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Investigation and management of stillbirth: a descriptive review of major guidelines

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Abstract: Stillbirth is a common and devastating pregnancy complication. The aim of this study was to review and compare the recommendations of the most recently published guidelines on the investigation and management of this adverse outcome. A descriptive review of guidelines from the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynecologists (RCOG), the Perinatal Society of Australia and New Zealand (PSANZ), the Society of Obstetricians and Gynecologists of Canada (SOGC) on stillbirth was carried out. Regarding investigation, there is consensus that medical history and postmortem examination are crucial and that determining the etiology may improve care in a subsequent pregnancy. All guidelines recommend histopathological examination of the placenta, genetic analysis and microbiology of fetal and placental tissues, offering less invasive techniques when autopsy is declined and a Kleihauer test to detect large fetomaternal hemorrhage, whereas they discourage routine screening for inherited thrombophilias. RCOG and SOGC also recommend a complete blood count, coagulopathies' testing, anti-Ro and anti-La antibodies' measurement in cases of hydrops and parental karyotyping. Discrepancies exist among the reviewed guidelines on the

definition of stillbirth and the usefulness of thyroid function tests and maternal viral screening. Moreover, only ACOG and RCOG discuss the management of stillbirth. They agree that, in the absence of coagulopathies, expectant management should be considered and encourage vaginal birth, but they suggest different labor induction protocols and different management in subsequent pregnancies. It is important to develop consistent international practice protocols, in order to allow effective determination of the underlying causes and optimal management of stillbirths, while identifying the gaps in the current literature may highlight the need for future research.

Keywords: definition; examination; guidelines; history; intrauterine death; investigation; laboratory tests; management; postmortem; stillbirth.

Introduction

Stillbirth is defined as fetal death after a prespecified gestational age and/or fetal weight, both of which have historically lacked uniformity among different countries [1]. It is a common pregnancy complication, occurring in approximately one in 160–200 deliveries per year, despite the advances in obstetric care [2, 3]. Importantly, the vast majority of stillbirths (~98%) occur in low/middle-income countries [4]. Stillbirth has a significant physical and psychological impact on both parents and wide-ranging economic consequences on the health systems and society [5].

The most prevalent risk factors associated with stillbirth include nulliparity, maternal age at either end of the reproductive age spectrum [6], non-Hispanic black race, obesity, co-morbid medical conditions such as pregestational/gestational diabetes [7, 8], hypertensive disorders of pregnancy [9, 10], untreated thyroid disorders [11] and antiphospholipid syndrome, smoking [12], illicit drugs and alcohol use [13], assisted reproduction, multifetal gestation [14, 15], fetal growth restriction [16], vasa previa [17, 18], male fetal sex [19], nutritional factors [20], unmarried status, low maternal education, low socioeconomic status and

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previous history of fetal death [21] or other adverse pregnancy outcomes [22].

Over the past several decades, the rate of late and term stillbirth has declined substantially, mainly due to the improvement of antenatal and intrapartum care, the reduction of some modifiable risk factors and the early detection of congenital anomalies followed by prompt management [23]. However, the overall stillbirth rate has remained relatively unchanged, as the incidence of important risk factors, i.e. obesity and advanced maternal age, is rising [24]. Moreover, several reports have indicated that parents receive inconsistent advice regarding management options following stillbirth [25]. Thus, the development and implementation of consistent international algorithms for the investigation, management and prevention of stillbirth may hopefully optimize pregnancy outcomes. The aim of this descriptive review was to synthesize and compare current recommendations from influential guidelines on the investigation and management of stillbirth.

Evidence acquisition

The most recently published guidelines on stillbirth were retrieved and a descriptive review was conducted. In particular, four guidelines were identified from: the American College of Obstetricians and Gynecologists (ACOG) [26], the Royal College of Obstetricians and Gynecologists (RCOG) [27], the Perinatal Society of Australia and New Zealand (PSANZ) [28] and the Society of Obstetricians and Gynecologists of Canada (SOGC) [29]. An overview of the recommendations is presented in Table 1 (investigation of stillbirth) and Table 2 (management of stillbirth). Of note, PSANZ and SOGC provide recommendations only for the investigation of stillbirth, whereas ACOG and RCOG also address the issue of management.

Definition and diagnosis

There is no universally accepted definition for stillbirth; in particular, ACOG, PSANZ and SOGC state that stillbirth is defined as the intrauterine death of a fetus at or beyond 20 completed weeks of gestation or, in case of unknown gestational age, weighing at least 350, 400 and 500 g respectively. On the other hand, RCOG has adopted the definition of the Perinatal Mortality Surveillance Report (CEMACH) according to which stillbirth is defined as “the delivery of a baby with no signs of life known to have died after 24 completed weeks of pregnancy” [30]. Moreover,

this medical society points out that real-time ultrasonography is the optimal method for the diagnosis of intrauterine death and should be preferred over auscultation and cardiotocography, as it allows not only the direct visualization of the fetal heart, but also the detection of secondary features, such as hydrops, collapse of fetal skull and maceration [31].

Following the diagnosis of stillbirth, healthcare providers should communicate with the parents at an appropriate isolated place, explain their choices regarding the investigation and the mode of delivery and provide emotional support, individualized bereavement care as well as written information (ACOG, RCOG, PSANZ). A prospective study of 808 families who suffered a stillbirth showed that parental choices vary widely and, thus, clinicians should provide personalized care based on their preferences [32].

Investigation

There is an overall consensus among the reviewed guidelines that a thorough investigation is warranted, when stillbirth occurs, in order to identify the underlying cause, ensure appropriate management of any potentially life-threatening maternal disease, determine the chance of recurrence and avoid further pregnancy complications. This investigation should include a structured personal, obstetric and family medical history of the mother, physical examination, laboratory tests, genetic analysis of the fetal and the placental tissues, gross and histological examination of the placenta and postmortem examination of the baby.

Medical history

All the guidelines highlight the importance of taking a detailed maternal medical history in order to determine the etiology of stillbirth, including a history of thromboembolic disorders, diabetes mellitus, hypertensive and autoimmune diseases, known thyroid dysfunction and cyanotic heart disease. Several epidemiological studies support this approach. Thus, a retrospective study of 913,255 pregnancies concluded that women with pregestational and gestational diabetes mellitus have an increased prevalence of intrauterine fetal death (Odds Ratio-OR: 4.197 and 2.511, respectively) [33]. Another cohort study of 1,419 singleton pregnancies found that a preconception history of venous thromboembolism is associated with increased risk of placenta-mediated complications, including stillbirth [34]

Table 1: Summary of recommendations on the investigation of stillbirth.

	ACOG	RCOG	PSANZ	SOGC
Country	United States	United Kingdom	Australia and New Zealand	Canada
Issued	March 2020	October 2010	January 2020	January 2020
Title	Obstetric care consensus: management of stillbirth	Late intrauterine fetal death and stillbirth. Green-top guideline no. 55	Clinical practice guideline for care around stillbirth and neonatal death	Clinical practice guideline no. 394-stillbirth investigation
Pages	23	33	301	8
References	139	176	380	79
Definition	Delivery of a fetus at or beyond 20 weeks of gestation or ≥ 350 g with no signs of life	Intrauterine fetal death after 24 completed weeks of pregnancy	Intrauterine fetal death after 20 completed weeks of pregnancy at least 400 g birthweight	Intrauterine fetal death after 20 completed weeks of pregnancy or weighing > 500 g.
Ideal method for the diagnosis of stillbirth	Not discussed	Real-time ultrasound. Second opinion if possible.	Not discussed	Not discussed
Best practice for discussing the diagnosis	Emotional support for the mother, the partner and the family. Good communication. Shared decision making.	Ask the mother to call for company. Explain choices. Provide written information as well.	Ask the mother to call for company. Emotional support. Appropriate place. Good communication. Shared decision making. Provide written information	Not discussed
Investigation	Recommended	Recommended	Recommended	Recommended
Detailed history (personal, obstetric and family)	Recommended, including three-generation pedigree	Recommended	Recommended	Recommended
Clinical examination	Recommended	Recommended	Recommended	Not discussed
Blood tests 1. Complete blood count	Not discussed. Indirect coombs in selected cases	Recommended	Not discussed	Recommended
Blood tests 2. Blood group	Not discussed	Not discussed	Recommended	Recommended
Blood tests 3. Coagulation tests	Not discussed	Recommended (including plasma fibrinogen)	Not discussed	Recommended in case of massive placental abruption or IUD > 4 weeks
Blood tests 4. Thyroid function tests	Not discussed	Recommended (TSH, FT3, FT4)	Not recommended in the absence of clinical signs	Not recommended in the absence of clinical signs
Blood tests 5. Biochemistry	Glucose screening is recommended in LGA	Recommended, including CRP, bile salt, random blood glucose (for occult DM), HbA _{1c} (for GDM)	HbA _{1c} (FPG/OGTT) if LGA or SGA. Bile acids and liver enzymes if suspected cholestasis (pruritus)	HbA _{1c} . Bile acids and liver enzymes if suspected cholestasis.
Blood tests 6. Kleihauer test	Recommended	Recommended	Recommended	Recommended
Blood tests 7. Hemoglobin electrophoresis	Not discussed	Not discussed	Not discussed	Recommended in case of hydropic fetus, anemic mother or possible a-thalassemia
Maternal serology for viral screen (TORCH, Parvo B19), syphilis, tropical infections, Listeria	TORCH not recommended. Testing for syphilis is recommended	Recommended for occult infection	Recommended if SGA/FGR or infection suspected by maternal history/autopsy/placental findings. Parvo in case of hydrops or anemia	Recommended when infection is suspected

Table 1: (continued)

	ACOG	RCOG	PSANZ	SOGC
Maternal bacteriology (blood cultures, midstream urine, vaginal and cervical swabs)	Not discussed	Recommended in case of fever, flu symptoms, abnormal liquor, prolonged ROM before stillbirth	Not discussed	Not discussed
Fetal and placental microbiology (blood and swabs)	Recommended (GBS, <i>Listeria</i> , <i>E. Coli</i> and syphilis)	Recommended	Recommended in case of suspected infection	Recommended (GBS, <i>Listeria</i> , <i>E. Coli</i>)
Maternal urine for illicit drug use	Recommended in suspected drug use or placental abruption	Recommended if history/presentation is suggestive	Recommended if maternal history is suggestive	Recommended according to maternal condition
Maternal thrombophilia screen – Testing for lupus anticoagulant, anticardiolipin antibodies, anti β 2-glycoprotein I antibodies	Not recommended for inherited thrombophilia, only for acquired thrombophilia (i.e. APS), especially when accompanied by severe pre-eclampsia, FGR or other evidence of placental insufficiency.	The association between inherited thrombophilias and stillbirth is weak. Recommended if evidence of fetal growth restriction or placental disease. If APS screening is abnormal, repeat testing.	Not recommended for inherited thrombophilia in the absence of other indications. Recommended for thrombosis, SGA/FGR, placental abruption or infarction	Not recommended (for inherited thrombophilia) recommended for APS according to maternal condition
Anti-red cell antibody serology	Not discussed	Recommended in case of fetal hydrops	Recommended in case of fetal hydrops, anemia or jaundice	Not discussed
Maternal anti-Ro and anti-La antibodies	Not discussed	Recommended in case of hydrops, endomyocardial fibro-elastosis or AV node calcification at postmortem	Not discussed	Recommended in case of hydrops, endomyocardial fibro-elastosis or AV node calcification at postmortem
Maternal alloimmune anti-PLT antibodies	Not discussed	Recommended if fetal intracranial hemorrhage at postmortem	Not discussed	Not discussed
Parental blood for karyotype	Not discussed	Recommended in case of fetal unbalanced translocation, other fetal aneuploidy, fetal genetic testing fails and history suggestive of aneuploidy (fetal abnormality on postmortem, previous unexplained IUFD, recurrent miscarriage)	Not discussed	Recommended in cases of ≥ 3 recurrent spontaneous abortions or previous/current fetus or newborn with congenital malformations or dysmorphic features
Fetal and placental tissues for karyotype	Recommended, using microarray analysis, especially when guided by clinical history and detected fetal abnormalities. Only with parents' written consent.	Search for aneuploidy and single gene disorders. Use multiple tissue samples. Only with parents' written consent.	Recommended, using microarray analysis if available. Only with parents' written consent.	Recommended, especially if evidence of congenital malformation, IUGR, hydrops, ambiguous genitalia or dysmorphic features. Only with parents' written consent. Microarray or QF-PCR
Determination of baby's gender	Not discussed	Examination of external genitalia by two healthcare practitioners. If doubt, rapid karyotyping with PCR or FISH	Recommended in case of autopsy	Not discussed

Table 1: (continued)

	ACOG	RCOG	PSANZ	SOGC
Placental gross and histological examination (plus membranes and cord)	Recommended when postmortem examination of the baby is declined, by a trained pathologist.	Recommended when postmortem examination of the baby is declined	Recommended when maternal and fetal indications are present	Recommended
Postmortem examination (autopsy)	Recommended only with parents' written consent. Weight, length and head circumference measurements. External examination for dysmorphic features. Photographs. Fetal whole-body X-rays.	Recommended only with parents' written consent, by a specialist perinatal pathologist. Seek for correlation with blood tests. Weight and length measurement, external examination, histology and X-rays.	Recommended, with parents' written consent or coroner-mandated, by a specialist perinatal pathologist. A detailed maternal history should accompany the baby. Offer less invasive autopsy if full autopsy is declined. Photographs. Internal and external examination. X-rays. Histology	Recommended by a specialist perinatal pathologist. Offer virtual autopsy if parents decline a complete fetal autopsy. Histology
Postmortem ultrasound and MRI	Indicated when autopsy is declined, along with sampling of tissues, gross examination, photographs and X-rays	Not recommended as a routine. MRI only as an adjunctive tool.	Indicated when autopsy is declined, along with needle biopsy of specific internal organs, external examination of the body, X-rays or laparoscopic autopsy	Indicated when autopsy is declined, along with needle biopsy of specific internal organs, external examination of the body with X-ray and CT

ROM, rupture of membranes; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; GDM, gestational diabetes mellitus; TORCH, toxoplasma, rubella; CMV, herpes simplex; QF-PCR, quantitative fluorescence polymerase chain reaction; FISH, fluorescence *in situ* hybridization; GBS, Group-B Streptococcus; LGA, large for gestational age; SGA, small for gestational age; FGR, fetal growth restriction; APS, antiphospholipid syndrome; MRI, magnetic resonance imaging.

Table 2: Summary of recommendations on the management of stillbirth.

	ACOG	RCOG
Management of rhesus D-negative women with stillbirth	Kleihauer test	Kleihauer test. Administration of RhD immunoglobulin as soon as possible. Increased dosage if large FMH. Repeat Kleihauer test at 48 h. Type the baby's blood type (cFDNA or serology on cord blood)
Indications for immediate delivery	Not discussed	Sepsis, preeclampsia, placental abruption/bleeding, membrane rupture, laboratory evidence of DIC
Expectant management	Consider as coagulopathies associated with prolonged fetal retention are uncommon.	Consider if no indications for immediate delivery exist. Blood tests twice weekly (for DIC) if delay >48 h. Consider amniocentesis for cytogenetic results
Management of women with unscarred uterus	Induction of labor is preferred. Alternatively, dilation and evacuation can be offered in the 2nd trimester. Cesarean should be reserved for unusual circumstances.	Vaginal birth is recommended. Consider cesarean in case of maternal wish/condition.
Induction of labor	<28 weeks: Misoprostol vaginally (or orally), 400–600 µg every 3–6 h +/- mifepristone 24–48 h earlier. High-dose oxytocin is also acceptable. >28 weeks: Usual obstetric protocol	Mifepristone and prostaglandin (E1-Misoprostol is preferred over E2, vaginally over orally)
Management of women with a history of lower segment cesarean section (LSCS)	<28 weeks: Insufficient data to guide clinical practice for the optimal dose and route of administration of misoprostol. >28 weeks: Induction of labor as per standard obstetric protocols for VBAC (+/- transcervical Foley catheter for cervical ripening). Cesarean is a reasonable option.	Advise labor induction for women with up to two LSCS (with mifepristone alone or low-dose misoprostol). Monitor for features of scar rupture. Oxytocin augmentation should be decided by a consultant obstetrician.
Management of women with a history of atypical uterine scars or >2 LSCS	Not discussed	Insufficient data to guide clinical practice
Intrapartum antimicrobial therapy	Not discussed	Not recommended as a routine. Broad-spectrum antibiotics in case of sepsis. Intrapartum antibiotics for GBS colonized women are not indicated.
Pain relief during labor	Not discussed	Diamorphine over pethidine. Regional anesthesia is recommended (assess for DIC and sepsis before)
Postnatal thromboprophylaxis	Not discussed	Recommended if risk factors are present (IUD is not considered a risk factor). Hematologist consultation in case of DIC.
Lactation suppression	Not discussed	Dopamine agonists are recommended (cabergoline over bromocriptine) unless preeclampsia or hypertension is present. Avoid non-pharmacological measures and estrogens.
Counseling and bereavement	Recommended	Recommended
Subsequent pregnancy	If previous stillbirth ≥32 weeks, once or twice weekly antenatal surveillance is recommended at 32 weeks or starting 1–2 weeks before the gestational age of previous stillbirth. If previous stillbirth <32 weeks, individualized antenatal care.	Obstetric antenatal care and screening for GDM are recommended. If stillborn baby was SGA, serial US for fetal growth is recommended.

Table 2: (continued)

	ACOG	RCOG
Subsequent delivery	Fetal kicks counting not routinely recommended. Assess the modifiable risk factors. Maternal request for scheduled birth and early term delivery should be taken into account. Can offer delivery up to 39 weeks.	Birth at a specialist maternity unit is recommended. Maternal request for scheduled birth should take into account the gestational age of the previous stillbirth, previous intrapartum history and the safety of induction of labor. Vigilance for postpartum depression.
	FMH, feto-maternal hemorrhage; DIC, disseminated intravascular coagulation; cfcDNA, cell-free fetal DNA; GDM, gestational diabetes mellitus; US, ultrasound; VBAC, vaginal birth after cesarean.	

and a study of 135,466 pregnant women showed that women with any hypertensive disorder are 1.4 times more likely to have a stillbirth [35]. Moreover, symptoms of intrahepatic cholestasis of pregnancy (i.e. pruritus) should be recorded, as a meta-analysis concluded that severe cholestasis of pregnancy (total bile acids $\geq 100 \mu\text{mol/L}$) is associated with increased risk of stillbirth compared to controls (Hazard Ratio: 30.5; 95% Confidence Interval-CI: 8.83–105.30) [36]. In addition, a careful documentation of antepartum hemorrhage or infection, as well as previous adverse pregnancy outcomes, are required to facilitate investigation; this statement is based on a systematic review and meta-analysis which proved that the risk of stillbirth in subsequent pregnancies is higher in women who experience a stillbirth in their first pregnancy (OR: 4.83; 95% CI: 3.77–6.18) [21] and on a retrospective cohort study which showed that complicated first births of live-born infants are associated with an increased risk of unexplained stillbirth in the next pregnancy [22]. Finally, questions regarding familial disorders, inherited conditions and consanguinity should never be omitted as they can also unveil potential causes of stillbirth.

Clinical examination

There is an agreement among all the medical societies that clinical examination of the mother is an integral part of stillbirth’s investigation. Clinicians should evaluate maternal weight and blood pressure and seek for signs of preeclampsia, chorioamnionitis, placental abruption, abdominal trauma, thyroid disease and substance use (ACOG, RCOG, SOGC).

Laboratory tests

The RCOG and the SOGC guidelines agree that a complete blood count along with maternal coagulation studies (including plasma fibrinogen levels) should be performed in case of stillbirth, in order to detect potential complications of preeclampsia and disseminated intravascular coagulation (DIC). The latter is more likely to occur in case of massive placental abruption, maternal sepsis, pre-eclampsia and expectant management of an intrauterine death of more than 4 weeks [37]. Thus, RCOG recommends testing for DIC twice a week for women who decide to delay labor more than 48 h.

With regards to the determination of the maternal blood group, PSANZ and SOGC point out that if it was not performed antenatally as a routine, it is crucial to be performed

after the diagnosis of stillbirth to exclude hemolytic disease of the fetus due to maternal sensitization to red cell antigens [38]. RCOG and PSANZ also recommend anti-red cell antibody screening in case of fetal anemia, hydrops or jaundice.

There is no agreement on the necessity of thyroid function tests as part of stillbirth's investigation; RCOG recommends measuring maternal TSH, FT3 and FT4 levels in all women with late stillbirth in order to rule out occult thyroid disease. On the other hand, PSANZ and SOGC state that routine thyroid testing in the absence of clinical signs of thyroid dysfunction is not justified, as a multicenter prospective cohort study of 1,025 women found no strong association of subclinical thyroid disease with stillbirth and no beneficial effect of treating thyroid dysfunction in such cases [39].

Likewise, maternal glucose screening is a matter of controversy. The RCOG and the SOGC guidelines favor routine measurement of HbA_{1c} in case of intrauterine death, while ACOG and PSANZ guidelines are against this strategy and recommend screening for diabetes mellitus only in cases of fetal growth restriction and large or small for gestational age (SGA) fetuses. The latter statement is based on a prospective cohort study, which found that diabetes causes stillbirth in less than 0.5% of cases and thus, routine testing is not necessary [40].

Three of the reviewed guidelines (RCOG, PSANZ, SOGC) highlight that, following a stillbirth, liver function and bile acid testing is required when obstetric cholestasis is suspected, i.e. when the patient reports pruritus during pregnancy [41].

Moreover, according to all medical societies, the performance of Kleihauer-Betke test to all women with stillbirth, irrespective of their RhD type, is necessary in order to detect large fetomaternal hemorrhage (FMH) and should preferably be performed antenatally (RCOG, PSANZ) as fetal red cells might clear from maternal circulation immediately after birth. In a multicenter prospective cohort study of 1,025 fetal deaths at or beyond 20 weeks of gestation, an abnormal Kleihauer-Betke was noticed in 11.9% of cases [40]. In addition, a cross-sectional study of 192,132 non-anomalous infants found that FMH accounted for 4.1% (34/828) of antepartum stillbirths [42].

Notably, the SOGC recommends hemoglobin electrophoresis assessment in case of fetal hydrops, maternal anemia or possible α -thalassemia, as part of stillbirth investigation.

Serology

Several discrepancies were detected regarding the indications of maternal serology testing for viral infections

and syphilis. In particular, ACOG, PSANZ and SOGC do not recommend routine testing for toxoplasmosis, rubella, cytomegalovirus (CMV) and herpes simplex virus (TORCH), based on a retrospective study of 745 stillbirths, which found no obvious benefit from congenital infection screening in the evaluation of such cases [43]. More specifically, SOGC mentions that serology for TORCH, Parvovirus B19 and *Listeria* should be performed only when the infection is clinically suspected and PSANZ supports a targeted investigation based on maternal history, SGA fetuses, autopsy and placental findings. Although CMV infection in pregnancy is strongly associated with stillbirth, it can be also randomly discovered [44]; targeted screening in case of placental histopathological evidence or SGA fetus is justified (PSANZ). Regarding toxoplasmosis, a systematic review concluded that it is not a common cause of stillbirth [45], rendering its routine testing unreasonable (PSANZ). Moreover, as Parvovirus B19 disease is apparent in the examination of the baby and/or the placenta when causing stillbirth, PSANZ recommends testing for this infection only in case of severe fetal anemia and/or non-immune hydrops [40, 46]. As for rubella and syphilis, if the initial antenatal screening was omitted, routine testing as part of stillbirth investigation is not recommended in the absence of specific indications, as they are both rare infections in high-income countries [46].

On the contrary, RCOG is in favor of routine maternal serology testing for TORCH, syphilis and Parvovirus B19, claiming that this strategy may reveal occult infections that can result in stillbirth. This recommendation is based on a prospective case-control study which proved that there is statistically significant correlation between viral infections and stillbirth, especially in advanced gestational age [47]. In addition, a multicenter study of 14,147 deliveries in Sweden concluded that the sensitivity of conventional diagnostic procedures for stillbirth could be greatly improved by addition of Parvovirus B19 PCR, as its presence in cases of late second- and third-trimester fetal death is relatively common [48].

Bacteriology (blood cultures, midstream urine, vaginal and cervical swabs)

According to RCOG, clinicians should offer maternal blood cultures, midstream urine culture and/or vaginal and cervical swabs when bacterial infection is suspected, i.e. when stillbirth is accompanied by maternal fever, flu-like symptoms, abnormal vaginal liquor or prolonged rupture of membranes. However, it is stated that abnormal results are of doubtful importance in the absence of clinical or

histological signs of chorioamnionitis, as a retrospective study failed to find a statistically significant association between positive cervicovaginal culture and stillbirth [49]. Of note, the other medical societies do not make any relevant recommendation.

Fetal and placental microbiology

There is an overall agreement that fetal and placental specimens (blood or swabs) should be tested for potential fetal infections that could result in stillbirth, as it has been showed that up to 24% of cases can be infection-related stillbirths [50]. Moreover, a case control study of placentas from 66 stillbirths and 66 term live births found that chorioamnionitis occurred 2.6 times more often in women with stillbirths than in women with live births [51]. RCOG points out that fetal tissues are more reliable and informative than maternal ones for the detection of viral infections. ACOG and SOGC recommend routine testing for group B *Streptococcus* (GBS), *Listeria*, *Escherichia Coli* and Syphilis, as these are the most common pathogens, while other bacterial cultures should be considered only if clinically indicated. A systematic review and meta-analysis of 14 studies concluded that 1% of all stillbirths in developed countries and 4% in Africa are associated with GBS [52]. On the other hand, the PSANZ guideline supports a more targeted investigation when infection is suspected [40, 46].

Maternal urine testing for illicit drug use

All the guidelines agree that testing for substance use following stillbirth should be considered when maternal history or presentation is suggestive; a case-control study showed that smoking, exposure to second-hand smoke and illicit drug use, separately or in combination during pregnancy, are associated with an increased risk of stillbirth [53]. The ACOG adds placental abruption as an indication for toxicology screening, based on two studies that proved its significant correlation with cocaine use and cigarette smoking [54, 55].

Thrombophilia screening

Screening for inherited thrombophilia as part of stillbirth's investigation is unanimously not recommended; to date, there is no robust evidence to convincingly support the association between otherwise unexplained intrauterine

fetal death and positive thrombophilia screening [56]. ACOG mentioned that it should only be considered in case of personal or family history of thromboembolic disease [57]. On the other hand, testing for antiphospholipid syndrome, which is a type of acquired thrombophilia, by measuring lupus anticoagulant, anticardiolipin and anti- β 2-glycoprotein I antibodies is recommended as a routine (ACOG, SOGC) or in case of fetal growth restriction, SGA, placental disease (RCOG, PSANZ) and family or personal history of thrombosis (PSANZ) [58]. A multicenter case-control study found a three- to five-fold increased odds of stillbirth when anticardiolipin and anti- β 2-glycoprotein I antibodies are elevated [59]. Moreover, a systematic review and meta-analysis showed that there is a strong association between positive lupus anticoagulant and late fetal loss in antiphospholipid syndrome patients [60].

Testing for autoimmune diseases (anti-Ro and anti-La antibodies)

The RCOG and SOGC guidelines recommend the measurement of maternal anti-Ro and anti-La antibodies, when investigating stillbirth accompanied by fetal hydrops, endomyocardial fibro-elastosis or AV node calcification at postmortem examination. A meta-analysis concluded that systemic lupus erythematosus increases the risk of stillbirth [61]. Of note, the other guidelines do not make any relevant recommendation.

Testing for alloimmune thrombocytopenia

According to RCOG alone, fetal intracranial hemorrhage found on postmortem examination is an indication for maternal alloimmune thrombocytopenia testing by measuring antiplatelet antibodies' levels [62].

Parental blood karyotype

Chromosome testing of both parents for mosaicism or balanced translocation is indicated in case of recurrent miscarriages and stillborn fetuses with congenital malformations or dysmorphic features reported on postmortem examination (RCOG, SOGC). This statement is based on a study of 77 couples with no apparent cause for recurrent spontaneous abortion, which found that the incidence of chromosomal abnormalities was 7.79% compared to 2.6% in the general population and, thus, supports parental

karyotyping in such cases [63]. According to RCOG, karyotype testing of the parents is also recommended when the fetus is diagnosed with an unbalanced translocation or other aneuploidy [64], as well as when fetal genetic testing is inconclusive and there is a history suggestive of aneuploidy, such as previous unexplained stillbirth. In addition, SOGC highlights that an additional indication for such tests is a previous history of fetus or neonate with a congenital malformation.

Cytogenetic analysis of fetal and placental tissues

As chromosomal abnormalities are present in about 6–13% of all stillbirths [40, 65], karyotypic analysis of fetal and placental tissues is recommended by all the reviewed guidelines, in terms of unexplained stillbirth investigation. More specifically, after parents' written consent, samples from the fetal skin or cartilage and the fetal surface of the placenta should be obtained, kept in culture fluid with antibiotics, in order to avoid contamination with bacteria (RCOG) and sent for cytogenetic analysis. Alternatively, invasive testing, i.e. amniocentesis, can be performed before delivery, when expectant management is chosen, as the amniotic fluid has the highest yield for fetal karyotyping. This statement is based on a study of 230 samples from stillbirth cases which found that invasive testing was superior to solid tissue testing in successful karyotyping [66]. The ACOG, SOGC and PSANZ guidelines point out that chromosomal microarray analysis (CMA) should be preferred over conventional karyotyping, as a systematic review and meta-analysis showed that this technique provides better detection of genetic abnormalities, improves the test success rate and thus, is more likely to set the diagnosis of stillbirth for the purpose of counseling on future pregnancies [67]. Moreover, ACOG and SOGC mention that the performance of fetal karyotyping is of greater importance and higher diagnostic yield in cases with congenital malformations, fetal dysmorphic features, hydrops, ambiguous genitalia and fetal growth restriction [68].

Of note, only RCOG refers to the determination of baby's sex; it highlights the difficulty and doubt that occur frequently, even after the inspection of external genitalia by two experienced healthcare providers, especially when the baby is hydropic, macerated or extremely preterm. In such cases, the performance of rapid karyotyping using quantitative fluorescent PCR or fluorescence *in situ* hybridization (FISH) is recommended [69].

Gross and histological examination of the placenta, the fetal membranes and the umbilical cord

Irrespective of full or limited autopsy, the meticulous gross and microscopic examination of the placenta along with the fetal membranes and the umbilical cord is an essential parameter of stillbirth investigation recommended by all the reviewed guidelines. It provides useful information regarding the cause of fetal death and the chorionicity of multifetal gestations and may reveal conditions such as placental abruption, infarcts, calcifications, hematomas, infection, preeclampsia, growth restriction, umbilical cord thrombosis, true knots, genetic abnormalities, velamentous cord insertion and vascular malformations [26, 29]. A systematic review supported the utility of the histopathological examination of the placenta as it found that the proportion of stillbirths attributed to placental causes ranges from 11 to 65% [70]. Moreover, a multicenter prospective cohort study of 1,025 fetal deaths at or beyond 20 weeks of gestation showed that placental examination was abnormal in 89.2% (95% CI: 87.2–91.1) of cases [40].

PSANZ mentions certain maternal, fetal and placental indications for the histopathological examination of the placenta, including preeclampsia, systemic maternal disorders, suspected infection or chorioamnionitis, preterm delivery either spontaneous or iatrogenic, stillbirth, fetal hydrops and anemia, abnormal placental or umbilical cord size, amniotic fluid abnormalities and placental abruption.

Notably, the ACOG guideline underlines that the finding of umbilical cord entanglement is insufficient evidence to explain stillbirth. This is based on a cohort study of 13,757 deliveries (including 98 stillbirths), which reported that a single nuchal cord encirclement was a very common finding, observed in 23.6% of deliveries and that multiple encirclements were found in 3.7% of them; importantly, no association with increased risk for stillbirth was identified (OR: 1.029; 95% CI: 0.64–1.6) [71].

Postmortem examination

There is an overall consensus that postmortem examination is one of the core investigations when trying to determine the accurate cause of stillbirth and thus, it is strongly recommended. A systematic review found that autopsy revealed a change in diagnosis or additional findings in 22–76% of cases [72]. Another study showed

that fetal autopsy is useful in identifying causes of death in 42.4% (95% CI: 36.9–48.4) of cases [73]. This examination may additionally exclude some potential causes of death, identify disorders that may implicate subsequent pregnancies, guide counseling in order to prevent recurrence, assist the bereavement care by helping the parents understand the underlying pathology and alleviate feelings of guilt [2, 28, 74]. A written informed consent by the parents is required even for minimally invasive procedures, allowing at the same time free choice and respecting cultural, religious and individual beliefs. A specialist perinatal pathologist should undertake the postmortem examination (RCOG, PSANZ), which should include external examination of the baby for dysmorphic features or structural anomalies, measurement of length, weight and head circumference, whole-body X-rays, photographs (ACOG, RCOG, PSANZ), histological examination of internal organs (RCOG, PSANZ) and tissue sampling for microbiological analysis [75].

All the reviewed guidelines agree that when parental consent for conventional autopsy is withheld, less invasive procedures should be offered. These procedures may include tissue sampling with needle biopsy of specific internal organs, gross examination, full-body X-rays, photographs, postmortem magnetic resonance imaging (MRI), ultrasound and/or computerized tomography scan of the baby. The PSANZ also suggests the laparoscopic approach as an alternative option for obtaining internal organ samples. In a prospective study, minimally invasive autopsy was found to have accuracy similar to that of traditional autopsy for the detection of death cause or major pathological abnormality after death in fetuses, newborns and infants, although being less accurate in older children [76]. In addition, a retrospective analysis of radiographic images from 2,032 stillbirths and second trimester losses showed that radiographs yielded a diagnosis in 45% of the infants with abnormalities and were crucial in setting a diagnosis that would otherwise be missed or incomplete in 1.5% of the total infants [77].

However, RCOG points out that MRI should not be used as a substitute of conventional autopsy, but only as an adjunctive tool. This recommendation is based on a retrospective study of 100 stillborn fetuses that underwent both postmortem MRI and autopsy, which found that in 54 of them there was complete agreement between the MRI and autopsy findings, in 24 the MRI added valuable information to the autopsy, but, in 17 of 24 cases (71%), if MRI had been the only investigation, essential information would have been lost [78].

Management

Recommendations for Rhesus D-negative women

All medical societies recommend the performance of Kleihauer-Betke test to all women who experience stillbirth. Moreover, RCOG points out this test must be undertaken urgently after an stillbirth diagnosis in order to timely detect an FMH and subsequently administer anti-RhD immunoglobulin within 72 h from the sensitizing event; the dosage should be increased in case of a large FMH [79]. If the Kleihauer test remains positive, the baby's blood group should be typed, either by conventional serology on umbilical cord blood or by free fetal DNA from maternal blood with the intention of making a differential diagnosis between a large FMH and a RhD negative baby.

Indications for immediate delivery after stillbirth – expectant management

According to the RCOG, following an intrauterine death, delivery should be expedited if there are signs of pre-eclampsia, sepsis, placental abruption or membrane rupture and if the laboratory tests are suggestive of DIC. Otherwise, expectant management may be considered for a short-term period, as the risk for coagulopathies and infections for up to 48 h is low (ACOG, RCOG) [80]. However, in the majority of cases (85–90%), spontaneous delivery occurs within three weeks from the fetal demise [81]. If postponement of delivery is decided for a period longer than 48 h from diagnosis, the RCOG recommends testing for DIC twice a week, as already mentioned. Moreover, the mother should be informed that this strategy reduces the diagnostic yield of postmortem examination.

Management of women with unscarred uterus

There is agreement between ACOG and RCOG that induction of labor (IOL) is the recommended method of delivery of a stillborn fetus [82], although ACOG also suggests the dilation and evacuation as an alternative for second trimester intrauterine deaths. Vaginal birth has the advantage of shorter convalescence period compared to cesarean delivery and provides the ability to preserve the baby and detect

dysmorphic features on postmortem examination compared to dilation and evacuation. Importantly, it can be accomplished within 24 h of IOL in 87.5% of stillbirth cases [83]. On the other hand, it is correlated with an increased risk of placenta retention and need for curettage, especially in the early second trimester (ACOG). In addition, a retrospective cohort study of cases with a fetal demise concluded that IOL is significantly associated with increased maternal morbidity, as a result of higher odds of infection requiring intravenous antibiotics, while dilation and evacuation is probably a safer approach (OR: 5.36; 95% CI: 2.46–11.69) [84].

Both guidelines (ACOG, RCOG) support that cesarean delivery may sometimes be considered depending on maternal wish and medical condition, always taking into consideration the increased risk of maternal complications and the absence of fetal benefit following this approach.

Methods for induction of labor

Regarding the appropriate method for IOL in case of stillbirth, both the ACOG and the RCOG guidelines suggest the vaginal administration of misoprostol, based on a systematic review, which proved the efficacy of this regimen in the second and third trimester [85]. A meta-analysis of 14 randomized controlled trials showed that among women with a stillbirth, both vaginal and oral misoprostol are highly effective in achieving uterine evacuation within 48 h, although the latter is more effective within the first 24 h [86]. In addition, combination of different routes of misoprostol (i.e. vaginal-sublingual/vaginal-oral) have been proven to be effective for the second trimester fetal demise [87]. Mifepristone could be considered as an adjunct to misoprostol given at a single dose of 200 mg 24–48 h before IOL in women with stillbirth as it reduces the induction-to-delivery interval by 7 h compared to other regimens (ACOG, RCOG) [83].

RCOG points out that misoprostol, which is a prostaglandin E1 analog, should be preferred over prostaglandin E2 as many studies have proven that these two prostaglandins demonstrate equally efficient and safe profile, but misoprostol costs significantly less, has fewer side-effects and is easier to store [88, 89]. The optimal dosage of misoprostol and the frequency of administration have not been ascertained to date. RCOG recommends adjustment of dose according to the gestational age (from 25 to 100 µg every 4–6 h), while ACOG suggests a dose of 400–600 µg every 3–6 h.

Of note, ACOG mentions that high-dose of oxytocin infusion may be a safe alternative to a combined mifepristone-misoprostol treatment and that stillbirths

occurring beyond 28 weeks of gestation should be managed according to usual obstetric protocols.

Management of women with a history of lower segment caesarean section (LSCS)

There is an overall agreement between ACOG and RCOG that IOL is a safe option for women with one previous hysterotomy and thus, should be preferred in case of fetal demise, as the most frequent severe risks of VBAC relate to the fetus [90]. A retrospective study of 611 stillbirths showed that IOL resulted in vaginal birth in 91% of women with a history of prior caesarean section with only two cases of uterine rupture [91]. However, they suggest a modified management of such women compared to those without previous hysterotomy.

The RCOG recommends the use of mifepristone alone or the administration of misoprostol in lower doses, close monitoring for features of uterine scar rupture and caution in the use of oxytocin augmentation. Nevertheless, there are no available studies on the efficacy and safety of IOL with misoprostol or oxytocin augmentation following stillbirth in women with an LSCS history. The RCOG also underlines that mechanical methods for IOL should be avoided in the context of previous LSCS history because, although safe and effective in achieving birth, they are associated with increased risk of ascending infection in case of fetal demise [92]. Women with two previous caesarean deliveries should also be advised to attempt IOL instead of caesarean delivery, according to the RCOG, as a history of multiple caesarean deliveries is not associated with an increased rate of uterine rupture in women attempting vaginal birth (0.9%) compared with those with a single prior operation (0.7%) [93]. Finally, for those patients with three or more caesarean sections as well as those with atypical uterine scars, RCOG states that there is inadequate evidence to recommend for or against IOL in cases of stillbirth.

On the other hand, the ACOG differentiates the recommendations based on the gestational age; for stillbirths occurring before 28 weeks of gestation, it mentions that there is insufficient data regarding the safety, the efficacy, the ideal regimen and the optimal route of administration, although a case-control study of 108 women with a previous caesarean delivery and 216 women without such a history failed to prove that a previous caesarean affects the incidence of complications when undergoing a mid-trimester pregnancy termination with misoprostol [94]. For stillbirths beyond 28 weeks of gestation, ACOG recommends IOL as per standard obstetric protocols for

vaginal birth after previous cesarean delivery. Contrary to the RCOG, ACOG recommends the use of Foley catheter for cervical ripening in patients with low Bishop score after 28 weeks and a history of previous hysterotomy; a retrospective study concluded that IOL using a transcervical Foley catheter is not associated with an increased risk of uterine rupture, although having lower rate of success in achieving vaginal birth after cesarean delivery [95].

Intrapartum antibiotic therapy and pain relief

RCOG recommends against routine antibiotic prophylaxis during labor even for group B streptococcus positive women, as this strategy primarily aims to protect the neonate from infection. However, in case of maternal sepsis, intravenous broad-spectrum antibiotics, including anti-chlamydial agents, should be administered, as the stillborn fetus can become a focus of severe secondary infections resulting in DIC, irrespective of the primary cause of death.

With regards to intrapartum analgesia, it is crucial that is offered to all parturients with stillbirth (RCOG). This statement is based on a population-based cohort study of 314 women with stillbirth and 322 women with live births which showed that delivery was harder and less sufferable for women in the first group and subsequently obstetric analgesia was more frequently required for them [96]. Diamorphine should be preferred over pethidine as it provides analgesia of better quality and longer duration, as mentioned by RCOG. In addition, maternal sepsis and DIC should be ruled out before the administration of regional anesthesia in order to prevent the formation of epidural or subdural abscess and hematoma, respectively.

Postpartum thromboprophylaxis and suppression of lactation

According to RCOG, stillbirth is not considered a risk factor for thrombosis and thus, routine thromboprophylaxis is not warranted. However, postpartum assessment for other risk factors should always be undertaken following stillbirth, as this complication is usually associated with advanced maternal age, maternal systemic diseases and increased body mass index. In case of DIC, the decision for heparin administration should be made by a hematologist.

For the inhibition of puerperal lactation, RCOG recommends the use of dopamine agonists over non-pharmacological measures and estrogens, based on two

studies, which showed that bromocriptine successfully suppresses lactation in more than 90% of women without major side effects and is significantly more efficient than breast binders [97, 98]. Another study comparing the safety and efficacy of cabergoline and bromocriptine concluded that the first agent is superior, as it is equally effective in preventing puerperal lactation, while at the same time it has considerably lower rate of rebound breast activity and adverse events, as well as simpler administration schedule [99]. Notably, hypertension is a contraindication for the treatment with dopamine agonists.

Counseling and bereavement care

There is a general consensus among three of the reviewed guidelines (ACOG, RCOG, PSANZ) that appropriate parental counseling, communication and emotional support are required following an intrauterine death, always taking into consideration that stress and sorrow may affect how people absorb, process and respond to information. Healthcare providers should individualize the bereavement care based on parents' personal cultural and spiritual beliefs, as they can have a significant effect on the acceptance and the recovery from such tragic events [100]. The acknowledgment of different grief responses and the recognition of parenthood are crucial in order to provide adequate support not only to the mother, but also to her relatives, as they may have already established an emotional relationship with the deceased baby. Shared decision making regarding the diagnostic and management procedure gives time to the parents to consider their options, understand their individual needs and concerns and conceptualize loss. The opportunity to see, hold, name and photograph the baby should also be provided; Importantly, practitioners should avoid influencing parent's choices (RCOG).

Management of subsequent pregnancies

A systematic review and meta-analysis has proven that the risk of stillbirth in future pregnancies is almost five times higher in women who experienced a stillbirth in their first pregnancy compared to those who had a previous live birth (OR: 4.77; 95% CI: 3.70–6.15) [21]; this is also highlighted by a Consensus Statement endorsed by the International Stillbirth Alliance and the SOGC [101]. Moreover, several studies have shown the association of prior fetal demise with increased risk for ischemic placental disease, chorioamnionitis, preterm delivery and neonatal morbidity in

subsequent pregnancies [102–105]. Based on these data, both RCOG and ACOG recommend a more intense antenatal care to pregnant women with a previous unexplained stillbirth, although not adopting a common approach. More specifically, RCOG suggests screening all these women for gestational diabetes and serial ultrasonographic evaluation of fetal growth in the next pregnancy if the stillborn fetus was small for gestational age. ACOG recommends antenatal surveillance once or twice weekly for patients with a previous history of stillbirth that occurred at or beyond 32 weeks of gestation, starting one to two weeks before the gestational age of the prior stillbirth. Individualized care is suggested for pregnant women with a history of stillbirth before 32 weeks of gestation. ACOG also underlines the importance of eliminating the modifiable risk factors, i.e. cessation of smoking, weight loss, optimization of glycemic control and screening for acquired thrombophilias in the setting of a future pregnancy. Moreover, based on a Cochrane review, which concluded that there is insufficient evidence to influence clinical practice, the same society discourages fetal movement counting as a means of preventing stillbirth recurrence [106].

With regards to the optimal setting, mode and timing of delivery, both RCOG and ACOG agree that clinicians should take under consideration the maternal request for scheduled birth. Delivery at a specialist maternity care unit is indicated for pregnant women with previous unexplained stillbirth according to RCOG. In addition, ACOG recommends IOL or planned cesarean section at 39 weeks of gestation or earlier if maternal and fetal comorbid conditions exist in the current pregnancy. This guideline points out that early term delivery, i.e. between 37 and 38⁺⁶ weeks of gestation, may be considered in case of maternal wish and anxiety, always balancing the risks of neonatal complications with those of further continuation of pregnancy.

Finally, RCOG recommends increased vigilance for postpartum depression and anxiety during the puerperium for women with previous history of stillbirth, as these women are more vulnerable to emotional distress in future pregnancies than those without such history [107].

Conclusions

To summarize, there is an overall agreement among the reviewed guidelines that the detailed documentation of maternal history and the postmortem examination of the fetus are crucial in the investigation of an apparently unexplained stillbirth. All the medical societies agree that the determination of stillbirth's etiology is important not only for the management of subsequent pregnancies and the

prevention of recurrence, but also for the parents' bereavement care and emotional support. They generally agree on the appropriate laboratory testing, although minor discrepancies exist regarding the thyroid function tests and the serology for viral screening. In addition, all guidelines are in favor of the genetic and microbiologic analysis of fetal and placental tissues as well as placental gross and histological examination and suggest minimally invasive procedures when autopsy is declined by the parents. RCOG and SOGC suggest screening for autoimmune diseases and testing parental blood for karyotype in selected circumstances.

On the other hand, the main issues of controversy include the definition of stillbirth, the management of subsequent pregnancies and the recommended protocols for IOL, although both ACOG and RCOG support that vaginal birth should be offered over cesarean section in case of stillbirth.

Of note, SOGC and PSANZ do not make any recommendations regarding the management of stillbirth. Finally, only RCOG provides guidance for intrapartum analgesia and antimicrobial therapy, postpartum thromboprophylaxis and suppression of puerperal lactation.

Regarding possible topics for future research, an international classification system for stillbirth, the efficacy and safety of induction of labor after a previous cesarean, the ideal follow-up, as well as the optimal psychological care for the parents, should be further investigated.

Stillbirth constitutes one of the most devastating obstetric complications despite the advances in antenatal and intrapartum care during the past several decades. It remains a significant and understudied problem that accounts for almost 50% of all perinatal deaths [80]. This descriptive review has been developed to distill the burgeoning literature and place emphasis on the importance of adopting and implementing a consistent international strategy for the optimal investigation and management of this severe complication. The ultimate goal is to achieve timely diagnosis and effective treatment of the underlying pathology, provide an individualized approach, which takes into consideration parental wishes, needs and cultural beliefs, facilitate emotional closure and prevent recurrence when possible.

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Athanasiadis cooperated in the analysis and participated in the revision. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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