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Understanding the clinical utility of stillbirth investigations: a scoping review

Tania Marsden[1,5*], Heidi Shukralla[2], T. Yee Khong[3], Jane E. Dahlstrom[4], Vicki Flenady[1] and Jessica Sexton[1]

Abstract

Background Investigating the causes of stillbirth is crucial for both parents and healthcare providers as it helps explain why the baby died, guides clinical care in future pregnancies, and aids in developing strategies to prevent stillbirth. The usefulness or utility of investigations for stillbirth is poorly defined and unclear. As a result, protocols for investigating the causes of stillbirth are currently based on clinical consensus and fail to prioritise investigative approaches that are most effective at determining a cause of death.

Objectives The objectives of this scoping review were to identify the available evidence, key characteristics, and knowledge gaps regarding the utility of stillbirth investigations.

Search strategy An a priori protocol was implemented and included a systematic search in MEDLINE, CINAHL, EMBASE, Scopus, and Cochrane from inception until 28 May 2024.

Selection criteria Studies examining stillbirth investigations, yield, and value were included.

Data collection and analysis Data were collected using a purpose-built data extraction tool and an analysis was undertaken.

Results 57 potentially eligible studies were identified, and 34 studies (with 11,410 stillbirths) were included. Three studies examined clinical utility using a comprehensive testing protocol. Definition of utility or value of investigations varied across the studies, classification system for cause of death and investigation protocols varied. Placental pathology was reported as the most useful investigation in 65%–96% of cases, identified a cause of death in 61–71% of cases and impacting the medical management in 36% of cases (13 studies, 5,169 stillbirths). Autopsy can identify the cause of death in 36–77% of cases and provided new information in 17–26% of cases (17 studies, 4,336 stillbirths). Genetic analysis was useful in 29% of cases (seven studies, 1,886 stillbirths). One study (512 stillbirths) examined the value of investigation by presenting clinical scenario.

Conclusions This review indicates that Investigation protocols for stillbirth should include placental pathology, autopsy, and genetic testing. Future studies should address the value of tests by presenting clinical scenarios, use of a consistent definition of stillbirth, classification system and measurement of investigation value.

Keywords Stillbirths, Yield, Value, Quality, Investigation, Tests, Autopsy, Placenta, Genetics

*Correspondence:
Tania Marsden
t.marsden@uq.net.au
Full list of author information is available at the end of the article

Introduction

Stillbirth is devastating and impacts over two million families globally each year, with a current stillbirth rate of 13.9 stillbirths per 1000 total births [1, 2]. In Australia, 17% of stillbirths are classified as unexplained, with up to 36% unexplained at term and a stillbirth rate of 7.7 per 1000 total births (using the definition of stillbirths at ≥ 20 weeks' gestation and/or ≥ 400 g birthweight) [3]. Globally, the number and rate of stillbirths can function as indicators of progress in reducing stillbirths [4]. Due to mixed availability and uptake of investigations, data collection, variation of classifications systems and protocols in use, many stillbirths remain unexplained [4, 5].

It is important for parents and clinicians to investigate the causes of stillbirth to help understand why the baby died, to inform clinical care in subsequent pregnancies, and to develop prevention strategies to decrease stillbirth rates [6]. When a cause of death is not identified in a stillbirth, this can cause additional distress and negatively impact the grieving process for families struggling to understand the reasons for their loss. The process of counselling families on stillbirth investigations can lead to an increase in emotional distress to families and families may regret the decisions they made [7]. The ability of clinicians to counsel families on the investigations that can provide most value in their individual circumstance, in a sensitive and appropriate manner, cannot be underestimated [8]. Clinicians' knowledge, education, training on the counselling process and on the investigations has been shown to impact the family's decision-making process [7, 8].

Stillbirth places a heavy psychological and economic burden on families and health systems, which may be exacerbated by the rising costs of investigations [2]. The costs associated with investigations are often absorbed by health services or families or both, which results in many families facing significant out-of-pocket costs [9]. Healthcare service providers might not provide a complete range of investigations due to financial constraints, which results in incomplete assessments [10]. The absence of a universally accepted investigation protocol will continue to hinder stillbirth prevention, especially where numerous classification systems are in use [11]. These challenges are underpinned by the lack of clarity around which investigations are most likely to confirm or exclude a cause of death [6, 12].

Defining and understanding the utility and value of investigations may support the development of a standardised protocol and help provides and parents alike prioritise investigations for stillbirth.

In literature and practice, many terms are used to describe the usefulness of investigations and include "value", "usefulness", "clinical utility", and "yield [13]. Understanding the evidence around which investigations for stillbirth are most useful and standardising terminology would provide decision support to families and clinicians, establish evidence for future clinical practice guidelines on recommended investigations, and inform decisions around resource allocation and service delivery priorities among health systems. Existing scoping reviews have focused on maternal and perinatal death surveillance and response policies [14, 15], needs of healthcare professionals [16], and causes of stillbirth [17]. A crucial gap of these reviews is addressing the characteristics and utility of individual investigations used to determine the cause of a stillbirth.

The aim of this scoping review was to summarise evidence surrounding the characteristics and utility of investigations for stillbirths. The results of this scoping review are expected to answer clinically meaningful questions, inform practice, clarify concepts and definitions, identify and analyse existing knowledge, establish a framework for investigation protocols and to inform future research.

Methods

Search strategy

The search strategy used a combination of MeSH terms "Stillbirths", "Perinatal Death", "Fetal death" and keywords, including Stillbirth AND Investigation OR test AND yield OR value OR quality. The search strategy was applied to MEDLINE, CINAHL, EMBASE, Scopus, and Cochrane 28 May 2024 for all indexed entries. This review focused on peer-reviewed articles and excluded animal and non-English studies. A detailed description of the search is presented in Additional File 1.

The research questions included: 'What investigations are being used to determine the causes of stillbirth?'; 'What is the definition of stillbirth?'; What is the definition of value?'; 'Do any factors affect the stillbirth investigation?' and 'What do we know about stillbirth investigations and how to they support or hinder our ability to correctly determine the cause or causes of a stillbirth?'.

Study eligibility and selection

Eligible studies included published clinical trials and cohort studies that report the yield or value of investigations in stillbirths. Non-English language publications, animal studies, grey literature, and other formats were not eligible. Screening and selection of eligible studies and data extraction was performed by two independent reviewers (TM, HS) via a three-step screen process using Covidence and documented via a PRISMA-ScR flow diagram (Fig. 1). Endnote citation management software was used to manage citations while screening and extraction took place using Covidence [18, 19]. The following

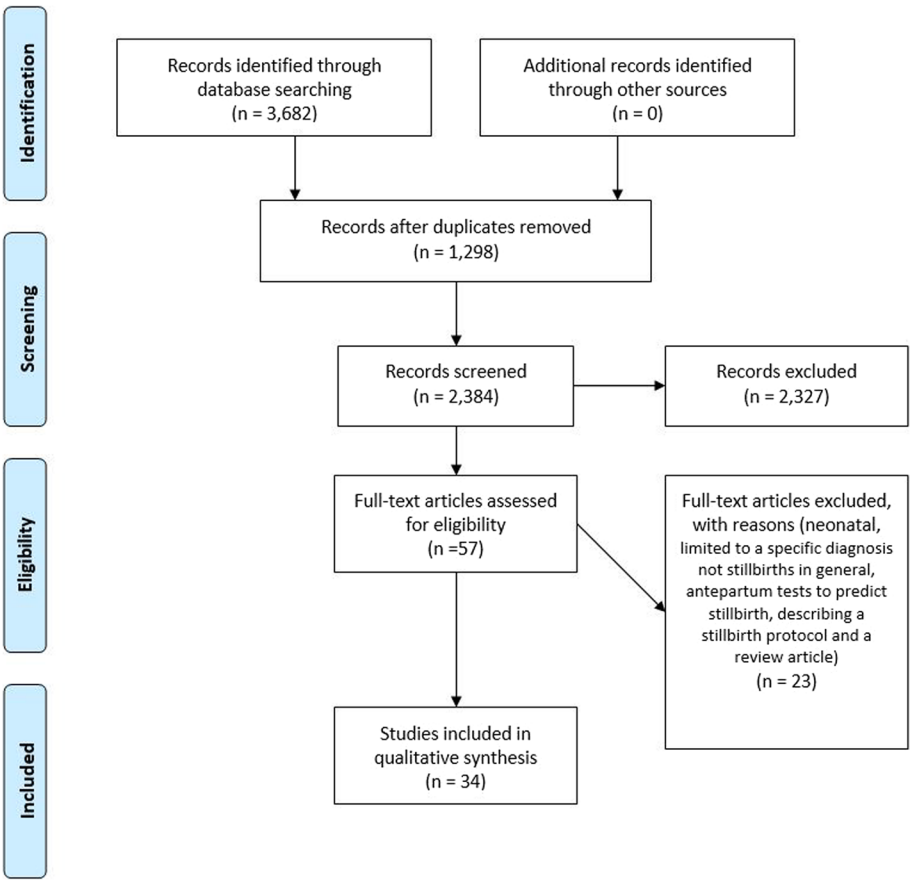

Fig. 1 PRISMA flow diagram for scoping review search and screening results

criteria were used to screen abstracts for relevance: (1) study type and (2) inclusion of stillbirth and yield or value of investigations. Stillbirths were defined as stillbirths according to the local setting. Yield or value was defined according to the local settings.

Data extraction and analysis

Data extraction was performed using a purpose-built data extraction tool based on the PRISMA-ScR checklist by two independent reviewers (TM, HS). Table 1

Table 1 Data extracted from included studies

1. Definition of stillbirth
2. Country setting
3. Study design (including use of a gold standard)
4. Investigations assessed and type
5. Number of participants
6. Measure used to assess the contribution of an investigation to the assignment of cause of death
7. How an assessment of investigation results was performed
8. Classification system used for assigning cause of death
9. How and whether a quality assessment of the investigations took place
10. Key characteristics of the study noted by the authors
11. Clinical threshold or definition used to determine the value of an investigation
12. How valuable were the investigations
13. Factors that may impact the clinical utility of investigations

summarises the data that were extracted. A descriptive summary analysis of findings was also undertaken.

Study data can be made available upon request.

Results

Literature search and study selection

Among 3,682 studies, 57 studies were eligible for full text review. A further 23 studies were excluded due to failing to meet the selection criteria. A total of 34 studies were included and represent 11,410 stillbirths from 14 countries.

Study characteristics

Of the 34 eligible studies, 10 were prospective cohort studies [20–29], 23 retrospective cohorts [12, 21, 30–50], and one was not defined (Table 2) [51]. Twenty-nine studies (85%) were undertaken in high-income countries (HIC): United Kingdom (26.5%), The Netherlands (5.9%), United States of America (29.4%), Saudi Arabia (2.9%), Norway (2.9%), Sweden (2.9%), Australia (2.9%), Ireland (5.8%), Denmark (2.9%) and Spain (2.9%) [12, 20–27, 30, 31, 34–37, 39–42, 44–57]. Three studies (9%) were undertaken in middle income countries: India (6%) and Turkey (3%) [28, 33, 43, 58]. Two studies (5.8%) were undertaken in low-income countries: Kazakhstan (2.9%) and Tunisia (2.9%) [29, 32].

Fifteen studies provided a stillbirth definition that was based on gestational age, birthweight, and/or additional clinical characteristic (e.g., APGAR score) [12, 21, 23, 25, 28, 29, 33, 37, 39, 45–48, 51, 56]. Stillbirths were most frequently defined as occurring between 20–22 weeks gestation and/or > 500g birthweight. Three studies referred to all gestations (from 13 to 43 weeks)[33, 43, 56] and two studies used over 28 weeks as the definition [46, 51]. Seventeen studies did not define a gestational age threshold for stillbirth [20, 22, 24, 26, 27, 30, 31, 34–36, 38, 40–42, 44, 49, 50].

The was no single or consistent definition of yield or value applied among all selected studies. The most common definition was 'the contribution to identification of cause of death' (8 studies) [12, 22, 23, 37, 39, 42, 43, 56]. Seven studies applied the definition of results [25, 28, 35, 41, 45, 48, 50] and five studies used the concordance between clinical and autopsy diagnosis [34, 36, 38, 47, 51]. Twelve studies used a blinded panel of assessors [12, 20, 21, 23, 28, 30, 31, 33, 39, 46, 47, 56].

Thirteen studies representing 4,317 stillbirths considered the value of investigations (Table 3). All 13 studies assessed autopsy examination in conjunction with other investigations [12, 21–23, 34, 37, 38, 40, 44, 47, 50, 56]. Two studies only assessed autopsy [21, 44] and the type of autopsy (full, limited, or external) was not described in any study. Three studies (2,282 stillbirths) examined the value of a comprehensive testing protocol and each individual investigation within that protocol [12, 23, 37]. The description of autopsy examination by the investigators ranged from a gross internal and external examination of the fetus and placenta to listing ancillary investigations performed including radiography, microbiology, viral studies, and genetic analysis. 12 studies (3,735 stillbirths) compared the value of diagnostic techniques in radiography, genetic analysis, and minimally invasive autopsy [12, 21–23, 34, 37, 38, 40, 44, 47, 50, 56].

Nine studies representing 3,082 stillbirths described the classification system for cause of death used in the study. This included Wigglesworth [21, 50], Tulip [32, 39], Initial causes of death [22, 23] and International Classification of disease- Perinatal mortality (ICD-PM) [29]. One study used and described their own criteria [46]. In eleven studies, the classification system was not relevant to the study. The remaining 14 studies did not describe if a classification system was used.

Yield of investigations

Low middle income countries (LMIC)

Three studies (1432 stillbirths) were conducted in middle income countries [28, 33, 43]. In a study of 486 stillbirths from Turkey, autopsy was found to identify the cause of death in 193 cases (39.7%) [43]. Two studies were performed in India. One study of 903 stillbirths, autopsy identified a definitive cause of death (COD) in 77% of cases [33]. Another study of 43 stillbirths, compared post-mortem magnetic resonance imaging (PMMR) and minimally invasive autopsy (MIA) to autopsy and found agreement in 81% of cases [28].

Two studies (162 stillbirths) were conducted in low income [29, 32]. In a study of 147 stillbirths from Tunisia, the value of placental pathology was reviewed. The cause of death according to the Tulip system was found in placental causes 89 (61%), maternofetal causes 23 (16%), fetal causes 14 (9%), multiple causes 13 (9%), and unknown 8 (5%) [32]. In a study of 15 stillbirths from Kazakhstan, MIA was compared to conventional autopsy (CA) and found to be concordant in 83% of cases [29].

High income countries

Radiography

Two studies (2,771 stillbirths) assessed radiographic images non-blinded to determine the role of radiography in determining cause of death in stillbirths [30, 49]. This evidence suggests radiographic images alone can identify the cause of death in up to 12% of stillbirths, with radiographs critically contributing to the diagnosis in 10% of cases [30, 49]. Clinical indications for radiography were present in up to 55% of cases. Misleading or 'unhelpful' radiographic findings were observed in 6% cases and

Table 2 Study characteristics of clinical utility of investigations and stillbirths

Study	*Country*	*Setting*	*Income setting*	*Study design*	*Study population of stillbirths*	*Cause of death Classification system*	*Investigation*	*Clinical Utility*	*Results*
Arthurs, 2014 [30]	London, United Kingdom	Single institute	High	Retrospective cohort	739	NA	Radiography	Diagnostic usefulness from 0–4	Babygram 0 = 665, 1 = 33, 2 = 18. 3 = 20, 4 = 3
Ashwin, 2017 [31]	London, United Kingdom	Two institutes	High	Retrospective cohort	201	NA	Conventional autopsy and MRI (PMMR)	Diagnostic, Non-diagnostic	143 diagnostic results on conventional autopsy. 123 on PMMR (91.58%) Autopsy non-diagnostic in 6 cases, PMMR diagnostic. PMMR non diagnostic in 12 cases, autopsy diagnostic. Diagnostic agreement 89.6%
Breeze, 2011 [20]	England, United Kingdom	Single institute	High	Prospective cohort	44	NA	MIA, conventional autopsy (CA)	MIA vs Conventional Autopsy	MIA equivalent to CA in 32/44 (72.7%). CA superior to MIA in 10 cases (22.7%). MIA superior to CA in 2 cases (4.5%)
Cartlidge, 1995 [21]	Wales, United Kingdom	Nation	High	Prospective cohort	232	Wigglesworth	Autopsy	How often clinical pathological classification was altered by necropsy	New information 60 (26%), 42 provided COD (18%), 10 (4%) implications for future pregnancies
Darouich, 2020* [32]	Tunisia	Single institute	Low	Retrospective cohort	147	Tulip	Placental pathology	Value of placental in cause of death	Placental causes 89 (61%), maternofetal causes 23 (16%), fetal causes 14 (9%), multiple causes 13 (9%), unknown 8 (5%)
Puri, 2016* [33]	India	Single institute	Middle	Retrospective cohort	903	NR	Autopsy, placental pathology	Cause of fetal abnormality	Definitive COD identified in 77%

Table 2 (Continued)

Study	*Country*	*Setting*	*Income setting*	*Study design*	*Study population of stillbirths*	*Cause of death Classification system*	*Investigation*	*Clinical Utility*	*Results*
Faye-Petersen, 1999 [34]	Alabama, United States of America	Single institute	High	Retrospective cohort	139	NR	Autopsy, placental pathology	Clinical diagnosis and autopsy findings	Identified COD in 130 (94%), 48 (34.5%) were abnormal, 91 (65.5) structurally normal
Gau, 1977 [51]	London, United Kingdom	Single institute	High	ND	78	NR	Autopsy	Concordance between clinical diagnosis and autopsy diagnosis	59 (75.6%) complete correlation, 10 cases additional information, 9 cases autopsy diagnosis radically different from clinical diagnosis
Hutchinson, 2019 [35]	London, United Kingdom	Single institute	High	Retrospective cohort	93	NA	MIA	Rate of tissue sampling success	Completed successfully in 91/93 (97.8%)
Hagerstrand, 1993 [36]	Sweden	Single institute	High	Retrospective cohort	104	NR	Autopsy, placental pathology	Concordance between clinical diagnosis and autopsy diagnosis	56 cases had clinical diagnosis, 50 confirmed at autopsy, 3 not confirmed. COD found at autopsy 24/104, not found 24/104, additional findings, 64/104
Incerpi, 1998 [37]	California, United States of America	Single institute	High	Retrospective cohort	745	NR	All	Contribution to cause of death	Explained 198. Unexplained 268
Killeen, 2004 [38]	Ireland	Single institute	High	Retrospective cohort	130	NR	Autopsy, placental pathology	Concordance between clinical diagnosis and autopsy diagnosis	Diagnostic 76 (36%), Confirmative 108 (51%), unexplained 29(13%), Additional 38 (18%), Recurrence risk 24(11%),
Korteweg, 2008 [39]	The Netherlands	Multi-centre institute	High	Retrospective cohort	508	Tulip	Cytogenetic analysis	Contribution to cause of death	Valuable in determining COD 140 (18.7%), established COD 21 (2.8%), COD excluded 54 (7.2%)

Table 2 (Continued)

Study	*Country*	*Setting*	*Income setting*	*Study design*	*Study population of stillbirths*	*Cause of death Classification system*	*Investigation*	*Clinical Utility*	*Results*
Korteweg, 2012 [12]	The Netherlands	Multi-centre institute	High	Prospective cohort	1025	Tulip	All	Contribution to cause of death	Placental pathology (95.7%), Autopsy (72.6%), cytogenetics (29%), FMH (11.9%)
Larsen, 1999 [40]	Denmark	Single institute	High	Retrospective cohort	341	NR	Autopsy and placental pathology	Comparison of placental findings with autopsy findings	Conclusive 6 (1.7%), Important 120 (35.2%), Supplementary 24 (7.1%), Doubtful 27 (7.9%), Non-contributory 164 (48.1%)
Marques, 2020 [41]	Spain	Single institute	High	Retrospective cohort	136	NA	Cytogenetic analysis	Success rate of test	Karyotype successful in 65 (66%). Amniotic fluid (83%), Placental biopsy (78%). Conventional microarray 100% successful regardless of sampled tissue
Miller, 2016 [22]	Illinois, United States of America	Single institute	High	Prospective cohort	144	Initial causes of fetal death (INCODE)	Autopsy, placental pathology	Contribution to cause of death	Step 1—probable COD 35 (24.3%). Step 2—probable COD 88 (61.1%). Step 3-probable COD 78 (74.3%)
Mueller, 1983 [42]	Seattle, United States of America	Single institute	High	Retrospective cohort	124	NA	Autopsy and ancillary investigations	Usefulness of test to determine cause of death	Not described
Nese, 2018* [43]	Turkey	Single institute	Middle	Retrospective cohort	486	NR	Autopsy, placental pathology	Contribution to cause of death	Autopsy valuable in 193 (39.7%)

Table 2 (Continued)

Study	*Country*	*Setting*	*Income setting*	*Study design*	*Study population of stillbirths*	*Cause of death Classification system*	*Investigation*	*Clinical Utility*	*Results*
Page, 2017 [23]	United States of America	Multi-centre institute	High	Prospective cohort	512	Initial causes of fetal death (INCODE)	All	Usefulness of test to determine cause of death	Autopsy identified Probable 312 (60.9%), Possible 78 (15.2%). More than one probable or possible 161 (31.4%). 122 no probable or possible COD; 105 (20.5%) had condition present and 17(3.3%) had no cause
Porter, 1987 [44]	Oxford, United Kingdom	ND	High	Retrospective cohort	300	NR	Autopsy	Clinical diagnosis and autopsy findings	60 (40%) complete agreement, additional information in 51 (34%) and disagreement in 39 (26%)
Raca, 2009 [45]	Wisconsin, United States of America	Single institute	High	Retrospective cohort	15	NA	Microarray	Results obtained	Abnormalities detected in 2 (13%)
Rasmussen, 2003 [46]	Norway	Two institutes	High	Retrospective cohort	325	Own criteria	Autopsy and placental pathology	Registry data versus clinical and pathology records	Unexplained according to 1 clinical data 129 (40%), 2-clinical/autopsy data 110 (34%) and 3-registry data 112 (35%)
Reddy, 2012 [24]	United States of America	Multi-centre institute	High	Prospective cohort	532	NA	Cytogenetic analysis	ND	Microarray yielded results more than karyotype 465 (87.4%) to 375 (70.5%)
Rosenfeld, 2015 [25]	Washington State, United States of America	Multi-centre institute	High	Prospective cohort	515	NA	Genetic testing	Results obtained	2004–2011 293 specimens had aCGH. 2012 to 2013 242 microarray, 20 (8.3%) failed to yield results Clinical significant abnormalities were identified in 64 (12.8%) cases

Table 2 (Continued)

Study	*Country*	*Setting*	*Income setting*	*Study design*	*Study population of stillbirths*	*Cause of death Classification system*	*Investigation*	*Clinical Utility*	*Results*
Saller, 1995 [47]	Rhode Island, United States of America	Single institute	High	Retrospective cohort	124	NR	Autopsy and placental pathology	Concordance between clinical and autopsy diagnosis	Confirm 52 (41.9%), change 34 (27.4%), add 8 (6.5%), inconclusive 30 (24.2), not done 44 (26.2%)
Sebire, 2012 [26]	London, United Kingdom	Single institute	High	Prospective cohort	10	NA	MIA, conventional autopsy	MIA v standard open autopsy	Adequate visualisation of most internal organs. Retroperitoneal structures such as pancreas and adrenals not seen. Marked autolysis made optimal visualisation difficult
Shamseldin, 2017 [27]	Saudi Arabia	Single institute	High	Prospective cohort	44	NA	Genetic analysis	Genomic analysis	Variants that potentially explain the lethal phenotype were identified in 84% of families, however only in 50% of families were the authors able to class them as pathogenic or likely pathogenic. The remaining 34% were classified as variants of unknown significance
Shruthi, 2018 [28]	India	Single institute	Middle	Prospective cohort	43	NR	Autopsy and MRI	Results obtained	35 (81.4%) agreement between conventional and virtual autopsy
Smith, 1990 [48]	Australia	Multi-centre institute	High	Retrospective cohort	136	NR	Cytogenetic analysis	Results obtained	Results obtained in 83 (61%)

Table 2 (Continued)

Study	*Country*	*Setting*	*Income setting*	*Study design*	*Study population of stillbirths*	*Cause of death Classification system*	*Investigation*	*Clinical Utility*	*Results*
Swenson, 2014 [49]	Wisconsin, United States of America	County	High	Retrospective cohort	2032	NR	Radiography	Role radiograph played in determining cause of death	235 (45.4%) Diagnostic. (31 critical, 204 confirmed) 196 helpful, 15 not helpful, 57 incidental, 15 misleading
Tanko, 2021 [29]	Kazakhstan	Single institute	Low	Prospective	15	ICD-10 (ICD-PM)	MIA	MIA vs Conventional Autopsy	MIA concordance with CA in 83.3%
Thornton, 1998 [50]	Ireland	Single institute	High	Retrospective cohort	174	Wigglesworth	Autopsy and placental pathology	Information obtained	Diagnostic 49 (28.2%), confirmatory 75 (43.1%), additional 23 (13.2%), none 27 (15.5%),
Vujanic 1995 [56]	Wales, United Kingdom	Multi-centre institute	High	Retrospective cohort	314	NR	Autopsy and placental pathology	Contribution to cause of death	52 (17%) new information, 27 (9%) additional, 36 (11%) audit, 199 (63%) no new information

NA Not applicable, *NR* Not reported, *Stillbirths including gestational ages from 14 weeks to one month

Table 3 Study characteristics of 13 studies which examined yield of investigations in stillbirths

Investigations assessed	*Study*	*Study population*	*Clinical Utility*	*Investigation*	*Results*
Comprehensive protocol	Page, 2017	512	Usefulness of test to determine cause of death	Autopsy, placental pathology, cytogenetics and antiphospholipid antibodies	Autopsy identified Probable 312 (60.9%), Possible 78 (15.2%). More than one probable or possible 161 (31.4%). 122 no probable or possible COD; 105 (20.5%) had condition present and 17(3.3%) had no cause
Comprehensive protocol	Korteweg, 2012	1025	Contribution to cause of death	Autopsy, placental examination, cytogenetics analysis, FMH	Placental pathology (95.7%), Autopsy (72.6%), cytogenetics (29%), FMH (11.9%)
Comprehensive protocol	Incerpi, 1998	745	Contribution to cause of death	Autopsy, placenta, feto-maternal haemorrhage	Explained 198. Unexplained 268
Autopsy	Cartlidge, 1995	232	How often clinical pathological classification was altered by necropsy	Autopsy	New information 60 (26%), 42 provided COD (18%), 10 (4%) implications for future pregnancies
Autopsy	Porter, 1987	300	Clinical diagnosis and autopsy findings	Autopsy	60 (40%) complete agreement, additional information in 51 (34%) and disagreement in 39 (26%)
Placental pathology	Darouich, 2020	147	Contribution to cause of death	Placental pathology	Placental causes 89 (61%), maternofetal causes 23 (16%), fetal causes 14 (9%), multiple causes 13 (9%), unknown 8 (5%)
Autopsy and placental pathology	Miller, 2016	144	Contribution to cause of death	Autopsy and placental pathology	Step 1—probable COD 35 (24.3%). Step 2—probable COD 88 (61.1%). Step 3-probable COD 78 (74.3%)
Autopsy and placental pathology	Killeen, 2004	130	Concordance between clinical diagnosis and autopsy diagnosis	Autopsy	Diagnostic 76 (36%), Confirmative 108 (51%), unexplained 29(13%), Additional 38 (18%), Recurrence risk 24(11%),
Autopsy and placental pathology	Faye-Petersen, 1999	139	Clinical diagnosis and autopsy findings	Autopsy	Identified COD in 130 (94%), 48 (34.5%) were abnormal, 91 (65.5) structurally normal
Autopsy and placental pathology	Larsen, 1999	341	Comparison of placental findings with autopsy findings	Autopsy and placental pathology	Conclusive 6 (1.7%), Important 120 (35.2%), Supplementary 24 (7.1%), Doubtful 27 (7.9%), Non-contributory 164 (48.1%)
Autopsy and placental pathology	Thornton, 1998	174	Information obtained	Autopsy and placental pathology	Diagnostic 49 (28.2%), Confirmatory 75 (43.1%), additional 23 (13.2%), none 27 (15.5%),
Autopsy and placental pathology	Saller, 1995	124	Concordance between clinical and autopsy diagnosis	Autopsy and placental pathology	Confirm 52 (41.9%), change 34 (27.4%), add 8 (6.5%), inconclusive 30 (24.2), not done 44 (26.2%)
Autopsy and placental pathology	Vujanic 1995	314	Contribution to cause of death	Autopsy	52 (17%) new information, 27 (9%) additional, 36 (11%) audit, 199 (63%) no new information

explained by post mortem artifacts or poor positioning [49].

Genetic analysis

Seven studies (1,886 stillbirths) examined genetic analysis independently and represented a range of diagnostic methodologies [24, 25, 27, 39, 41, 45, 48].

Three studies representing 1,183 stillbirths (defined as greater than 20 weeks gestation in one study and not defined in two studies) examined microarray, karyotyping, and quantitative fluorescent polymerase chain reaction (QF-PCR) methods [24, 25, 41].

Genetic analysis performed during pregnancy (amniocentesis, chorionic villus sampling or preimplantation diagnosis) yielded results in 100% of cases [39]. Genetic analysis performed after death yielded results in 39.7–100% of cases [39, 41]. Microarray was found to be a more sensitive technique compared to karyotyping with a success rate of 87–100%. Karyotyping yielded results in 60–70.5% of cases. Karyotyping is impacted by tissue type and maceration status. Karyotyping showed variation in sampled tissue with the results obtained from amniotic fluid (83%), placental tissue (60–78%), fetal skin (13–34%), umbilical cord (32.1%), and fetal blood (6.3%) [41]. Non-macerated stillbirths yielded significantly more results 58.5% cases compared to 36.6% in macerated stillbirths [39, 48].

Autopsy and placenta

Twenty-three studies (4,775 stillbirths) assessed autopsy and/or placental examination [20–22, 26, 28, 29, 31–36, 38, 40, 42–44, 46, 47, 50, 51, 56, 59]. The assessments included autopsy, MIA and placental pathology. The description of autopsy examination by the investigators ranged from a gross internal and external examination of stillbirth and placenta to listing ancillary investigations performed including radiography, microbiology, viral studies, and genetic analysis.

There were six studies (406 stillbirths) that compared PMMR and MIA to gold standard autopsy examination [20, 28, 29, 26, 31, 35]. PMMR and MIA was found to be concordant with conventional autopsy in 72.5–81.4% of cases [20, 28]. The diagnostic accuracy of sensitivity, specificity, positive and negative predictive values of PMMR and MIA was very high indicating it may be an acceptable alternative to conventional autopsy [28]. PMMR and MIA It was superior to autopsy in cases with intracranial abnormalities [20, 31, 36]. PMMR and MIA was not diagnostic in cases where there was organ anomalies and infection [31].

There were 17 studies (4,336 stillbirths) that assessed autopsy examination. Autopsy was found to be a valuable investigation in 36–77% of cases [33, 34, 43]. It provided new information in 7–26% of cases that changed the cause of death in 9% of cases and impacting future pregnancies in 4% of cases [36, 38, 44, 47]. In one study the autopsy provided new information in 26% (60/232) compared to the clinic-pathological summary, disclosing the cause of death in 18% (42/232) and impacting future pregnancies in 4% (10/232) [21]. Many studies reviewed the correlation between autopsy and clinical diagnosis [36, 38, 44, 47]. In a study of 104 stillbirths, complete correlation was observed in 75.6% (59/104), with additional information obtained in 10% (10/104) and the autopsy changed the diagnosis in 9% (9/104) [36]. In a study of 124 stillbirth, the autopsy confirmed the clinical diagnosis in 42% (52/124), was different in 27% (34/124) and provided additional information in 7% (6/124) [47].

Thirteen studies (5,169 stillbirths) assessed placental pathology. Placental pathology is the most useful investigation in 65% to 96% of cases [12, 22, 23]. This investigation can identify a cause of death in 61–71% of case and change the medical management in subsequent pregnancies in 36% of cases [22, 32, 37].

Comprehensive protocol

Three studies (2,282 stillbirths) examined a comprehensive stillbirth investigation protocol including all ancillary investigations [12, 23, 37]. A comprehensive protocol involved a detailed review of maternal and obstetric history, maternal laboratory investigations for infection (cytomegalovirus, parvovirus, toxoplasmosis, syphilis), acquired thrombophilia, and fetomaternal haemorrhage, external examination of fetus including radiography, microbiology, histological sampling, genetic analysis, and placental examination including microbiology and genetic analysis.

Incerpi et al. in 1998 studied 745 stillbirths and identified placental pathology and autopsy as the most valuable investigation defined as contributing to cause of death [37]. When an autopsy was performed, the number of unexplained fetal deaths was reduced from 44 to 31%. In this study a specific placental abnormality was identified in 30% (169/529) of placentas examined. They found several routinely performed tests to yield little definitive information. This included antinuclear antibody testing 13% (55 of 419), Kleihauer-Betke tests 5% (11 of 219) and screening for congenital infections 5% (28 of 520) (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and other viruses).

Korteweg et al. studied 1025 fetal deaths and found the most valuable investigation in establishing or excluding a cause of death to be placental pathology (95.7%), fetal autopsy (72.6%), and genetic analysis (29%) according to determination of cause of death [12]. Investigations found abnormal results in 11.9% of Kleihauer-Betke,

51.5% autopsies, 89.2% of placental pathology and 11.9% of cytogenetic analysis.

A study by Page et al. representing 512 stillbirths measured value by the usefulness of the investigation in establishing a cause of death. The most valuable investigations were placental pathology (64.6%), autopsy examination (42.4%) and genetic analysis (11.9%) [23].

The autopsy was most useful in early gestations and the placenta became more useful with increasing gestational age. [23]. This is the only study to examine the value according to gestation and presenting clinical scenario.

Discussion

Main findings

This is the first scoping review to define and analyse the clinical utility of investigations in stillbirths. Current investigation protocols are based on clinician consensus and limited evidence on the clinical utility [6, 12]. The most useful investigations in stillbirths observed are placental pathology, autopsy, and genetic testing. All eligible studies agreed that autopsy is a valuable investigation and provides information on the cause of death in up to 84% of cases, resulting in a change in the cause of death in up to 26% of cases. Despite the completion of a comprehensive investigation protocol, 15–60% of stillbirths remain unexplained [60]. Many stillbirths in high income countries (HIC) do not undergo full investigation due to lack of clinician awareness, availability of recommended tests, or concerns from the family. In LMIC where stillbirths are underreported, the cause of death is often determined by clinical judgement in absence of any other pathology tools or resources [5]. This highlights key gaps in our understanding of the underlying causes of stillbirth and critical need for improving the availability of resources and investigations to accurately determine a cause of death across all settings.

Three studies examined a comprehensive stillbirth investigation protocol and concluded that existing protocols follow either a comprehensive suite of investigations or apply a modified, selective approach. Page et al. [23] developed an approach to stillbirth investigation based on clinical scenario [23]. This was the first and only study to consider clinical scenario and gestational age. The autopsy was most useful in early gestations and the placenta became more useful with increasing gestational age [23]. Future studies should consider clinical scenario, gestation, and maceration status of the tissue.

In the Page et al. study, all stillbirths had all investigations performed as part of a stillbirth protocol [27]. This is in comparison to Incerpi et al. and Korteweg et al. who had recommended tests that were at the clinician's discretion [12, 37]. Korteweg et al. found how often the tests were performed varied significantly from 98.7% for placental pathology to 3.2% for expert external fetal examination [12]. Despite the stillbirths in these studies undergoing a comprehensive investigation protocol, 16% to 36% of stillbirths remained unexplained. Whilst a comprehensive investigation protocol can provide more information to determine the cause of death, it does not in many cases, indicating a wider issue in stillbirth investigation, prevention, cost and management for this reason.

One study used a stepwise selective approach to determine the cause of death and to quality the contribution of placental examination and autopsy in identifying the cause of death [22]. This is the first and only study to consider a step wise approach to determining the cause of death. Miller et al. found after the clinical history and laboratory investigations were reviewed a cause of death was probable in 24% of cases. After the placental examination was performed, a cause of death was identified in 61% of cases and changed clinical management in 36% of cases. The further addition of the autopsy report identified a cause of death in 74% of cases and led to additional clinical management in 6% of cases.

Imaging has been widely reported in stillbirths with baby grams being useful in cases of skeletal abnormalities and more recent articles focusing on the potential of MIA and PMMR. This review found PMMR and MIA to be concordant with conventional autopsy in 72.5–81.4% of cases with the diagnostic accuracy of sensitivity, specificity to be very high [20, 28]. Imaging combined with less invasive autopsy has been shown to be more acceptable to families who would normally decline conventional autopsy [61].

A common observation in this review is the inconsistent use of investigations and lack of clarity around the availability of investigators or resources that could explain under-investigated stillbirths. Differences in investigations were observed at all levels, most notably across countries, institutions, and cases. While the studies in this review did not identify a reason for excluding or missing investigations, a key driver may be availability of resources due to cost. An Australian study found an average of $4200 was spent on investigations for each stillbirth with 76% of stillbirths having five to eight core investigations performed [9]. According to this study, the most expensive investigations were autopsy and genetic analysis. In Australia, many investigations are not funded under the Medicare Benefits Scheme (MBS) for stillbirths, with health departments or services funding a portion of the cost, and not the true costs of the investigation. The funding of these investigations impacts the availability of investigations and may be cost-prohibitive to services in low resource settings or where the cost burden is shifted to the families directly. This is consistent

with the United Kingdom, where autopsy is not funded by the National Health Service (NHS) [62]. Academic institutions in the United States often receive grants to assist with costs, though families often pay significant out-of-pocket expenses for investigations [63].

There have been significant developments in antenatal care and diagnostic pathology techniques in the past two decades leading to better diagnostic rates and fetal and maternal outcomes. This is due to technological advancements in automation, reducing the cost of techniques and investigations and for the investigation to be more acceptable to families and clinicians [39]. Recent studies have shown microarray analysis to be superior to karyotype when performing genetic analysis [25, 41]. The diagnostic outcome of magnetic resonance imaging (MRI) has improved with the advances in technology leading to the possibility of minimal invasive techniques including autopsy [31, 35].

This review found only two studies that have considered the quality of an autopsy examination in the last 20 years, despite significant diagnostic changes within this period with advances in technology [43, 52]. Wright et al. found a strong association between the amount of information in a report and the quality of the interpretation [57]. Reports that complied with the RCPath guidelines observed an adequate summary in 69% of cases compared with 30% of those that did not meet the guidelines [57]. Other contributing factors to the poor quality of reporting includes lack of placental examination, limitations in radiographic and genetic analysis, and poor comprehensive maternal medical history [52, 58]. Quality can be impacted by the type of service and the pathologist performing the examination. Studies have found that specialist paediatric pathologists provide a higher quality report than general pathology services, emphasising the importance of having expert perinatal and paediatric pathologists perform the autopsy examination [50, 56, 59]. These factors contribute to a common theme that poor quality or incomplete reporting can have a profound impact on the value of an investigation, though this was not able to be examined in this review.

The classifications captured by this review include Tulip, Wigglesworth, and Initial Causes of fetal death method (INCODE) and ICD–10 (ICD–PM) [12, 21–23, 29, 32, 39, 50]. The lack of a universally accepted classification system for stillbirths limits the comparison of studies performed [64]. One major difference is the classification of placental abnormalities. Further investigation into a universally accepted classification system is required to enable direct comparison of data and to enable further prevention strategies to reduce stillbirths.

This review identified five articles from LMIC. The findings of these studies are similar to the findings from HIC. In a low resource setting including regional and remote areas, the availability of investigations can be limited. PMMR, MIA, minimally invasive tissue sampling or placental pathology can be used to determine the cause of death. If access to pathology services is not possible, verbal autopsies in conjunction with case notes may be used to identify a cause of stillbirth in some cases [65].

Strengths and limitations

A strength of this review was that we employed a comprehensive, well described, and replicable search strategy. Two independent reviewers examined the titles and abstracts and conducted full text review. This review was limited to papers written in English only. The publication year of the studies ranged from 1977 to 2020. During this time, there has been significant developments in antenatal care, diagnostic pathology techniques, and centralisation of perinatal autopsy services. This is evident in the amount of information presented in the studies, with later studies comprise more information and would be able to be replicated. The earlier studies present limited information which could hamper replication of the study. This review identified articles from high-income, middle-income countries and few from low-income countries. We recognise that there are cultural and healthcare differences in other countries. The definition of stillbirth varies between countries, and this made comparing results more difficult. Some studies did not define stillbirths, some included all gestations, and some included neonatal deaths under the definition of perinatal death. Some studies included termination of pregnancies in articles involving stillbirths. The nature of the autopsy performed was not always detailed, so some autopsies may not have included an internal examination and tissue sampling. Not all studies describe the classification system used to determine the cause of death. In the studies that did, there was not a consensus in the classification system used, with four different ones utilised.

The terminology used to determine clinical utility is not consistent across the disciplines in healthcare and this makes it challenging when reviewing the literature. Value, usefulness, yield and clinical utility have all been used in the literature [13]. As previously reported, we defined clinical utility as the usefulness of the investigation in contributing to identification of the cause of death, with the term "useful" defined as being practically applicable to confirm or exclude cause of death [13]. Consistent terminology could allow for a systematic review and a meta analysis to be conducted to inform clinical practice.

Conclusion

Our scoping review found placental pathology, autopsy, and genetic testing using microarray analysis were frequently reported as the most useful investigations for confirming or excluding a cause of death. Future studies on investigation protocols should also consider gestational age, presenting clinical scenario and classification system used. For global and regional benchmarking, a global stillbirth definition and a standardised classification system would further enhance the ability to understand clinical utility of stillbirth investigations.

Abbreviations

CA	Conventional autopsy
COD	Cause of death
HIC	High income countries
ICD–10	International classification of diseases, tenth edition
ICD–PM	International classification of diseases-Perinatal Mortality
LMIC	Low middle income countries
MBS	Medicare Benefits Scheme
MIA	Minimally invasive autopsy
MRI	Magnetic resonance imaging
NA	Not applicable
ND	Not described
NHS	National Health Service
PMMR	Post-mortem magnetic resonance imaging
QF-PCR	Quantitative fluorescent polymerase chain reaction

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

TM had full access to all of the data in the study and takes responsibility for the integrity of the data. TM with VF conceived the idea of the study and developed the search strategy. TM and HS carried out independent reviews of abstracts and full text articles. TM developed the first manuscript and HS, YK, JD, VF, JS critically revised the manuscript for important intellectual content. All authors approved the final version.

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Data availability

Study data can be made available upon request.

Declarations

Ethics approval and consent to participate

Ethical approval for this type of study is not required by our institute.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]NHMRC Centre of Research Excellence in Stillbirth, Mater Research Institute – University of Queensland, Brisbane, Australia. [2]Linear Clinical Research, Perth, Australia. [3]SA Pathology, Women's and Children's Hospital, Adelaide, Australia. [4]ACT Pathology, Canberra Health Services and School of Medicine and Psychology, ANU College of Health and Medicine, Canberra, Australia. [5]NHMRC Centre of Research Excellence in Stillbirth, Level 3 Aubigny Place, Mater Research, Raymond Terrace, South Brisbane, QLD 4101, Australia.

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