Are non-invasive or minimally invasive autopsy techniques for detecting cause of death in prenates, neonates and infants accurate?

Background

Loss of a child is devastating for any parent. Sadly, prenatal, neonatal and infant mortality still occurs across the globe. Knowing why this loss has happened can provide some comfort to the parents. This is best achieved through autopsy where answers can be drawn and potential risks for future pregnancies can be identified. In addition, autopsies can help the medical and scientific community to understand the reasons why early mortality still occurs and develop new interventions to reduce the risk during pregnancy and infancy (1). However, the rate of uptake for traditional autopsies is declining (1-3). To combat this, non-invasive or minimally invasive techniques, which are currently used to support traditional autopsy in the United Kingdom (UK), could be used alone rather than as an adjunct. This review proposes to assess the accuracy of non-invasive or minimally invasive techniques in discerning the cause of death for prenatal, neonatal and infant mortality cases. To date, one Cochrane review of interventions and six systematic reviews of diagnostic test accuracy have been conducted in the field of non-invasive autopsy techniques (4-10). However, they have provided limited knowledge of the effectiveness of less than a handful of techniques and have not fully addressed these in relation to early loss of life. A clearer picture of suitable alternatives to traditional autopsy in a population whose anatomy differs substantially to childhood and later life phases, can be gained by using a wider approach to assess multiple techniques in a well-defined early life population, as proposed here. This is important to ensure that all parents who suffer the loss of a child prior to 1 year of life have access to appropriate techniques and are able to make informed decisions about the post-mortem care of their child.

Description of the population and condition

The prenatal period encompasses the time from conception to birth. The standard length is 40 weeks, although this is based upon the first day of the last normal menstruation. The neonatal period is considered as the 28 days following birth, with the first 7 days classed as early neonatal. Following on from this up to the first year of life is denoted as infancy (11).

Despite medical advances, the UK still has relatively high rates of mortality in these age ranges (12, 13). In England and Wales, the rate of infant mortality in 2018 was 3.8 per 1000 live births. Similarly, stillbirths at ≥24 weeks gestation and neonatal mortality stood at 4.0 and 2.8 per 1000 live births, respectively (14). These figures are according to the office for national statistics which record these statistics based on birth and death registrations. Currently, deaths before 24 weeks gestation do not legally require registration, therefore, the office of national statistics does not collate this data (14).

The office for national statistics uses ≥24 weeks gestation as its requirement for registering deaths as medical abortions cannot be legally performed at ≥24 weeks in the UK (15, 16). In keeping with this, the UK classifies any birth without signs of life occurring at ≥24 weeks gestation as a stillbirth. Fetal loss before this period is classified as a spontaneous abortion (17). Whilst terminology is generally consistent within the UK, it varies across the globe. The World Health Organization (WHO) state that a stillbirth is *"baby born with no signs of life at or after 28 weeks' gestation"*, whereas, the Center for Disease Control and Prevention (CDC) defines a stillbirth as *"loss of a baby after 20 weeks of pregnancy"* (18, 19). Similar discrepancies are seen in the reporting of chronological ages when birth is premature. The definition surrounding neonates is generally consistent, despite premature or full term birth, yet reports vary in the use of one adjusted year when discussing infants. One adjusted

year refers to the date at which an infant born prematurely would have turned one year old had it been born at the full gestational term of 40 weeks. This is calculated by deducting the number of weeks born premature from the infants age. Adjusted years are a way of ensuring that those born prematurely can be compared to those born at full gestation (20).

In this review, non-invasive or minimally invasive autopsy techniques will be assessed for their accuracy compared to standard practice of partial or full autopsy. The UK cut off of 24 weeks gestation will be used for consistency (15). Any loss <24 weeks gestation will be classified as prenatal mortality (21); loss occurring ≥24 weeks gestation will be classified as stillbirth (22); loss occurring ≤28 days from birth will be classified as neonatal mortality (23); loss occurring ≥29 days from birth up to one adjusted year of life will be classified as infant mortality (14). Cases where gestational age is not given, or it is not possible to distinguish between those either side of the 24 weeks cut off, will be classified separately as loss *in utero*. The pathology of prenates, neonates and infants differ from other age ranges (24). Therefore, children >1 year, adolescent and adult mortality are beyond the scope of this review.

Clinical pathway

Following a loss, autopsy may be suggested by the clinician or requested by the parents. As there is no single cause for such losses, there are multiple clinical pathways which could lead to autopsy. Loss may be detected during routine antenatal checkups, as a complication during birth or the expectant mother, neonate or infant may present with symptoms which result in loss of life. Similarly, the point at which the index tests may be offered varies according to the situation.

Role of the index test

Current guidelines from the Royal College of Pathologists state that imaging or other non-invasive or minimally invasive techniques should not be used alone. The concern surrounding this is due to the perceived accuracy of the techniques and a lack of widely available equipment and specialists. Instead, the recommendation is that these techniques be used alongside traditional autopsy to support the findings (21-23).

Antenatal ultrasound is offered as part of routine antenatal care. When abnormalities are detected and the pregnancy is lost, autopsy is used to confirm that the abnormality is the cause of death. This is generally applicable to spontaneous abortions and still births. Amniocentesis, chorionic villus sampling and fetal free DNA analysis may be offered upon detection of abnormalities during antenatal ultrasound where the pregnancy is viable. In cases of medical abortion, autopsy is used to confirm the findings of these tests. If there is a high degree of accuracy between these antenatal tests and traditional autopsy findings, then there may not be a need for traditional autopsy as a confirmation (25, 26).

Percutaneous or endoscopic biopsies are taken through the skin or alimentary canal, respectively. These techniques provide a way of acquiring samples for histology purposes and are used in clinical practice. They could be applied to post-mortem examination and would negate the need for traditional autopsy to retrieve biospecimens (27).

Placenta and umbilical cord examination are currently conducted as part of the autopsy in cases of prenatal loss, still birth and early neonatal loss, if available. As these techniques are already in use as part of traditional autopsy, it would not be difficult to employ them as an alternative strategy (28).

MRI, CT scan, *ex utero* ultrasound and verbal autopsy are sometimes offered alongside traditional autopsy. These tests are considered as the main alternatives to traditional autopsy as they are applicable to all stages of life (25, 28, 29).

Description of index test

There is a range of non-invasive or minimally invasive autopsy techniques available, many of which are used in other mainstream medical diagnostic settings. In this review, imaging techniques, verbal or visual analysis and laboratory tests will be considered.

The use of imaging techniques, either alone or in combination has been termed Virtopsy, an amalgamation of the words virtual and autopsy (25). MRI, CT scans, *ex utero* Ultrasound and antenatal Ultrasound Imaging techniques have come to light as valuable tools for assessing cause of death without the need to perform invasive techniques. Centres across the UK have invested in equipment for this purpose, yet it is not routine and must be specifically requested by the family (30-32).

Any abnormalities detected by imaging are usually followed by histology. Histology is used to identify changes in cellular, tissue and organ morphology (33). Percutaneous and endoscopic biopsy techniques have been suggested as a minimally invasive way to obtain samples, leaving minimal external damage (27). Similarly, Examining the placenta or umbilical cord and taking samples for histology can allow pathologists to ascertain cause of death without performing traditional autopsy on the child. This can be useful in situations such as infection, blood disorders or oxygen deprivation (28). Similarly, if the mother has previously requested an amniocentesis, chorionic villus sampling or the examination of fetal free DNA, the results may indicate genetic, cellular or amniotic fluid abnormalities as the cause of death (26).

In countries where autopsy proceedings are not as well established, typically Low and Middle income countries, verbal autopsies are used (34). Verbal autopsies involve discussion with family members, medical personnel and others who were in contact with the deceased prior to or at the time of death. These discussions are used to record symptoms displayed by the deceased prior to death which can be used to deduce the cause of death (34). Current verbal autopsy tools do not allow for the assessment of multimorbidity, however, this is much less applicable to prenates, neonates and infants which makes verbal autopsy a plausible non-invasive alternative to traditional autopsy (29).

In many cases, these non-invasive or minimally invasive tests can be conducted by radiographers and pathologists that are not specialised in prenatal and paediatric mortality. If specialist input is required, images and test results can be securely transferred electronically for review by a prenatal and paediatric pathologist (1).

Why it is important to do this review

Rates of autopsy have declined in prenates, neonates and infants over the last 10 years (2, 3). Numbers have been falling for some time, however, this was worsened by the Alder Hey hospital organ retention inquiry in 1999-2001 (35). Recent studies have indicated that amongst the main concerns surrounding consent for autopsy were disfigurement of the child and what would happen to the organs (1, 36). Non-invasive and minimally invasive techniques may provide a way to combat these fears as Y-incisions, cranial incisions and removal of organs for inspection would not be necessary. Non-invasive or minimally invasive techniques can be performed relatively quickly and may also reduce the autopsy time, allowing the child to be returned to the parents more rapidly

than current practice permits. These factors are particularly important in certain religions where any disfigurement or a delay in burial goes against their beliefs (1).

Autopsies in these age ranges are generally not required by law, with the exception of sudden infant deaths, and will not be referred to HM Coroners Office. Therefore, gaining consent from the parents is paramount if an autopsy is to be conducted (37). With the declining number of autopsies concerns are being raised about the implications for research, collation of medical statistics and specialist training. Without accurate cause of death, statistics cannot provide support for research proposals or indicate where researchers should focus efforts and new interventions cannot be developed. There are a limited number of prenatal and paediatric pathology specialists in the UK, reportedly far fewer than needed to fill all the available posts, and very few trainees (38). With declining numbers it may soon be unnecessary to have so many posts available but it risks the speciality becoming obsolete. If this were to occur, it could further damage the possibility of research and result in parents not receiving accurate diagnoses or advice on risk management of future pregnancies (39). A wealth of qualitative evidence supports that the availability of effective non-invasive or minimally invasive autopsy techniques would increase the number of parents willing to consent to autopsy, benefitting parents, researchers and specialists alike (1, 40). This review aims to assess the quantitative evidence around the accuracy of non-invasive or minimally invasive techniques.

There are currently seven systematic reviews in this area, however, no one of them covers the depth of index tests and gestational and chronological age ranges proposed in this review. Thayyil, *et al*. 2010, conducted a diagnostic test accuracy review of post-mortem MRI. They included studies with fetal, newborn, child and adult mortality. Of the nine included studies, 5 included data for fetal or newborns and one included data for infants (4). Dawood *et al*. 2020, conducted a systematic review of post-mortem CT and MRI in the fetal population, including 39 studies in their review. However, they only searched two databases (5). Filograna, *et al*. 2017, investigated the diagnostic potential of post-mortem MRI for identification of fetal central nervous system anomalies. They included 8 studies but the review was conducted by radiographers who only searched the PubMed-Medline database (6). Wojcieszek, *et al*. 2018, conducted a Cochrane review of interventions for investigating stillbirth and no studies were identified for inclusion (7). Eriksson, *et al*. 2017, considered the diagnostic test accuracy of imaging techniques amongst any age range, including 71 studies in the review. However, the populations were referred to as fetal, child or adult and only 8 of the 71 studies contained information regarding fetal or child loss (8). Shelmerdine, *et al*. 2019, also considered any age range for inclusion in their review of post-mortem ultrasound. They included 4 studies in the review, all of which were based on gestational losses between 11 and 42 weeks (9). Interestingly, this review was conducted by radiographers at Great Ormand Street Childrens Hospital where the technique has been offered to parents since 2017 (30). Rossi and Prefumo, 2017, considered the parallel between abnormalities detected by antenatal ultrasound and traditional autopsy findings in cases of spontaneous or medical abortion and still birth, including 19 studies (10).

With the seven systematic reviews of autopsy techniques dating as far back as 2010, there is a possibility that the body of evidence has grown. In addition to this, evidence surrounding non-image based techniques in population groups other that stillbirth have not been considered previously. This review proposes to expand upon the current reviews with a wider intervention base and distinct gestational and chronologically aged populations, in line with the Royal College of Pathologist guidelines and UK classifications.

Objectives

To determine the diagnostic accuracy of non-invasive or minimally invasive autopsy techniques for detecting cause of death in prenates, neonates and infants. Index tests will be compared to the reference standard. Comparisons will be made for the following index tests:

- MRI
- CT scanning
- Ultrasound imaging, *ex utero*
- Antenatal ultrasound
- Amniocentesis
- Chorionic villus sampling
- Fetal free DNA analysis
- Percutaneous biopsy
- Endoscopic biopsy
- Umbilical cord examination
- Placental examination
- Verbal autopsy

Methods

Methods proposed for this review are in line with the Cochrane collaborations conduct of Diagnostic Test Accuracy reviews and the PRISMA-DTA reporting standards (41, 42).

Criteria for considering studies for this review

Types of studies

All studies with a sequential design assessing any of the index tests against a reference standard will be included in this review. Studies were the index test has been performed after the reference standard will be excluded as manipulation of the body caused by the reference standard may affect the accuracy of the index tests. Given the nature of the index tests, both prospective and retrospective studies will be considered. Mixed populations will be included if it is possible to isolate the populations of interest. Abstracts will be considered if there is enough information to clearly ascertain the methods and sufficient data is available to identify cause of death detected by the index test and reference standard or summary statistics are provided. Systematic reviews will be accepted for reference checking purposes only. Qualitative evidence is beyond the scope of this review and will not be considered for inclusion.

Types of participants

All prenatal, neonatal and infant mortalities will be considered for this review. Prenatal mortality will include spontaneous abortion <24 weeks gestation and medical abortion following detection of fetal anomalies. Stillbirth will include gestational loss at ≥24 weeks. Loss *in utero* will include gestational losses where no gestational age is given or where gestational age is given as a range which straddles the 24 weeks cut off point for prenatal loss and stillbirth. Neonatal mortality will include death occurring within 28 unadjusted days of life. Infant mortality will include those who have lost their life up to one adjusted year. All causes of mortality will be included except in the case of elective abortion where a medical indicator of fetal compromise is required for inclusion in this review.

Types of index test

This review will focus on less invasive techniques for determining cause of death in this population group. Index tests carried out on individuals before the reference standard techniques will be accepted. In some circumstances, the index test may be carried out prior to loss of life. (See above 'Description of index tests' and 'Clinical pathway' for further details).

Types of reference standard

Traditional full or partial autopsy techniques will be considered as reference standards in this review. Full autopsy is the complete physical examination of the body and internal organs. Partial autopsy is the physical examination of particular areas or organs of the body.

Search methods for the identification of studies

Electronic searches

The following bibliographic databases will be searched:

- Medline
- Embase
- CINAHL
- Cochrane library
- Scopus

Other sources

The reference list of systematic reviews and the following alternative sources will be searched:

- Web of Science – Conference Proceedings Citation Index (CPCI)
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)
- Royal College of Obstetrics and gynecology
- Royal College of Midwives
- Royal College of Pediatric and Child Health

Data collection and analysis

Selection of studies

Studies identified through electronic searches and other sources will be screened by a single reviewer (HO) with 20% independently screened by a second reviewer (RS or MB). Initially, titles and abstracts will be screened against the inclusion and exclusion criteria. Full texts will be retrieved for those meeting the inclusion criteria at title and abstract stage. These full texts will then be screened against the inclusion and exclusion criteria by a single reviewer (HO) with 20% independently screened by a second reviewer (RS or MB). Those eligible for inclusion in the review at full text stage will be put forward for data extraction. Discrepancies between reviewers decisions will be discussed and resolved by mutual agreement or by a third reviewer when agreement cannot be met. Details of each stage will be reported in a PRISMA flow diagram.

Data extraction and management

Data from eligible studies will be extracted using an approved form. Data extraction will include study design, sample size, population age, type of index test and stage of delivery, reference standard, final cause of death, sensitivity and specificity, discrepancies or agreements between index

test and reference standard. All data extraction will be performed by a single reviewer (HO) and 20% will be checked by a second reviewer (RS or MB). Attempts will be made to contact authors where data is missing or unclear.

Assessment of methodological quality

Quality assessment and risk of bias will be conducted using the QUADAS-2 tool which will be tailored to this review as recommended by the tool authors (43). The assessment will be conducted by a single reviewer (HO) with 20% independently assessed by a second reviewer (RS or MB). Any discrepancies will be resolved by mutual agreement or by a third reviewer where an agreement cannot be met. Given the nature of this review, the following changes to the QUADAS-2 signalling questions are proposed:

Domain	Signalling question	Proposed change
1.q1.	*Was a consecutive or random sample of patients enrolled?*	Applicable only to studies with ≥10 participants, otherwise mark as 'Yes'
1.q2.	*Was a case-control design avoided?*	Removal of the question
1.q3.	*Did the study avoid inappropriate exclusions?*	No change
2.q1.	*Were the index test results interpreted without knowledge of the results of the reference standard?*	No change
2.q2.	*If a threshold was used, was it prespecified?*	No change
3.q1.	*Is the reference standard likely to correctly classify the target condition?*	Was the reference standard conducted by a prenatal and paediatric pathology specialist?
3.q2.	*Were the reference standard results interpreted without knowledge of the results of the index test?*	No change
4.q1.	*Was there an appropriate interval between the index test and reference standard?*	Were there any unexpected delays between the index test and reference standard?
4.q2.	*Did all patients receive the same reference standard?*	No change
4.q3.	*Were all patients included in the analysis?*	No change

The QUADAS-2 tool guidelines state that patients with suspected disease should be enrolled in a consecutive or random manner to avoid sampling bias (43). However, this review will include study designs that do not lend themselves to this type of sampling. Instead, it is proposed that the question is only applied to studies where 10 or more participants are enrolled. Studies with <10 participants should be marked as 'Yes' when answering the question. The inclusion criteria stipulate that a sequential element for all participants must be present in the study design. Therefore, the question regarding case-control designs is not applicable and should be removed. In regard to the reference standard, full or partial autopsies are considered the gold standard in attributing cause of death and are highly likely to correctly classify this. However, as the pathology of this population differs to that of other populations, conduct by a specialist will give more accurate, consistent results (24). It is proposed that the question be rephrased to reflect this. Generally, any post-mortem index test and reference standards should be conducted in a relatively short time frame so that the child

may be returned to the parents as quickly as possible. Index tests conducted in the antenatal period and the reference standard may be have highly varied intervals. The question regarding an appropriate interval should be rephrased to note any unanticipated delay between the tests. Applicability sections for each domain will remain the same, however, it is notable that in domain 3., the applicability section is not necessary as the target condition defined by the reference standard in any included study will match the review question (43).

Data synthesis strategy

Diagnostic test accuracy requires two measurements, sensitivity and specificity. This is achieved by comparing the number of true positives and false negatives derived from the index tests (44). However, given the varied nature of cause of death and anticipated small sample sizes, this may not be conceivable in the context of this review. In which case, studies in this field lend themselves to a narrative synthesis. This review will use the Synthesis without Meta-analysis (SWiM) guidelines for reporting of narrative syntheses (45). Data will be presented in a summary of findings table and, if feasible, harvest plots (46). A harvest plot will be produced for each index test, demonstrating the individual studies of the test in each age category; prenates, stillbirth, loss *in utero*, neonates and infants. The studies will be plotted according to the outcomes of each index test as a binary measure of its performance against the reference standard, categorised as non-agreeable or agreeable.

If sufficient sensitivity and specificity data is available, studies will be grouped by index test and cause of death (e.g. those who died of cardiac malformations and those who did not) in order to provide dichotomous outcomes for analysis in 2x2 tables. Analysis of 2x2 tables will result in diagnostic odds ratios and 95% confidence intervals for the index tests when determining a nominated cause of death (44). Forest plots and summary receiver operator curves (sROC) will be produced using a random-effects meta-analysis model. This will determine if the index tests are appropriate for all causes of death or a subset of diagnoses, contributing towards decisions around the suitability of index tests as alternatives to traditional autopsy. However, it is anticipated that threshold values for cause of death will not be reported. Therefore, summary curves will be estimated using a HSROC statistical model which will limit the interpretation of the plots and the clinical relevance of the findings. Separate analysis will not be conducted for each reference standard, due to the similarities between full and partial autopsy it is considered acceptable to pool the data. Production of sROC plots will be conducted using MetaDTA software and Forest plots will be produced using RevMan5 (47, 48).

Investigating heterogeneity

Age category will be used as a covariate for investigating heterogeneity. Forest plots and sROCs will be produced to visually demonstrate the sensitivity and specificity of the index tests for each cause of death in each age group. The area under the curve is representative of the tests ability to discern the diagnosis, a value between 0-1 is calculated, those closer to 1 show greater sensitivity and specificity whereas those falling near 0.5 show little or no discrimination (44). Heterogeneity is highly likely to exist in diagnostic test accuracy studies and study positioning in ROC space is not considered a good indicator. However, heterogeneity can be assessed by determining how closely each study point sits to the line of the curve (44).

Sensitivity analysis

Sensitivity analysis will be conducted by limiting to those studies with a low risk of bias and high applicability if sufficient data is available.

Assessment of reporting bias

As current guidelines are uncertain about the benefit and harms of assessing reporting bias in diagnostic test accuracy reviews and techniques for analysing funnel plots are not robust, no assessment will be undertaken (41, 49).

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