

Stillbirth and Bereavement: Guidelines for Stillbirth Investigation

This guideline was developed by the Maternal-Fetal Medicine Committee and reviewed by the Clinical Practice Obstetrics Committee. It was approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objectives: To provide an investigation protocol to help health care providers determine the cause of a fetal death.

Options: Consideration has been given to protocols for the investigation of fetal death that are currently available in Canada and in other countries.

Outcomes: Identification of possible causes of stillbirth and their relationship to future pregnancies.

Evidence: Articles related to the etiology of fetal death were identified in a search of MEDLINE (January 1993 to December 2004), the Cochrane Library, and investigation protocols from the American College of Obstetricians and Gynecologists, the Alberta Medical Association Committee on Reproductive Care, and the Centers for Disease Control and Prevention National Center for Health Statistics.

Key Words: Intrauterine fetal death investigation, fetal demise, stillborn

Benefits: To provide better advice for women regarding possible causes of fetal death and implications for future pregnancies.

Recommendation: A protocol should be used to investigate the possible cause of a fetal death. (II-B)

Validation: The evidence obtained was reviewed and evaluated by the Maternal-Fetal Medicine Committee and the Clinical Practice Obstetrics Committee of the Society of Obstetricians and Gynaecologists of Canada. The level of evidence and quality of the recommendation made was described using the Evaluation of Evidence criteria of the Canadian Task Force on the Periodic Health Examination.

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INTRODUCTION

Stillbirth is defined as death that occurs prior to the complete expulsion or extraction from the mother of a fetus of more than 20 weeks' gestation or weighing more than 500 g.¹

Stillbirth remains a relatively common complication in pregnancy. Although the rate decreased from 4.9 per 1000 total births in 1991 to a low of 4.1 per 1000 total births in 1998, in 2000 the rate was 4.5 per 1000 total births.² Health care providers are responsible for providing support to families and for investigating the causes of stillbirth. A complex chain of events can often precede the occurrence of stillbirth and, in retrospect, may be difficult to elucidate.

A large number of factors have been associated with the risk of fetal death. Some of them can be directly associated with fetal death; others may be indirectly associated. For example, hypertensive disorders may lead to placental insufficiency and fetal growth restriction or placental abruption and subsequently to hypoxia and fetal death. In order to make appropriate comparisons, standard definitions of causes of fetal death are necessary. Although the definitive cause of fetal death is unrecognized in the majority of cases,

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Table 1. Criteria for quality of evidence assessment and classification of recommendations

| Level of evidence* | Classification of recommendations† |
|---|---|
| I: Evidence obtained from at least one properly designed randomized controlled trial. | A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination. |
| II-1: Evidence from well-designed controlled trials without randomization. | B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination. |
| II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. | C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination. |
| II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category. | D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination. |
| III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. | E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination. |

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.⁶³

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.⁶³

certain broad categories can be defined: genetic, maternal systemic, infectious, placental, and fetal pathology. A systematic approach to fetal death may be valuable in determining a cause. A detailed questionnaire may help to isolate an etiology. This must include questions about the family history which can identify an inherited cause for stillbirth, the maternal history, including the past obstetrical and medical history, as well as history of the current pregnancy. It is important to look for specific fetal pathologic conditions, and, at time of delivery, to carefully examine the placenta and the umbilical cord.

Existing protocols were reviewed to establish this protocol.³⁻⁹ This list of suggested investigations is not intended to be exhaustive; it is intended as a guide to help physicians determine the cause of stillbirth when the etiology is not obvious.

MEDICAL HISTORY

Family History

In cases of unexplained fetal death, it is important to review the family history in detail to identify a possible inherited cause to explain the stillbirth. Familial disorders,¹⁰⁻¹⁵ a history of recurrent spontaneous abortions,¹⁰ venous thromboembolism or pulmonary embolism,¹¹ a previous child born with a congenital anomaly,¹² abnormal karyotype or syndrome,¹³ other inherited conditions,¹⁴ a child with a documented developmental delay, and consanguinity¹⁵ must be taken into account.

Maternal Disease

Maternal conditions have also been identified as a major cause of fetal deaths. Some medical conditions have been associated with stillbirth, including thromboembolic disorders,¹¹ diabetes mellitus,^{16,17} hypertensive disorders,¹⁸ presence of thrombophilia,^{19,20} autoimmune disease,^{21,22} epilepsy,²³ severe anemia,²⁴ and maternal cyanogenic heart disease.²⁵

Maternal Risk Factors

Documentation of the past obstetric history as well as the history of the current pregnancy may be important in identifying the cause of fetal death. Identified maternal risk factors include advanced maternal age, nulliparity, maternal smoking during pregnancy, and high pre-pregnancy weight.^{9,26-30} Several studies have shown that the risk increases with younger and older maternal age, high parity, prior fetal loss, inadequate prenatal care, smoking, lower socio-economic status, and reproductive tract infections.³⁰⁻³³ A study by Salihu et al. found an increased risk among older smokers than among younger smokers.³⁴ In contrast, in a recent Canadian study cohort of 196 unexplained fetal deaths, Huang et al.²⁷ observed no significant association between stillbirth and the following factors: maternal age under 20 years, pre-pregnancy weight under 45 kg, low maternal BMI, low rate of weight gain, no visit in the first trimester, cigarette smoking, alcohol consumption, fetal sex, ratio of placental weight to birth weight, previous fetal death, or previous abortion (spontaneous or induced). These different results warrant further investigation before these factors can be excluded as potential causes of fetal

death. Some researchers have found an increased risk of stillbirth with illicit drug use, attributable to direct toxicity or the indirect effect on other risk conditions such as abruptio placentae.³¹

Recently, Glantz et al. reported from a prospective cohort study in Sweden that included 445 485 pregnancies that intrahepatic cholestasis of pregnancy was associated with fetal complications such as spontaneous preterm delivery, asphyxial events, fetal death, and meconium.³⁵ In fact, the probability of fetal complications increases by 1% to 2% per additional $\mu\text{mol/L}$ of serum bile acids above 40 $\mu\text{mol/L}$. Williamson et al. documented the clinical features of obstetric cholestasis pregnancies in women of European heritage in the UK. Of the affected pregnancies, 352 (7%) were complicated by intrauterine death, which mainly occurred after 37 weeks' gestation. No association was found between the intensity of pruritus and fetal death. These results suggest that fetal monitoring in presence of cholestasis and delivery after 37 weeks' gestation is warranted.³⁶

Fetal Conditions

Traditionally, fetal conditions such as congenital anomaly¹² or infection,³⁷ fetal growth restriction,³⁸ or previous fetal growth restriction,³⁹ previous fetal demise,⁴⁰ massive placental abruption,⁴¹ and maternal-fetal hemorrhage,⁴² have been mentioned as important causes of stillbirth. Fretts et al.⁶ demonstrated temporal changes in cause-specific fetal death rates from the 1960s to the 1980s. They found that fetal death caused by Rh alloimmunization had almost disappeared with a significant decline in those caused by fetal growth restriction.⁶ Likewise, Benirschke and Robb⁴³ reported that viral infections no longer represent a major cause of fetal death. They specifically noted, as well as Incerpi et al.,⁷ that congenital infections with toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus are uncommon causes of fetal death. However, infection with parvovirus B19 and subsequent non-immune hydrops, remains a significant infectious cause of fetal death.^{44,45} Complications of multiple gestations (e.g., twin-twin transfusion syndrome,^{46,47} stuck twin,⁴⁸ and placental insufficiency⁴⁹) are still associated with an increased risk of fetal death.

This systematic approach to stillbirth is not complete without a meticulous examination of the placenta,^{50,51} membranes, and umbilical cord.⁵²⁻⁵⁴ Placental or cord complications can be detected by ultrasound or by macroscopic evaluation. Rayburn et al. demonstrated significant placental aberrations in 87 of 89 stillbirths.⁵⁰

INVESTIGATIONS

The following investigations are based on the above factors and on the results of studies evaluating protocols.^{55,56} This suggested list may be modified when a specific cause of stillbirth is obvious.

Maternal Investigations

Maternal investigations must include the following:

1. Complete blood count (CBC)
2. Blood group and antibody screen
3. Glycosylated haemoglobin
4. Kleihauer Betke test
5. Serology for toxoplasma, other viruses, rubella, cytomegalovirus, herpes virus (TORCH), and parvovirus B19
6. Karyotype on both parents (in cases with 3 or more recurrent spontaneous abortions, or previous or current fetus or newborn with congenital malformations)
7. Hemoglobin electrophoresis (in cases where the fetus is hydropic, the mother is anemic, or α -thalassemia is considered in the differential diagnosis)
8. Anti-platelet antibodies (if alloimmune thrombocytopenia is suspected such as previous neonatal thrombocytopenia)
9. Thrombophilia should be done 6 to 8 weeks after delivery as protein S normally decreases in pregnancy⁵⁷ (in cases where a maternal thrombophilia is suspected based on clinical history, or there is no other explanation for the stillbirth). These investigations include antithrombin, protein C and protein S deficiency, factor V Leiden, factor II mutation, mutation of the methylene tetrahydrofolate reductase enzyme or hyperhomocysteinemia, lupus anticoagulant, and anticardiolipins antibodies.
10. Disseminated intravascular coagulopathy (in cases of a massive placental abruption as the cause of intrauterine fetal death)

Fetal Investigations

Autopsy

An autopsy is one of the most useful steps in determining the cause of fetal death⁵⁸ and its importance should be emphasized to the family. The special expertise of a pathologist in perinatal medicine and a consultation with a geneticist may be useful with methodical gross and microscopic examination of the fetus and the placenta at delivery.⁵⁸ However, despite careful examination of the fetus and placenta at autopsy, failure to determine a specific cause of death still occurs in as many as 25% of fetal losses.⁵⁹ When autopsy is declined, examination of the fetus and placenta

by consultation with someone with special expertise is important.⁵⁸

Karyotype

Practitioners should consult their genetics and/or pathology departments regarding the most effective means of obtaining a karyotype. A cord blood sample for cytogenetic studies should be collected after delivery from all stillbirths. The specimen should be stored until the geneticist or the clinical pathologist determines whether the specimen should be sent for cytogenetic studies. Another option is to perform an amniocentesis for culture of amniocytes, which offers the best likelihood of obtaining a fetal karyotype, especially in cases where it is anticipated that autolysis will interfere with cytogenetic analysis of fetal tissues.⁶⁰ Tissues suitable for karyotype analysis include (1) spleen, skin, and cartilage, if consent for autopsy granted; (2) Achilles tendon and/or intracardiac fetal blood (when available), if baby macerated; (3) placental wedge, if consent for autopsy withheld; (4) fetal body fluid: ascites, hygroma, and pleural effusion.

Cytogenetic studies should be considered if there is evidence of any of the following: (1) congenital malformation, (2) intrauterine growth restriction, (3) hydrops, (4) ambiguous genitalia, (5) dysmorphic features. Cytogenetic studies should also be considered if a parent is known to be a carrier of a chromosome re-arrangement or if a parent has a history of any of the following: recurrent miscarriages or previous stillbirth, neonatal death, or child with congenital anomalies.

Clinical photographs and X-rays: should be taken if clinically warranted.

Placenta Investigations

The clinician who delivers the fetus should examine the placenta and report any observations or findings. In the case of twins, chorionicity of the placenta should be determined. The pathologic examination of the placenta should include the following: (1) cord: thrombosis and true knot; (2) placenta: infarcts, calcifications, thrombosis, hematoma, abruption (clot), and vascular malformation; (3) signs of subclinical infection: funicitis, amnionitis.^{50-54,61}

A bacterial culture of the chorion is recommended. Bacterial cultures of the fetal surface of the placenta, including Group B *Streptococcus*, *Listeria*, *E. coli*, must be performed. Other cultures may be considered if clinically indicated.

GRIEF MANAGEMENT AND FOLLOW-UP

In addition to investigating the medical aspects of a stillbirth, it is important to consider the psychological effects on the family. Referral to local or community support services is recommended. A recent article in *Journal of Obstetrics*

and *Gynaecology Canada*⁶² discusses grief management and may assist the practitioner in helping patients deal with their grief. After investigations are completed and the results are available, it is important that information about the cause of death and whether it might affect future pregnancies be provided to the family as soon as possible.

Despite an exhaustive review of the potential factors associated with fetal death, one-quarter remain unexplained.⁵⁹ A systematic approach to fetal death remains our most valuable tool to elucidate this devastating complication.

Recommendation

1. A protocol should be used to investigate the possible cause of a fetal death. (II-B)

CHECKLIST

The following checklist is added to help the clinician at time of delivery to better investigate the potential cause of stillbirth.

A. Family History

(i) Review of family conditions

- Recurrent spontaneous abortions¹⁰
- Venous thromboembolism (VTE) or pulmonary embolism (PE)¹¹
- Congenital anomaly¹² or abnormal karyotype¹³
- Hereditary condition or syndrome¹⁴
- Developmental delay¹⁴

B. Maternal History

(i) Review of maternal medical history

- VTE or PE¹¹
- Diabetes^{16,17}
- Chronic hypertension¹⁸
- Thrombophilia^{19,20}
- Lupus²¹
- Autoimmune disease^{21,22}
- Epilepsy²³
- Severe anemia²⁴
- Consanguinity¹⁵
- Maternal heart disease²⁵

(ii) Review of maternal past obstetric history

- Recurrent miscarriages¹⁰
- Baby with anomaly or hereditary condition¹²⁻¹⁴
- Growth restriction³⁹
- Gestational hypertension with proteinuria with adverse sequelae¹⁹
- Massive placental abruption⁴²
- Fetal demise⁴¹

C. Current Pregnancy History

- Maternal age⁹
- Gestational age at fetal death
- Hypertension¹⁹
- Pre-existing or gestational diabetes^{17,18}
- Smoking, alcohol, or substance abuse³¹
- Pre-pregnancy weight^{28,29}
- Abdominal trauma⁴²
- Cholestasis^{42,43}
- Placental abruption⁴¹
- Maternal-fetal hemorrhage⁴²
- Preterm premature rupture of membranes or prelabour⁶⁰

(i) Specific fetal conditions

- Alloimmunization⁴⁵
- Non-immune hydrops⁴⁴
- Growth restriction^{17,18,48}
- Infection⁴²⁻⁴⁴
- Congenital anomalies¹²
- Chromosomal abnormalities^{13,14}
- Complications of multiple gestations (e.g., twin-twin transfusion syndrome, stuck twin, placental insufficiency, polyhydramnios-oligohydramnios sequence)⁴⁶⁻⁴⁹

(ii) Placental or cord complications detected by ultrasound or macroscopic examination⁴⁷⁻⁵³

- Large or small placenta
- Hematoma
- Edema
- Large infarcts
- Abnormalities of structure, length, or insertion of the umbilical cord
- Cord prolapse
- Cord knots
- Placental tumours

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