespective of mode of death were pleural effusions (98/101, 97%), pericardial effusion (97/101, 96%), soft tissue chest wall oedema (98/101, 97%), ascites (93/101, 92%) and abdominal wall oedema (93/101, 92%). These features are likely to be

physiological changes which occur following death, rather than attributable to feticide or mode of death.

Regardless of laterality, a pneumothorax (6, 23.1% vs 1, 1.3%; p = 0.0010), haemothorax (11, 42.3% vs 3, 4%; p = 0.0001), pneumopericardium (8, 30.8% vs 4, 5.3%; p = 0.0018) or haemopericardium (9, 34.6% vs 0, 0%; p = 0.001) was statistically associated with a prior history of feticide **(Figures 1 – 3).**

Bilateral findings within the thorax were more common in the feticide group than the control group for all variables assessed, however the only finding showing a statistical difference between groups was the presence of haemopericardium, higher in the feticide group (6, 23.1% vs 0, 0%; p = 0.0002).

Although there was a higher proportion of feticide cases with intracardiac gas and intra-abdominal free air, blood and ascites, these were not found to be significantly different between the two groups. Within the thorax, pleural effusions, pericardial effusion and soft tissue oedema were also not significantly different between the two groups.

Diagnostic Accuracy:

A summary of the diagnostic accuracy rates for the four radiological features more commonly associated with the feticide group (i.e. pneumothorax, haemothorax, pneumopericardium, haemopericardium) are shown in **Table 3.**

The radiological finding with the highest positive predictive value was haemopericardium (100%, 95% CI 70.1 – 100%), with also the highest specificity (100%, 95% CI 95.1 - 100%). When several features were taken in combination, the presence of at least three different radiological signs (irrespective of laterality or type) also provided a PPV of 100% (95% CI 56.6 – 100%).

Control Group imaging:

Several features were more likely to be seen following feticide, but these were not exclusive to the feticide group and were seen in either alone or in combination within 6 non-terminated ‘control group’

fetuses. In two cases the cause of death was unexplained, however a pneumopericardium was seen on imaging. In one case there were bilateral small haemothoraces. Whilst the cause of death at autopsy was unexplained, this fetus was part of a twin pregnancy and, since their sibling was developing normally in utero, the deceased fetus underwent a prolonged intra-uterine retention period of 21 days.

In one further case, the fetus had not been electively terminated, however was known to have complex congenital heart disease and had undergone an intra-uterine intervention the day prior to being miscarried. The intervention (pulmonary valvular balloon dilatation) required a puncture to be made to the heart but potassium chloride was not injected. On PMMR a left sided haemothorax and pneumothorax were present **(Figure 4).**

In two cases the cause of death was due to ascending maternal genital tract infection. One of these fetuses was noted to have a pneumopericardium and the other was seen to have a right sided pneumothorax and pneumoperitoneum **(Figure 5).**

Discussion:

This study has shown that the presence of pneumothorax, haemothorax, pneumopericardium or haemopericardium on PMMR was more common in cases of feticide with high positive and negative predictive values. Almost all fetuses (irrespective of mode of death) demonstrated pleural effusions, pericardial effusions and soft tissue oedema, which are likely to represent features of post mortem change. This confirms imaging expectations [9].

The sensitivity rates for the most common radiological signs seen in feticide were low, given that their presence is relatively rare overall (i.e. not seen in all feticide cases). Nevertheless the high specificity, PPV and NPV rates imply that when identified on imaging, they are indicative of feticide with high diagnostic accuracy. Higher PPVs were also seen when more signs were present at the same time and thus where any of the four radiological features are identified, a prior history of feticide should be considered and excluded before assigning the imaging appearances to other pathological causes.

In the UK, feticide is performed by use of intracardiac potassium chloride injection as per national guidelines (usually with 1-5mls of solution)[10]. The presence of blood and/or gas in the pericardial or pleural cavities imply that needle puncture of the fetus in-utero causes trauma to the chest wall causing internal bleeding, and introduction of gas into the cardiac chambers. Larger haemothoraces or haemopericardium might be more commonly expected with larger administration volumes of potassium chloride or a more technically difficult procedure with reinsertion or movement of the needle, although we did not assess the sizes of the radiological signs and acknowledge that there is international variation in potassium chloride volume administration.

There are a variety of methods by which to induce late terminations of pregnancy which can include fetal intra-cardiac injection of other substances (such as a fibrin adhesive [13], lidocaine [14]); other routes of injection, for example intracranial injection [15] or intra-placental injection of methotrexate [16], intra-umbilical air embolism [17], intra-amniotic digoxin [18] as well as surgical methods (such as radiofrequency ablation and cord occlusion). Whilst we do not expect significant differences in imaging features with different substances injected via an intra-cardiac route, this has not been formally assessed in our study.

Despite our discovery that the four radiological signs described were more common in feticide, six cases in our control group demonstrated at least one “imaging feature” of feticide. In one case there had been in-utero fetoscopic surgery for a congenital cardiac abnormality during which we may speculate that cardiac puncture caused the observed haemo and pneumothorax (Figure 4), although we were unable to confirm this. This highlights both the importance of an accurate antenatal history and that the common feticide imaging appearances may be more related to the traumatic nature of the interventions than to a substance injected.

In another case a haemothorax was presumed to be due a prolonged in-utero retention period (i.e. maceration) in a twin pregnancy. Whilst previous studies have tried to quantify maceration changes on PMMR [19], haemothorax was not a common feature, and more research and understanding into this process may be needed. The remaining cases included those with an unexplained or infectious cause of death, mostly associated with an abnormal accumulation of gas in pleural and pericardiac

spaces rather than blood, and may be from gas-forming organisms or related to autolysis and decomposition, although the origin of this feature is difficult to prove with certainty.

The strengths of our study include the use of two independent readers to assess pre-defined imaging features and the review of imaging on 3D volumetric sequences, meaning that reformatting in different planes was possible for better characterisation of findings. Whilst our sample size is relatively small and we excluded several cases due to inaccurate or incomplete referral information, it was still large enough to yield statistically significant results.

Although our readers were blinded to the antenatal history of feticide, this may have been inferred if a significant congenital abnormality was detected. To counteract this, the majority of our feticide group underwent termination of pregnancy for antenatally diagnosed neurological anomalies, and the readers did not examine the head, thereby minimising risk of bias. Finally, we did not quantify the amounts of each imaging feature (e.g. we did not measure the size of any effusions, pneumothoraces, haemorrhages etc.). Whilst this information could be helpful to correlate with time since feticide, volume of potassium chloride or time since death (as in a previous study [20]), we only sought to determine imaging features relating to feticide.

This comprehensive review of post-mortem MRI appearances in perinatal death investigation can provide radiologists and fetal medicine clinicians with a range of evidence-based imaging features on PMMR relating to feticide. We hope that the results also aid in highlighting the importance of an accurate antenatal history (particularly of any intervention) and also possibilities for alternative differential diagnoses where features of feticide are present, but where no intervention has occurred.

Conclusion:

Feticide cases were significantly more likely to demonstrate pneumothoraces, haemothoraces, pneumopericardium or haemopericardium on imaging, regardless of laterality. Almost all fetuses had pleural effusions, pericardial effusions and soft tissue oedema and these findings are likely to represent normal post mortem change. In the presence of imaging findings of feticide and absence of

detailed antenatal history, diagnosticians should consider a previous iatrogenic event before considering other pathogenic differential diagnoses.

Figure Legends

Figure 1: T2-weighted PMMR imaging of a 32 week gestation fetus, who underwent termination of pregnancy following an antenatal diagnosis of intracranial anomalies. The imaging was acquired 3 days after delivery, with intra-uterine retention period of 5 days post-feticide. (a) Axial and (b) coronal imaging of the thorax reveals a haemopericardium (white arrows) and intracardiac gas (dashed arrow). There are also bilateral pleural effusions and a pericardial effusion.

Figure 2: T2- weighted PMMR images of a 31 week gestation fetus, who underwent termination of pregnancy following an antenatal diagnosis of absence of the corpus callosum. The imaging was acquired 9 days after delivery, with intra-uterine retention period of 1 day post-feticide. (a) Axial imaging through the thorax reveals both a right sided haemothorax (solid arrow) and left haemopericardium (asterisk). There are also bilateral pleural effusions and a small pericardial effusion. (b) A photograph of the fetus at autopsy correlates with the imaging findings of haemopericardium (solid arrow) and haemothorax (asterisk).

Figure 3: T2- weighted PMMR images of a 36 week gestation fetus, who underwent termination of pregnancy following an antenatal diagnosis of absent corpus callosum. The imaging was acquired 12 days after delivery, with intra-uterine retention period of 3 days post-feticide. Axial imaging through the (a) thorax reveals a right haemopericardium (dashed arrow), right haemothorax (solid arrow), bilateral large pleural effusions and a pericardial effusion. The axial imaging through the (b) abdomen reveals bilateral retroperitoneal haemorrhages (arrowheads).

Figure 4: T2 weighted PMMR images of a 22 week gestation fetus who suffered an intra-uterine death, with estimated intra-uterine retention period of 1 day. The imaging was acquired 12 days after delivery. The patient was diagnosed antenatally with critical pulmonary stenosis and underwent intra-

uterine pulmonary valve dilatation the day before the intra-uterine death was diagnosed. Axial imaging through the mid-thorax (a) and lung bases (b) reveal locules of gas in the pericardium (solid arrow) and left lateral chest wall (dashed arrow), with a left sided haemothorax (arrowhead). These may be attributable to fetal surgery.

Figure 5: T2 weighted PMMR images of a 27 week gestation fetus who suffered an intra-uterine death, with estimated intra-uterine retention period of 1 day. The imaging was acquired 10 days after delivery. The mother was admitted to the intensive care unit with septicaemia a day prior to the patient's delivery and fetal demise was thought to be secondary to ascending maternal infection. Axial imaging through the lung apices (a) reveal right sided locules of gas in the pleural space (solid arrow). Axial imaging of the upper abdomen (b) demonstrates free intra-peritoneal gas (dashed arrow) and gas within the hepatic veins and branches. These may be attributable to fetal sepsis.

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