Fetal death
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General introduction and outline of the thesis
Fetal death

Fetal death or stillbirth is a major obstetrical complication and a devastating experience for parents and caregivers. For bereaved parents it is among the most stressful life events and it is not seldom that they show acute emotional distress and symptoms of depression. Stillbirth is defined as the delivery of a baby showing no signs of life as indicated by the absence of breathing, heartbeats, pulsation of the umbilical cord, or definite movements of voluntary muscles. Fetal death, the largest subgroup of perinatal mortality worldwide consists of intrauterine antepartum fetal deaths (IUFD) and intrapartum fetal deaths.

There is not complete uniformity internationally with regard to birth weight and gestational age criteria for reporting fetal death and perinatal mortality as a whole. In 1992, the WHO introduced the 10th revision of the International Classification of diseases (ICD-10) which defines for perinatal mortality the period commencing at 22 completed weeks of gestation (birth weight is normally about 500 grams) and ending 7 days postnatally. However, the suggested requirement is to report intrauterine fetal deaths at 20 weeks of gestation or greater, or a weight greater than or equal to 350 grams if the gestational age is unknown. Worldwide an estimate of at least 3.2 million stillbirths occur each year. The majority of these deaths occur in developing countries. In developed countries approximately 1 in 200 pregnancies ends in stillbirth. In the US approximately 25,000 stillbirths are reported annually. For the Netherlands this is 1200-1400 stillborn babies ≥ 22 weeks of gestation. This is five times higher than deaths due to the sudden infant death syndrome and nearly double the number of lethal traffic accidents in the Netherlands. Of these stillborn babies 900-1200 are intrauterine antepartum fetal deaths. There has been no reduction in the intrauterine fetal death rate over the past 20 years. While neonatal death and intrapartum fetal death rates have continued to steadily decline with improvements in care, antepartum fetal death has emerged as the leading category of perinatal mortality. Many IUFDs occur unexpectedly towards the end of pregnancy.

Peristat is a perinatal monitoring programme initiated by the European Committee to benchmark perinatal mortality between European countries. The Peristat studies showed that perinatal mortality above 22 weeks of gestation, especially fetal mortality, was substantially higher in the Netherlands when compared to other European countries. In Peristat-I the Netherlands had the highest fetal mortality rate (7.4 per 1000 total number of births). In Peristat-II after France, the Netherlands had the second highest fetal mortality rate (7.0 per 1000 total number of births). The Netherlands has a relatively high number of home births but these do not seem to increase the risk of perinatal mortality and severe perinatal morbidity.
among low-risk women if the maternity care system facilitates this choice through the availability of well-trained midwives and a good transportation and referral system.\textsuperscript{10} The Netherlands has a relatively high number of older mothers and multiple pregnancies, both only partly explain the high Dutch perinatal mortality rate.\textsuperscript{9} In addition, Dutch parents make less use of prenatal diagnosis and subsequent termination of pregnancy for congenital anomalies while Dutch neonatologists are more likely to refrain from treating very preterm newborns if their prospects are unfavourable. The Peristat group ended their conclusion with an advice for a more prominent position for perinatal health and the quality of perinatal healthcare in Dutch research programmes.

Fetal death is an under-recognised and under-researched public health problem. Health care providers are responsible for providing support to parents and their families and for investigating the cause of fetal death. Although many risk factors have been identified unfortunately the cause of death remains unexplained in about two-thirds of cases.\textsuperscript{11-13} Efforts to address this problem are limited by the lack of information on causes of death. Underpinning this lack of information is that there is internationally no consensus regarding classification of cause and diagnostic investigations into causes of fetal death. In most cases, fetal death certificates are filled out before a full postmortal investigation is performed, and amended death certificates are rarely filled when additional information from the fetal death evaluation emerges.

**Classification of cause of perinatal mortality**

While there will always be a degree of uncertainty about whether any particular perinatal death was actually caused by a particular condition, there are intensified demands on medical, political and epidemiological grounds for proper determination and classification of cause of perinatal death. This is essential for parents in their process of mourning and to alleviate feelings of guilt, which parents often experience. It can also give parents and caregivers insight into why it happened. Determination of a cause is needed in order to be able to ascertain the recurrence risk and for aiding counselling for future pregnancies, siblings and families. In addition it enables comparison of national and international health care and aids prevention and future research.\textsuperscript{8,14-16} Even when a cause of death is not identified exclusion of other causes is also valuable.

Classification of perinatal mortality is complex due to the complicated pathophysiological processes encountered in the mother, fetus and placenta, and as a result of their interaction.\textsuperscript{17} Often there is a complex chain of events preceding death. The multiplicity of contributing factors and the different background of the clinicians involved, adds to the confusion.
More than thirty classification systems for perinatal mortality have been introduced since 1954. Different classification systems have been designed for diverse reasons with different purposes, approaches, definitions, levels of complexity and availability of guidelines. These systems have differing categories for classifying causes and varying definitions for relevant conditions. Clear uniform definitions and classification guidelines make a model easy to use and uni-interpretable. However, definitions of cause of death categories and guidelines are incomplete or not described in more than half of the systems. As a result, no single classification system is universally accepted and each has strengths and weaknesses.

Guideline for investigation of fetal death

While the approach to classification is partly responsible for inadequately investigated fetal deaths, the level of investigation also plays an important role. The value of any classification system is primarily dependent on identifying and collecting all important information for each mortality case. This is best achieved through a systematic approach to diagnostic investigation or work-up and review of findings in the context of the clinical setting in which the death occurred. Such protocols increase and enhance the diagnostic accuracy and consistency of the investigation process. The purpose of a formal stillbirth investigation guideline is to guide health professionals in the stillbirth investigation process and to provide information concerning the cause of death. The proportion of unexplained stillbirths is lower in centres that conduct a systematic and well defined evaluation for causes of stillbirth. However, in many studies of investigation protocols, still a large proportion of stillbirths remain unexplained ranging from 36% to 60%. Due to limitations in current research and the complexity of the issue, the optimal workup after fetal death is unknown. Both internationally and in the Netherlands there is no uniform evidence-based workup guideline after fetal death. Local protocols have often been designed on expert opinion; they differ and are extensive. This brings along high costs and a strain for parents. The value of many commonly used diagnostic tests for determination of cause of fetal death is unclear. Consequently, there is discussion about which tests and examinations should be included in a routine investigative workup to ensure an acceptable chance of determination of the cause of fetal death. A comparison of the components of currently used protocols identified wide variation. The authors of a recent review concluded that autopsy and placental pathology were valuable. Due to a lack of high quality data on the value of other investigations, no formal scientific judgement could be made on which is the most appropriate guideline for stillbirth investigations, or which components should be considered for the most relevant and efficient investigative
The aim of investigation is to optimise diagnostic accuracy while limiting the burden of testing for women so soon after the tragedy of stillbirth. In current practice, the majority of stillbirths are inadequately investigated and therefore important information may often be missed. We demonstrated earlier that up to 50% of diagnostic test results after fetal death are incomplete or missing, resulting in disappointment, frustration and emotional burden for parents and caregivers.

**ZOBAS study**

In 2002 we initiated the ZOBAS (Zinnig Onderzoek Bij Antepartum Sterfte) study. This is a prospective cohort study investigating the value of diagnostic tests after intrauterine antepartum fetal death for determination of cause of death. This study was performed in 50 secondary and tertiary referral hospitals in the Netherlands (Appendix 1: ZOBAS participating hospitals), serving rural as well as urban populations from 2002 to 2008. Inclusion criteria were singleton intrauterine fetal deaths diagnosed antepartum (heartbeat ceased before labour) after 20 weeks of gestation. Pregnancy terminations and intrapartum deaths were excluded. A total of 1025 intrauterine antepartum fetal deaths were included. The study was approved by the review boards of all hospitals and written informed consent was obtained from all participants. Each couple whose fetus died, was managed in the same way. Data were collected for each intrauterine antepartum fetal death, including medical and obstetric history, maternal and fetal characteristics, and pregnancy and birth details (Appendix 2: case record form). Our diagnostic work-up protocol was based on currently used local protocols and diagnostics were included if most Dutch hospitals performed these tests after fetal death (Appendix 3: diagnostic flowchart). The protocol included: maternal blood tests including full blood count, chemistry and viral serology; coagulation tests for couples performed centrally in the laboratory in Groningen; fetal blood tests including viral serology; microbiological cultures from the mother, fetus and placenta; autopsy; placental examination (Appendix 4: pathology protocol); and cytogenetic analysis. Multidisciplinary panel classification sessions were set up for determination of cause of all fetal deaths and the value of diagnostics in this determination.
Outline of this thesis

The studies in this thesis discuss the dilemmas around classification of the cause of perinatal mortality and diagnostic work-up after intrauterine antepartum fetal death to determine the cause of death. *Part I - Classification of perinatal mortality* focuses on diverse aspects of different classification systems for perinatal mortality. *Part II - Value of diagnostic tests after intrauterine antepartum fetal death* focuses on different causes of fetal death, their clinical manifestations and the value of different diagnostic tests in allocating an underlying cause of death. *Part III - Fetal death workup guideline* describes a proposal for fetal death diagnostic work-up after evaluation of the ZOBAS cohort.

**Part I**

Classification of perinatal mortality

Classification of perinatal mortality has been a topic of interest for several decades. No national or international consensus has been achieved on which system to use. In Chapter 1 a newly developed classification system, the Tulip classification is discussed which separates cause, mechanism, origin of mechanism and contributing factors of perinatal mortality for the purpose of counselling and prevention. The goal was to propose a well defined, unambiguous, single cause system aiming to identify the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death, based on the combination of clinical findings and diagnostic test results including pathological findings. In Chapter 2, use of the Tulip classification for allocation of cause of fetal death is compared to other currently used international classification systems. The focus is on placental causes of death and whether information was gained or lost by classification in the different systems because this could have consequences for counselling parents, targeting research and preventive strategies, and for the validity of statistics. In Chapter 3 existing classification systems are compared regarding their definition of the perinatal period, level of complexity, inclusion of maternal, fetal and/or placental factors and whether they focus on a clinical or pathological viewpoint. This led to proposal of a systematic multilayered approach for the analysis of perinatal mortality using one or more of the previously published classification systems.
Part II

Value of diagnostic tests after intrauterine antepartum fetal death

A second topic that will be discussed in this thesis is the value of diagnostic tests after intrauterine antepartum fetal death for allocation of different causes of death. A large cause of death category is placental pathology. The value of placental examination and the occurrence of different placental causes related to different gestational age periods, and their clinical manifestations during pregnancy in the ZOBAS cohort are described in Chapter 4. One of these placental causes is the relatively unknown villus immaturity causing unexpected fetal death after 36 weeks of gestation. The prevalence and clinico-pathological associations of this entity are described in Chapter 5. A substantial proportion of intrauterine antepartum fetal deaths are caused by genetic abnormalities. Criteria for investigation into chromosomal abnormalities after fetal death differ internationally with recommendation of different techniques and different groups to be tested ranging from testing all fetal deaths to a select group. In Chapter 6, success rates are estimated for cytogenetic analysis in different types of tissue after fetal death in the ZOBAS cohort. In addition, selection criteria for cytogenetic analysis are studied and the value of this test for determination of the cause of fetal death. This led to recommendations for a fetal death cytogenetic flowchart. Maternal inherited thrombophilic defects are recognized as risk factors for pregnancy complications such as severe pre-eclampsia, placental abruption, intrauterine growth restriction and fetal death. However, this has not been demonstrated consistently. In a retrospective family cohort study (Descartes study) of women with hereditary deficiencies of either antithrombin, protein C and S, the absolute risk of fetal death comparing deficient women to non-deficient female relatives was calculated and the contribution of additional thrombophilic defects to this risk (Chapter 7). The pathophysiology of fetal death associated with thrombophilia is presumed to be thrombosis in the uteroplacental circulation. Although this association remains uncertain this has resulted in routine thrombophilia work-up after fetal death in many hospitals. In Chapter 8 prevalence of maternal thrombophilic defects, either acquired or inherited, and paternal thrombophilic defects in the ZOBAS cohort were compared to prevalence in the normal population. Furthermore, the association between these thrombophilic defects and the various causes of fetal death within this cohort was assessed.
Part III

Fetal death workup guideline

There is no international golden standard fetal death work-up guideline. This limits investigation into causes. Chapter 9 describes identification of valuable tests for determining the cause of intrauterine antepartum fetal death by a multidisciplinary evaluation of diagnostic procedures performed prospectively in the ZOBAS cohort. This led to recommendations for a basic and selective workup guideline for fetal death.

Finally, the results of the studies are summarized in English and Dutch and in the ‘general discussion and future perspectives’ section currently ongoing and new research developments in the field of fetal death classification, investigation and prevention are discussed.
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