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# Perinatal death investigations: What is current practice?

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A B S T R A C T

Perinatal death (PD) is a devastating obstetric complication. Determination of cause of death helps in understanding why and how it occurs, and it is an indispensable aid to parents wanting to understand why their baby died and to determine the recurrence risk and management in subsequent pregnancy. Consequently, a perinatal death requires adequate diagnostic investigation. An important first step in the analysis of PD is to identify the case circumstances, including relevant details regarding maternal history, obstetric history and current pregnancy (complications are evaluated and recorded). In the next step, placental examination is suggested in all cases, together with molecular cytogenetic evaluation and fetal autopsy. Investigation for fetal–maternal hemorrhage by Kleihauer is also recommended as standard. In cases where parents do not consent to autopsy, alternative approaches such as minimally invasive postmortem examination, postmortem magnetic resonance imaging, and fetal photographs are good alternatives. After all investigations have been performed it is important to combine findings from the clinical review and investigations together, to identify the most probable cause of death and counsel the parents regarding their loss.



## 1. Introduction

Perinatal death (PD), including stillbirth (SB) and neonatal death until seven days after birth, is a devastating obstetric complication and a global health problem. Determination of the pathophysiological pathways that eventually resulted in perinatal death helps in understanding why and how it occurred. This will aid parents in their mourning process. It will be of value in determining recurrence risk, which is necessarily for counseling and management of future pregnancies. It will provide better insight in the underlying pathological mechanisms and contributing risk factors, which can help to develop intervention strategies. For determination of the cause of death, adequate diagnostic investigations are needed. An important difference exists between a well-investigated and audited unexplained perinatal death and an unexplained cause of perinatal death, which is not evaluated and therefore classified as unexplained. In the evaluation of PD, especially for stillbirth, protocols are under-used, and often knowledge regarding epidemiology, risk factors, and valuable diagnostic tests are lacking [1,2]. In many hospitals, a local protocol for the evaluation of SB is absent [2]. We searched the past 10 years of literature for evidence-based investigations in PD and our aim was to review existing opinions on evaluation of PD. In the reviewed literature the focus is mainly on SB investigations. Information about current practice related to investigations after neonatal death is limited; therefore, in this article we have focused on the investigations of SB. In most cases of neonatal death, the clinical scenario resulting in death is more obvious and investigations will mostly be guided by the clinical condition. In cases of complicated pregnancy or labor, followed by a neonatal death, we are of the opinion that investigations of SB are applicable. These also include placental investigations, as the underlying cause (the first event in the chain of events resulting in death) is often similar.

## 2. Clinical circumstances of stillbirth

An important first step in the diagnostic work-up of SB is to carefully evaluate the circumstances. Each SB is related to a particular clinical scenario. For example, questions should be asked

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to determine exactly when and how the fetal death was identified? What was the maternal (clinical) condition? Under what circumstances did death occur? Did the mother, fetus or placenta suffer from any relevant medical conditions or complication? Several risk factors are associated with PD such as maternal obesity, smoking, or previous stillbirth [3]. Box 1 lists relevant details regarding maternal medical history, obstetric history, current pregnancy (complications), drugs or medications and other risk factors that are associated with PD and that therefore should be evaluated and recorded.

## 3. Maternal diseases

Some maternal diseases are associated with a higher risk of perinatal death (Box 1). However, in the analysis of the cause of death one should not only focus on maternal disease, often this is not related to the cause of stillbirth. After a case of perinatal mortality, routine investigation for maternal diseases such as thyroid (dys)function or diabetes without clinical features is not recommended [8,12,13]. For example, it seems unlikely that SB could be caused by an undiagnosed mild glucose intolerance or by subclinical thyroid disease [9]. Additional testing for maternal diseases should be guided by maternal medical history or relevant maternal or fetal clinical conditions determined by clinical examination.

### 3.1. Screening for inherited or acquired thrombophilia

Inherited thrombophilia has been described as a risk factor for SB, that may result in either impaired implantation and placentation or placental thrombosis and placental insufficiency by infarction or abruption [14,15]. Published literature regarding the prevalence of inherited and/or acquired thrombophilia in women with SB, without a history of deep venous thromboembolism or positive family history for inherited thrombophilia, is conflicting. In two small cohorts of women with SB, an increased prevalence of the G2010A prothrombin mutation (factor II) was reported. For antithrombin activity, factor V Leiden, protein C/S deficiencies, and acquired thrombophilia, prevalence was similar in the group with and without fetal mortality [16,17]. In another cohort of 67 women with fetal death, 57% of all women tested positive for at least one thrombophilia and prevalence was even higher when placental pathology was identified as cause of fetal death (62.3%) [18]. In another study concerning 94 women with SB, factor V Leiden mutation was associated with an otherwise unexplained cause of fetal death [odds ratio (OR): 3.8; 95% confidence interval (CI): 1.2–11.6] and SB with placental abruption or infarction (OR: 10.8; 95% CI: 2.1–55.3) [19]. In contrast to these findings, no increased risk of inherited thrombophilia was reported in the analysis of two large cohorts of women with SB. In a group of 750 couples with SB, prevalence of inherited thrombophilias (including factor V Leiden, prothrombin G20210A mutation, and lupus anticoagulant) was not higher than in the general population, although prevalence of thrombophilic defects was higher compared to the general population if SB was caused by placental abruption or infarction [124]. In another cohort, maternal and fetal/placental thrombophilias were analyzed in almost 500 women with SB compared to a cohort of mothers with live birth, and only maternal factor V Leiden was weakly associated with SB (2/488, 0.4% vs 1/1380, 0.0046%; OR: 87.4; 95% CI: 7.8–970.9), whereas all other maternal and fetal/placental thrombophilias (including G20210A prothrombin mutation) were not [20]. In conclusion, routine testing for inherited thrombophilias as part of an evaluation for SB is not supported unless there is pathological confirmation of abruption, severe infarction or thrombosis which caused fetal death. Screening for thrombophilia may be considered in women with a history of venous thromboembolism or with a family history of hereditary thrombophilias to prevent maternal thromboembolism in the future [14,20,21].

### 3.2. Screening for antiphospholipid antibodies

Antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin and antiprothrombin, are associated with SB. These antibodies can contribute to placental insufficiency through abnormal placental development or placental damage caused by inflammation, thrombosis or infarction [22]. In a cohort of more than 500 women with a stillborn baby, elevated levels of anticardiolipin antibodies were found when compared to women with a live birth and the prevalence was even higher in the group women with an unexplained SB. However, antiphospholipid antibodies are also found in 6% of mothers with healthy live births [22]. In a cohort of 1025 women with SB, 40 tested positive for lupus anticoagulant and/or anticardiolipin antibodies suggesting antiphospholipid syndrome (APS). In this series of SB with suggested APS the underlying cause of death, classified according to the Tulip classification, was diverse – placental bed pathology such as infarction (12 cases), other causes of death (23 cases) – and five were unexplained [12,14]. When SB is accompanied by placenta-mediated complications such as fetal growth restriction (FGR) or severe pre-eclampsia, there is increased likelihood to test positive for antiphospholipid antibodies [8]. In cases of SB with additional clinical features of APS (such as a history of recurrent miscarriage) accompanied by placenta-mediated complications or if cause of death remains unexplained, antiphospholipid antibody testing may be considered. If this is performed it is important to test for positive

**Box 1**
Checklist of major relevant clinical circumstances of stillbirth [3–11].

| |
|---|
| General history |
| Ethnicity (African, African-Caribbean, Indian, Pakistan, first-generation immigrants) |
| Low socio-economic status |
| Intoxications (smoking, drugs, alcohol) |
| Advanced maternal age (>35 years) |
| Parity (para 0 and para ≥3) |
| Maternal medical history |
| Overweight/obesity (body mass index >25 kg/m$^2$) |
| History of mental health problems |
| Previous stillbirth |
| Recurrent miscarriage |
| History of venous thromboembolism |
| Known thrombophilia |
| Pre-existing diabetes |
| Pre-existing hypertension |
| Autoimmune disease (e.g. systemic lupus erythematosus) |
| Renal disease |
| Thyroid disease |
| Complications in current pregnancy |
| Structural or chromosomal abnormalities |
| Pregnancy-induced hypertension |
| Pre-eclampsia |
| Fetal growth restriction |
| Macrosomia |
| Antepartum hemorrhage (including placental abruption) |
| Clinical signs of infection |
| Trauma |
| Cholestasis of pregnancy |
| (Premature) rupture of membranes |
| Umbilical cord complication (prolaps/knot/strangulation) |

antibodies at least twice with at least 12 weeks' interval, since the levels of antibodies may fluctuate over time and may be false positive during or just after pregnancy.

## 4. Pregnancy-induced conditions

Several pregnancy complications are associated with an increased risk for SB (Box 1). For example, untreated intrahepatic cholestasis of pregnancy (ICP) has an estimated SB risk of between 2% and 11% [10]. However, a study of 581 women with SB compared to 1546 women with live births reported that routine screening for bile acids is not of value if there are no clinical features to suggest ICP [10]. Similarly, fetal–maternal hemorrhage (FMH) was found in 2–14% of SB cases in several studies [3,11,12,23–25]. In a cohort of 1025 women with SB, FMH was reported in 12% of cases but it was only considered significant enough to represent the cause of fetal death in around 1.3% of cases. In the majority there were no signs of fetal anemia on placental examination and/or autopsy [12]. Delivery of a stillborn baby may possibly affect the results of testing for FMH. Therefore, we advise imminent testing for FMH at diagnosis of SB. In general, pregnancy complications will mostly be accompanied by clinical maternal and/or fetal conditions. Additional testing should be guided based on these clinical presentations.

## 5. Infections

In high-income countries, up to 25% of SBs are caused by infection [12,26–30] whereas in low- and middle-income countries, more than 50% of SB probably are caused by infection [28]. More than 40 organisms have been associated with SB including bacteria, viruses, protozoa, spirochetes, and fungi [26–28].

### 5.1. Infectious mechanisms causing SB

Infections can initiate a chain of events that finally results in PD by several mechanisms [28]. Severe maternal illness resulting in a systemic inflammatory response or circulatory dysfunction may cause the fetus to die through indirect mechanisms without fetal infection. Some organisms will infect the placenta and cause placental damage resulting in a reduced fetoplacental function. For example, maternal malaria infection during pregnancy may result in placental malarial involvement characterized by parasites and leukocytes in the intervillous space, accumulation of lymphocytes and macrophages, thickening of the trophoblast basement membrane, and increased release of pro-inflammatory cytokines that may result in abnormal fetomaternal circulation [27]. Infectious organisms may also infect the fetus directly and damage vital organs [27]. In transplacentally transmitted infections, the liver is often the first organ that is infected since pathogens enter the fetal circulation through the umbilical vein [28]. Syphilis and *Haemophilus influenza* are examples of potential transplacental infections which may cause SB [28]. *Listeria monocytogenes* is a rare, hematogenously spread infection which usually results in placental involvement with microabscess formation [31]. Parvovirus B19 crosses the placenta and infects fetal erythropoietic tissue causing severe fetal anemia, non-immune fetal hydrops (in around 4% of infected cases), and in some cases myocarditis, all of which may result in SB [28,32]. Some infections in early pregnancy cause congenital anomalies that result in SB at a later stage in pregnancy, for example rubella [28]. Maternal ascending genital tract infection can result in preterm labor causing intrapartum SB and (early) neonatal death [26,28]. In ascending bacterial infections, the fetal lung is first infected through inhalation of contaminated amniotic fluid, with most of the adverse effects mediated through activation of fetomaternal inflammatory cascades. From a global perspective, infection-related stillbirths represent a major burden and in developing countries infection-related SBs are more often caused by *Treponema pallidum*, malaria, and intrauterine infection with common vaginal organisms [27]. In areas where syphilis is highly prevalent, up to 50% of all SBs may be caused by this infection [33].

### 5.2. Infectious outbreak causing SB

Several reports of SB caused by epidemic infectious outbreaks have been published. After a maternal H1N1 influenza infection, risk of fetal death is increased especially after severe disease [34,35]. During an outbreak of hepatitis E virus in Bangladesh, pregnancies complicated by jaundice more often resulted in miscarriage or perinatal mortality [36]. Maternal cholera is associated with an increased risk of fetal death [37]. In Jordan an outbreak of Middle East respiratory syndrome coronavirus resulted in acute respiratory illness and SB [38]. In Brazil, SB is now reported in association with the Zika virus, which results in severe microcephaly, intracranial calcifications, hydrothorax, ascites, and FGR [39]. Awareness of population-based health issues including incidences of infectious diseases associated with SB is therefore important for determination of specific indications for investigations.

### 5.3. Diagnostic work-up for infectious etiologies

The proportion of SB attributed to infection in the literature is related to both the extent of investigation carried out and the classification system used to record the cause of death [28]. Some classification systems use strict criteria, where simultaneous histopathological and microbiological evidence should be present, whereas others include cases based on clinical signs without proven infection [40,41]. Previous studies evaluating diagnostic work-up for SB have included predominantly serological tests and traditional microbiological cultures of the placenta and fetus [12,23]. More recent studies have reported the use of molecular techniques such as polymerase chain reaction (PCR), which is more sensitive for identifying specific viral and bacterial DNA and RNA compared to routine microbiological methods [26]. After evaluation of tissue samples (including heart, kidney, liver, lung, and placenta) from 73 cases of fetal death, viral DNA was found in one or more tissue samples in 34% of cases including cytomegalovirus, herpes simplex virus, parvovirus, HHV-7, and HHV-6. However, positive PCR assays alone do not necessarily imply a causal association with death. Acute chorioamnionitis, of any degree, frequently occurs in SB cases as well as in around 10–20% of live-born babys [42]. Therefore chorioamnionitis may represent a contributing factor or secondary association rather than a causal association with SB in many cases in the absence of a fetal inflammatory response [43]. It should be emphasized that positive serological testing or identification of organisms in the placenta or fetus does not prove causation. It is therefore important to perform further autopsy and placental examination together with serological studies, cultures and molecular testing for DNA/RNA to evaluate whether an infectious agent is likely to be the cause of SB or simply a confounding or contributing factor [28,44].

## 6. Fetal autopsy

Fetal postmortem examination, or autopsy, is traditionally an essential component in the diagnostic investigation of SB [7]. A standardized postmortem protocol will help to evaluate SB consistently to address the pathogenesis [45,46]. Fetal autopsy will identify intrinsic underlying dysmorphic abnormalities, congenital

anomalies, signs of infection, fetal anaemia, fetal growth restriction by elevated brain:liver ratio, and more subtle findings that may determine the cause of SB [8].

In the absence of clinical signs it remains important to exclude specific causes [12]. For example, in one cohort of 500 SBs, in 30% of all cases a possible or probable cause of fetal death was identified by fetal autopsy [24]; in another cohort of 1.025 SBs, autopsy was considered valuable in around 70% of the cases [12]. However, there are numerous components of postmortem examination, such as clinical review, external examination, placental examination, histological evaluation, and ancillary testing. The majority of studies have not determined which components are of most value. In a stepwise analysis of 144 cases, probable cause of fetal death was found by performing clinical and placental examination in around 60% of cases. Additionally performed invasive fetal autopsy led to a further 14% with a probable cause of death identified. Placental examination alone changed subsequent clinical management in 36% of cases. In 6% of all cases, medical recommendations for the management in a subsequent pregnancy changed, based on overall autopsy findings [47]. In another cohort with 230 fetuses, including miscarriages <20 weeks of gestation, SBs, and neonatal deaths, prenatal findings were confirmed in 23% of cases, and in 37% additional findings were observed. In around one-third of all cases, autopsy led to refinement of genetic counseling for the risk of recurrence [48].

### 6.1. Considerations regarding autopsy

It should be noted that despite full autopsy, determination of the underlying cause of death remains subjective in many cases. Variation exists in the interpretation of clinical significance of several factors that affected fetus and placenta. This is well illustrated by the effect of classifying the same SB case in different classification systems [49]. In cases with impaired antenatal visualization by ultrasound in pregnancy, such as with maternal obesity or reduced amniotic fluid, fetal autopsy may be of particular value, whereas in others – for example, antenatally diagnosed aneuploidy – autopsy examination adds little in terms of management of future pregnancies [47]. However, there has been a consistent fall in the proportion of parents who consent to fetal autopsy. In the UK, for example, it decreased from 54.7% in 2000 to 42.4% in 2007 [50,51]. Finding a cause of death and prevention of future SBs are the most frequently mentioned reasons for parents to consent to autopsy, whereas emotional distress and prolonged interval for results are important barriers to consent [50]. Other reasons for failure to offer or perform fetal autopsy are lack of knowledge regarding the procedure, discomfort with the discussion of death and fetal autopsy, and concerns about cost and limited availability of specialist services [24]. Clinicians reported workload, negative publicity, religion, and cultural issues as important barriers [50]. In one study more than 30% of parents who declined fetal autopsy subsequently regretted their decision [50] therefore it is necessary to explain to the family the potential additional value of fetal autopsy, including the value of 'negative' findings for future discussions [47]. To help parents with their decision about fetal autopsy, it is necessary to provide clear and consistent user-friendly information. Clinicians need to be trained to improve their knowledge and ability to guide and support parents through this difficult decision using personalized and sensitive approaches [52]. Education for midwives and obstetricians to increase their knowledge about fetal autopsy, counseling by senior staff regarding the procedure and the availability of specialist perinatal pathologists will increase the uptake of perinatal autopsy [50,51]. If possible, a perinatal pathologist is involved in the counseling regarding autopsy [50].

## 7. Placental examination

The placenta may provide important information regarding events in the antenatal period and its examination therefore plays a major role in investigation of SB. Depending on the classification system used, placental pathology is allocated as causal in 11–65% of SBs in some series [53,54]. If for any reason placental function is impaired and the fetus is deprived of oxygen and nutrients, intrauterine death may occur. Placental processes that result in impaired function may be acute or chronic. Chronic processes evolve over time and can generally be recognized by clinical presentations. For example, maternal vascular malperfusion with defective placental implantation may result in maternal hypertensive disease, FGR, oligohydramnios, reduced fetal movements, and, in the absence of timely delivery, fetal death. In such cases, in addition to specific histological features, the placenta is often small, and low placental weight in relation to birth weight has been suggested as an independent risk factor for SB in some studies [55]. The placenta may demonstrate signs of compensation for chronic hypoxemia and abnormal blood flow, such as increased syncytial knotting, chorangiosis, or fibrin deposition. Chronic inflammation processes, due to infection by pathogenic micro-organisms or other (auto)immune mechanisms, may result in chronic villitis with FGR and SB [56]. Chronic villitis is observed more frequently in SB than controls (18 versus five in one study) [43], nevertheless interpretation of clinical significance in individual cases remains difficult. Risk factors and early pregnancy markers for such chronic processes have beenextensively studied and many prediction models have been developed that may aid the identification of fetuses at risk for SB, such as defective Doppler profiles in uterine arteries combined with biomarkers in maternal blood [57,58]. None of these has been accepted as an effective method to identify high-risk pregnancies.

Several acute placental processes can also be recognized clinically and pathologically – for example, ascending infection and placental abruption. These processes occur rapidly, although they may be superimposed on underlying chronic processes, such as abruption with underlying maternal vascular malperfusion. Acute umbilical cord complications, such as entanglement and compression, occur, but postmortem pathological confirmation of such processes is difficult in the absence of confirmatory changes such as stricture or florid underlying parenchymal alterations [59]. Abnormalities of cord coiling, direction as well as pattern have been reported in association with SB, sometimes with presumed chronic vascular obstruction, although determination of significance again remains controversial [60]. In one series, analysis of 104 cases of perinatal death reported that in almost 70% of cases some placental changes were present, but whether or not these represented the underlying cause was uncertain [61]. Cases for which standard placental assessment was combined with the ReCoDe classification system [62] were less likely to be unexplained (OR: 0.17; 95% CI: 0.04–0.7). In 47% of cases, placental examination contributed to the classification of SB and in 16% of cases placental examination provided the only source of information regarding the cause of SB [63]. In the TULIP classification the underlying cause of death was considered to be placenta-related in almost 65% in one series of 750 cases [53]. Furthermore, placental pathology findings vary according to gestational age at death; placental bed pathology has been suggested to cause more than half of SBs occurring at 24–28 weeks but with a sharp decline after 32 weeks to less than 15% of cases at term [64]. In some series umbilical cord complications have been suggested as the cause of fetal death at term in 10–50% of cases, but, with no definite diagnostic criteria, there are difficulties in ascertainment and variation between studies [40,65].

A consistent issue is the appropriate interpretation of placental lesions present in any given SB case. In a case–control study of

placental lesions in SB and live-borns, almost all pathological entities were present in both groups, albeit with different prevalences. For example, fetal vascular thrombi were found in 6% of cases of term live-born and in 35% of term SBs [66]. Interpretation is further complicated by the fact that, by definition, a 24-week infant cannot be considered as a truly "healthy control". After extreme preterm birth, placental findings may have prognostic value for live-born infants and be used as explanation for the loss in SBs. For example, in live-borns, accelerated maturation has been reported associated with better outcome, whereas fetal vascular thrombosis and placental hypoplasia were associated with adverse outcomes [67].

In contemporary practice, the assessment of placental pathology is likely to move beyond macroscopic and microscopic assessment of structural abnormalities; there are other investigations of the pathophysiological pathways in which the placenta contributes to fetal demise, and these are likely to become of increasing importance. Genome-wide copy number variations are linked with clinical and pathologic findings and have demonstrated specific copy number variations, deletions as well as amplifications, and the introduction of more widespread whole genome sequencing along with proteomic and metabolomic approaches will lead to the definitions of placental pathways that involve fetal well-being, which, when disturbed, may result in fetal death [60]. Placental examination, in whatever form, remains a major important component of investigating fetal death and is likely to become more important with the introduction of novel future approaches.

## 8. Genetic evaluation

The prevalence of chromosomal abnormalities in SB varies from around 2%–20%. This variation can be explained by differences in availability for prenatal screening, the gestation of fetal deaths included in the study cohort, and legal status of pregnancy termination for congenital disorders between studies [68]. Most women (>90%) who pursue a prenatal diagnosis of chromosomal abnormalities choose to terminate pregnancies after the diagnosis of a chromosomal anomaly [69]. Of these cases, a significant proportion of fetuses would have died in utero, if the natural course of pregnancy would have been followed. In general, terminated pregnancies are not reported in the SB statistics. Subsequently, SB rates will fall if more chromosomally abnormal pregnancies are terminated. Molecular cytogenetic evaluation is recommended as standard practice for any SB with dysmorphic features or structural malformations, and in some centers testing is routine for all cases of SB, as dysmporphic features can be very subtle [8,12,70,71]. For several decades, fetal karyotyping has been performed by standard chromosome analysis using G-banded karyotype in fetal tissue obtained by either amniocentesis or fetal tissue collected post delivery [72]. The placenta or umbilical cord closest to the placenta appears to provide the greatest yield of viable tissue, followed by fetal cartilage from the costochondral junction or patella [70,71,73]. However, several limitations have been described with the use of this technique. First, in only 45–65% of SBs may karyotype be obtained due to high rate of culture failure, especially in macerated SBs as adequate viable tissue is diminished/lacking [72,73]. Second, with this traditional technique submicroscopic abnormalities are not identified [72]. The use of newer techniques, e.g. molecular karyotyping, may therefore provide better results. For example, use of quantitative fluoresence (QF)-PCR for the most prevalent trisomies or use of microarray analysis search for copy number variants of genomic segments including those caused by deletions or duplications is well-described and becomes standard practice [73–75]. Several types of microarray are available: comparative genomic hybridization arrays and absolute quantification arrays such as single nucleotide probe [75]. QF-PCR and microarray analyses in SB have been reported to have superior diagnostic yield compared to traditional karyotyping (87% versus 71%), mainly because these tests can in most cases be performed on DNA from non-viable or sometimes even macerated tissue [74]. In some cases, it is also possible to perform similar molecular karyotyping on formalin-fixed, paraffin-embedded (FFPE) tissue processed from fetal autopsy samples, placental tissue, or on FFPE umbilical cord samples, allowing additional diagnostic evaluation at a later stage when, for example, histological findings indicate the need for specific genetic testing [60,72]. Furthermore, microdeletions and microduplications are detected more effectively using microarray compared to karyotyping, with microarray analysis superior for detection of chromosomal abnormalities in SBs with congenital abnormalities when compared to traditional karyotype analysis (30% versus 20% in one study) [73].

In a group of unexplained SBs, genome wide-array based profiling of placentas may result in the detection of copy number variations that are not found with cytogenetic methods. However, the aetiological role of small genomic imbalances found in such cases remains undetermined and requires further investigation, although is likely to contribute to a small proportion of non-anomalous otherwise unexplained SBs [74]. Balanced rearrangements and low-level mosaicism are not detected by microarray analysis but it is unlikely that these types of genetic abnormalities are a significant contributing factor to SB [72,73]. It is important to emphasize good genetic counseling prior to the use of microarrays, since copy number changes or variants of unknown significance will be found which may lead to increased parental anxiety [76]. Investigation of the placenta may reveal placental mosaicism. When microarray analysis is applied to fresh chorionic villous sampling/biopsies, the presence of feto-placental mosaicism in about 1–2% of samples may pose challenges because the differentiation in cytotrophoblastic and mesenchymal tissue separately is lost when DNA is extracted [77]. Type 1 confined placental mosaicism (CPM) in the cytotrophoblast appears to be associated with spontaneous abortion and FGR. The effect on fetal development of type 2 CPM in the mesenchyme is unknown [78]. Although CPM is associated with abortion and FGR, most fetuses with CPM are born alive. Determining CPM as the cause of stillbirth in an individual case should therefore be considered with care [79]. Although molecular karyotyping can often be performed on non-viable tissue, it still worthwhile to try to obtain viable fetal tissue (fibroblasts) by amniocentesis. These fibroblast can be frozen and, if needed, cultured again, in order to obtain fresh fetal DNA in cases where the fetal DNA, obtained from non-cultured tissue, was of insufficient quality to perform an array of where all the fetal DNA was used by the array; if, after autopsy a genetic condition is suspected, fetal DNA of good quality will still be available for mutation analysis in specific genes or for whole genome analysis.

## 9. Radiologic evaluation

Imaging techniques have traditionally been used as a minor adjunct to standard autopsy but with decreasing consent rates, less invasive techniques that use radiologic evaluation are increasing in importance. The application of such techniques is rapidly developing and the possibilities for evaluation of SB may increase.

### 9.1. Plain radiographs

Skeletal radiography can provide detailed information of bone structure and generalized bone abnormalities, including long-bone

length measurements, which traditionally were used for estimation of gestational age (although this is of much less relevance in contemporary practice due to widespread implementation of antenatal sonography for dating). However, in terms of diagnostic value, one study of 739 cases of routine babygrams reported that in only 0.3% of cases was a potentially significant abnormality identified that would have been missed if only selected imaging had been performed [80]. In another cohort of 409 radiographs of SBs, some abnormality was reported in 7% but there was only one case in which it identified the cause of death [12]. Another study of 517 cases of SB suggested that plain radiographs provided a cause of fetal death in 12% of cases including 1–2% in which the diagnosis would otherwise have been missed. The greater proportion of apparently anomalous radiographs in this study may be explained by the fact that a clinical geneticist rather than a radiologist performed evaluation of radiographs, or may be a consequence of selection and referral practice [81]. Whereas skeletal radiographs are often performed routinely as a part of all fetal autopsies, their value appears limited and therefore is not recommended as standard. They are likely to be of most value when fetal skeletal abnormalities are suspected or gestational age is unknown.

### 9.2. Postmortem magnetic resonance imaging (PMMRI)

Non-invasive cross-sectional imaging such as PMMRI is accepted by nearly all parents, in contrast to fetal autopsy [82]. In an unselected series of 400 cases of fetal and child deaths (not only SB), the value of PMMRI for identification of cause of fetal death was evaluated. Minimally invasive autopsy (including PMMRI without percutaneous or other tissue sampling) identified the same cause of death or major pathological lesions comparable to conventional autopsy in 95% of cases. In cases where a pathologist and radiologist predicted that full autopsy was unnecessary, concordance rate for cause of death or major pathology was almost 100% [83]. For identifying cerebral/neurological abnormalities, PMMRI is a highly accurate diagnostic technique with an overall sensitivity of 88% and specificity of 95%, which is even greater for cerebral malformations (sensitivity 100%, specificity 99.1%). In addition, in this series, in 16% of the cases, formal neuropathological examination at fetal autopsy was not possible due to maceration and autolysis, and in these cases PMMRI supplied diagnostic information in around 50% of cases. However, limitations apply; in particular, PMMRI is poor for detection of cerebral hypoxic ischemic injury [84]. PMMRI is of value in detection of cardiac pathology, with an overall sensitivity of 73% and specificity of 96% for any cardiac pathology, being more accurate for major structural heart disease (sensitivity 93%, specificity 99%) [85]. PMMRI is not accurate in detecting other intrathoracic pathologies such as infection or hemorrhage (overall sensitivity 40% and specificity 86%), but it is useful for detection of anatomical abnormalities, such as pleural infusions and lung or thoracic hypoplasia [86]. PMMRI detects abdominal pathology accurately (overall sensitivity 73%, specificity 91%); it is especially good at detecting renal abnormalities, but relatively poor at detecting intestinal abnormalities [87]. PMMRI is accurate for exclusion of musculoskeletal abnormalities with a negative predictive value of 94%. In cases where PMMR is performed combined with clinical examination and skeletal radiographs, all skeletal and soft tissue abnormalities of clinical relevance were detected [88]. Although encouraging, interpretation of PMMRI requires specialist expertise including knowledge about normal postmortem changes such as maceration and autolysis, to ensure correct interpretation [89,90]. Through cellular breakdown, changes of fluid accumulation will occur in subcutaneous tissues; therefore provision of adequate clinical information is essential for pleural space, pericardial sac and peritoneal cavity [86].

Fetal body weight is the most important factor to influence the diagnostic value of PMMRI, being highly likely to provide adequate diagnostic images for fetuses with a body weight >500 g [91]. Protocols for postmortem imaging, specifically for SB, need further evaluation and the local logistics of offering such services need to be determined as such approaches are not available on a routine basis in most centers.

### 9.3. Virtopsy or minimally invasive autopsy

If parents do not consent to a complete fetal autopsy but fetal tissue sampling is required, minimally invasive autopsy can provide an acceptable alternative since some parents may accept this approach [92]. Definitions of minimally invasive autopsy vary, but most studies describe the use of postmortem cross-sectional imaging, such as PMMRI, in combination with some form of less invasive histological tissue sampling, such as by percutaneous or laparoscopically guided biopsy [93].

Parents appear to have no preferences between postmortem percutaneous biopsy and laparoscopically guided biopsy [92].

### 9.4. Limited external examination

External non-invasive examination and medical photographs of the whole body, face, hands and the feet, and all other (suspected) external anomalies is an alternative if parents do not consent to fetal autopsy or minimally invasive autopsy, particularly in cases of fetal abnormalities. This can help the clinical geneticist when suspecting a diagnosis based on dysmorphologies and interpreting subsequent DNA analysis.

### 9.5. Other techniques

Several techniques are being developed and may in future be valuable for SB evaluation. For example, the use of microcomputed tomography (micro-CT) is a technique for the high-resolution evaluation of anatomical features in organs and small fetuses. A study on ex-vivo isolated fetal heart and fetal heart–lung blocks using micro-CT provided highly accurate three-dimensional rendering of complex congenital heart diseases [94]. For the evaluation of very small and early-age fetuses, high-frequency postmortem ultrasound, high-field PMMRI, and micro-CT are being evaluated [91].

## 10. Conclusion

The diagnostic work-up after SB should depend on the specific clinical features per case. For example, in case of pregnancy-induced hypertension and placental abruption and a growth-restricted stillborn infant, placental examination is likely to be the most valuable test. However, in a case of clinically unsuspected SB identified in the late third trimester following a history of reduced fetal movements, the diagnostic yield will be lower and the potential range of investigations more extensive. Based on current published evidence, placental examination, autopsy, and cytogenetic evaluation are advised in all SB cases. Testing for fetal maternal hemorrhage is also advised at the time of diagnosis unless the cause of death is obvious, e.g. massive placental abruption. In cases where parents do not consent for autopsy, alternative approaches should be considered such as minimally invasive postmortem examination, PMMRI, external examination, and fetal pictures (see Fig. 1). The parents should be informed about other diagnostic tests according to the clinical features presented. When test results are available it is then important to

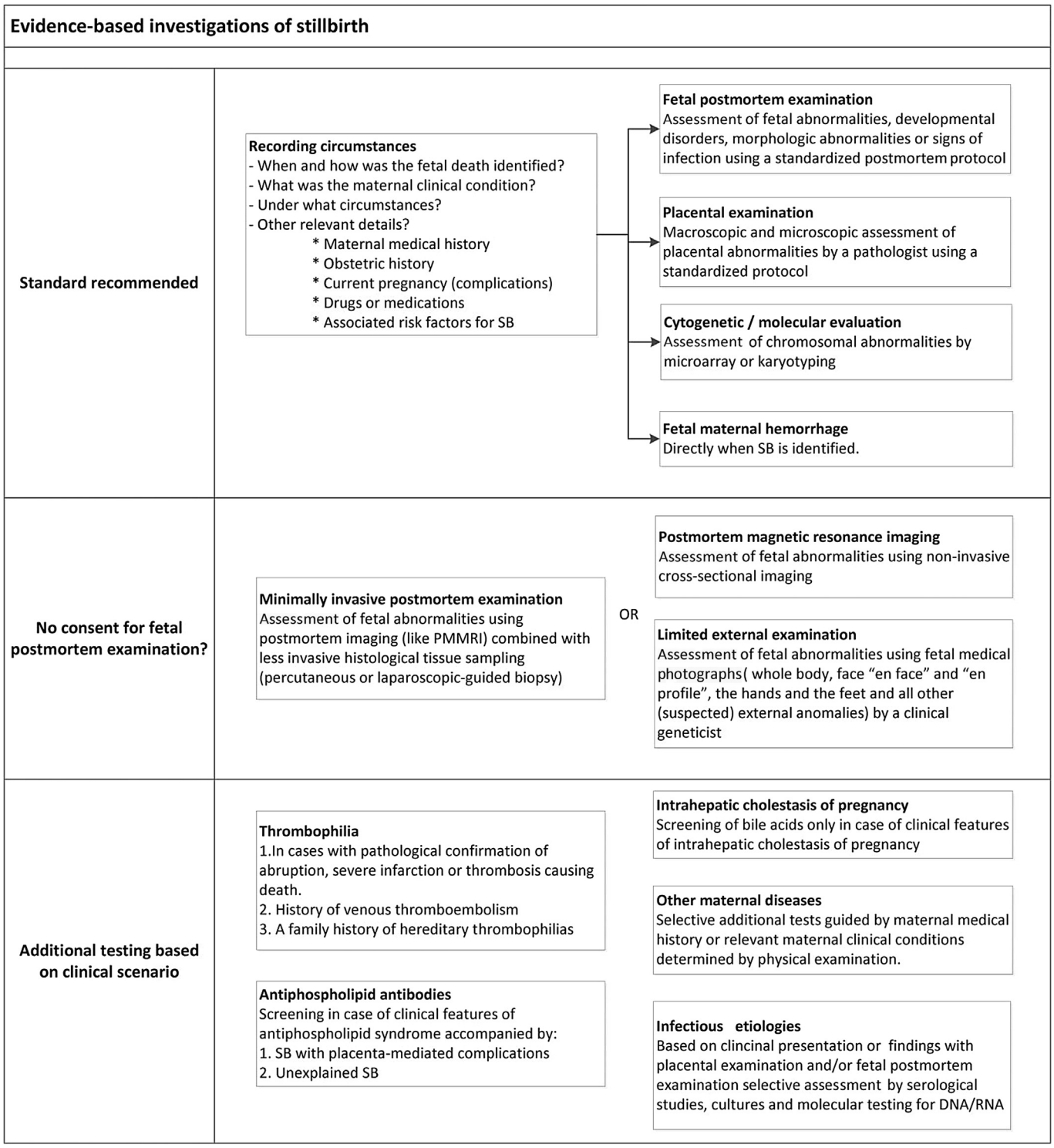


**Fig. 1.** Evidence-based investigations of stillbirth (SB).

combine findings from the clinical review and investigations after death to identify the most probable cause of the fetal death, preferably in a multidisciplinary panel with parental input. Without a known cause of fetal death, no estimation of the recurrence risk can be calculated. Further development of evidence-based protocols should aim to optimize the diagnostic work-up for SB according to specific clinical scenarios.

## Practice points

- Identification of the clinical circumstances of perinatal death is essential.
- Placental examination, cytogenetic evaluation, fetal autopsy, and investigation for fetal maternal hemorrhage are recommended for all perinatal deaths.

- If parents do not consent to autopsy, alternative approaches such as minimally invasive autopsy or postmortem MRI are good alternatives in specific circumstances.
- Routine testing for inherited thrombophilias for SB investigation is not supported by the evidence.
  - Testing for antiphospholipid antibodies may be considered in cases of stillbirth with additional clinical features of antiphospholipid syndrome accompanied by placenta-mediated complications or if cause of death remains unexplained.

## Research directions

- Whole genome sequencing in unexplained stillbirth could learn us more about the pathophysiology of stillbirth. For example, a specific cardio gene panel might reveal more evidence about the suggested cause of arrhythmia of stillbirth.
- Early identification of placental abnormalities in utero.
- Identification of women at risk of having SB.
- Prevention and intervention strategies for the known placental lesions with high recurrence risk such as lymphohistiocytic villitis of villitis of unknown etiology (pravastatine is currently being tested; may immunomodulation be useful?).
- Stratification of placental lesions in intervention studies.
- How to implement a standard classification procedure in local clinical practice.

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