Seminars in Fetal & Neonatal Medicine xxx (2017) 1–9

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Perinatal death investigations: What is current practice?

J.W. Nijkamp [a, *], N.J. Sebire [b], K. Bouman [c], F.J. Korteweg [d], J.J.H.M. Erwich [a], S.J. Gordijn [a]

[a] Department of Obstetrics and Gynecology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[b] Department of Pediatric Pathology, Clinical Molecular Genetics, Great Ormond Street Hospital for Children and UCL Institute of Child Health, London, UK
[c] Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[d] Department of Obstetrics and Gynecology, Martini Hospital, Groningen, The Netherlands

Keywords:
Perinatal death
Stillbirth
Investigation
Placental histology
Postmortem
Autopsy

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

* Corresponding author. Department of Obstetrics and Gynecology, University Medical Centre Groningen, CB 21, P.O. box 30001, 9700 RB Groningen, The Netherlands.
E-mail address: j.w.nijkamp@umcg.nl (J.W. Nijkamp).

http://dx.doi.org/10.1016/j.siny.2017.02.005
1744-165X/

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)

Please cite this article in press as: Nijkamp JW, et al., Perinatal death investigations: What is current practice?, Seminars in Fetal & Neonatal Medicine (2017), http://dx.doi.org/10.1016/j.siny.2017.02.005