Fetal death
Korteweg, Fleurisca Joyce

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General discussion and future perspectives
As described in this thesis, to gain more insight into causes of intrauterine antepartum fetal death and perinatal mortality as a whole an optimal multidisciplinary classification of cause of death, mechanism, origin of mechanism and contributing factors to death are essential. By improving diagnostic work-up after intrauterine antepartum fetal death, we can enhance the chances of determining the cause of fetal death. By studying occurrence and clinical manifestations of different causes of death the pathophysiology can be further unravelled. The following paragraphs describe aspects of focus and currently ongoing and future research on fetal death, the development of audit of perinatal mortality, consensus regarding diagnostic investigations into causes of fetal death and the development of possible strategies to bring down fetal death rates.

Fetal death

Fetal death is gradually being recognised as a global major health problem. One of the millennium goals of the World Health Organisation (WHO) was “Make Every Mother and Child Count”. This project examines the reasons why so many children under five years of age and women in pregnancy, during childbirth or soon after continue to die from causes that are largely preventable. In addition to this project, the WHO considers stillbirth as an indicator for performance of health care service delivery systems. A WHO global goal is to bring down fetal death rates, to raise the issue of this public health tragedy and to secure political commitment for adequate investment. In 2000 the International Stillbirth Alliance (ISA) was introduced, a non-profit coalition of organizations dedicated to understanding the causes and prevention of stillbirth. In the meantime, this organisation has brought together international leading researchers in the field of stillbirth enabling collaboration on different aspect of work and discussion on international consensus regarding definition, classification and diagnostic work-up after fetal death. In order to compare perinatal mortality rates including stillbirth, uniform definitions concerning the perinatal period are needed. Globally these differ. Despite earlier recommendations, definitions within Europe also still differ.1 Nationally there is now definition consensus; this was accomplished by linking the datasets of the national obstetric registration (LVR 1-2) and the national neonatology registration (LNR). Perinatally related deaths beyond 20 weeks of gestation are defined as stillbirths, early neonatal deaths are deaths up to seven completed days after birth, late neonatal deaths are deaths from eight up to 28 completed days after birth and perinatally related infant deaths are deaths from 29 days up to six completed months after birth during hospital admission from birth onwards.
Raising public awareness is also one of ISA’s goals. Regarding this aspect in the United Kingdom, SANDS a large stillbirth and neonatal death charity has recently initiated the public champagne: “Why are 17 babies a day dying and what can be done to halt this national tragedy?” In the Netherlands this public awareness has partly been raised by the results of the Peristat studies, revealing that the Netherlands is among the European countries with the highest perinatal mortality rates. However, there is little publicity regarding perinatal mortality compared to the amount of campaigns for instance on lethal traffic accidents, which is half the number of perinatal mortality. In addition, in the Netherlands it is very difficult to acquire money for research in the field of perinatal mortality; there are no fund raising organisations and few grants for this research field.

Classification of cause of perinatal mortality

The presented studies in this thesis addressed the need for a uniform classification system for perinatal mortality to be used in multidisciplinary panel meetings. Our proposed “Tulip classification” aids in classification of underlying cause of death, mechanism, origin of mechanism and contributing factors to perinatal mortality. In comparison to other classification systems, this system studies fetal death by considering all three entities mother, fetus and placenta and their interaction. The Tulip system does not confuse underlying cause of death with mechanism of death, risk factors and clinical manifestations. It has accessible user guidelines with case examples and defined agreements. We acknowledge that this system is ambitious and extensive requiring adequate perinatal mortality input data. However, in a well-developed country as the Netherlands we should be able to meet these quality requirements. The Tulip classification mainly answers the question “why” perinatal mortality occurred. By combining this system with other classification systems in sequence of increasing difficulty our proposed multilayered classification system also answers the questions “when” and “what” concerning perinatal mortality. By using a combination of classification systems this may compensate for shortcomings of individual systems. The high proportion of unexplained stillbirths in developing countries is a major barrier to future improvement in the stillbirth rate. A substantial proportion of unexplained stillbirths are almost certainly a result of inadequate investigation rather than a medical mystery. Classification systems that facilitate storage and retrieval of important information in the understanding of the death are essential. In countries with fewer resources, health care workers are able to classify perinatal deaths in the multilayered classification system to the extent of what is possible.
Multidisciplinary audit groups

For an optimal review and classification of perinatal deaths multidisciplinary audit groups consisting of obstetricians, perinatal pathologists, neonatologists, geneticists and in some cases other specialists are essential. Discussions in these meetings provide the best insight into the pathophysiology of these deaths and may result in an optimal counselling of parents on the outcome. In developing and developed countries, suboptimal factors that contribute to perinatal death have been identified. The EuroNatal study involving ten European countries showed that substandard care was possibly or likely to have contributed to death in about half of the 1619 perinatal deaths reviewed.4 The most frequent suboptimal factors in this study were maternal smoking and failure to detect fetal growth restriction in the antenatal period. Assessment for the presence of potentially avoidable contributing factors or suboptimal care should also be recognized and documented in these multidisciplinary audit meetings and are the backbone of practice improvement through feedback of information and lessons learned.

In England and Norway, a national system of perinatal audit has been established. This has resulted in better collaboration around perinatal mortality, recommendations for guideline development, education and a higher quality of care.5,6 In the Netherlands further national perinatal audit activities are being developed. In response to the Peristat results2,3 the possible influence of substandard care was studied by a national feasibility study for audit of perinatal mortality: the National Perinatal Audit Study (LPAS). This study concluded that in 19% of perinatal mortality different substandard factors were possibly related to death and in 9% related to death and potentially avoidable.7 Methods for initiation of national multidisciplinary perinatal audit were developed and the authors advised to organise local perinatal audit meetings. Subsequently, the study of Implementation of structural feedback by means of Perinatal Audit to Caregivers in cases of perinatal mortality in the northern region of the Netherlands (IMPACT) was set up. This project aids in the initiation of structured multidisciplinary perinatal audit meetings for health care workers involved in perinatal mortality.

The ministry of Health, Welfare and Sport (VWS) has supplied a grant until 2012 for national introduction of perinatal audit. From 2007 the National Institute for Public Health and the Environment (RIVM) further developed this national audit study. In June 2010 the PAN (Perinatal Audit Netherlands) foundation will further take over these activities. This foundation is an already active collaboration of the national professional organisations of midwives, gynaecologists, pathologists, paediatricians and general practitioners working on perinatal audit. Their goal is to audit all Dutch cases of perinatal mortality. Our proposed multilayered approach for perinatal mortality including the Tulip classification is being used for these
national audit activities. National perinatal audit has three pillars: local, regional and national giving possibilities for investigation of national trends and areas of focus for training, amendment of guidelines and prevention. Essential in the process of implementation of audit is adequate and open communication regarding this issue. One of these aspects is coaching of professionals in the background of perinatal mortality, familiarity with use of classification systems and distribution of classification guidelines with agreements and case examples. This will enhance their motivation to participate in these meetings.

Consensus on classification of perinatal mortality
To accomplish comparison of European perinatal mortality rates we need to reach European consensus on classification of perinatal mortality. The European Board and College of Obstetrics and Gynaecology (EBCOG) should take the initiative to reach an agreement about this. Only then will we be able to identify why Dutch perinatal mortality figures are higher than the rest of Europe.
Consensus internationally on classification of perinatal mortality is the ultimate goal. Recently, the National Institute of Child Health and Human Development (NICHD) in the United States initiated an international stillbirth classification workshop. Participants came to a consensus regarding the pathophysiology of various conditions underlying stillbirth to improve the classification of causes of death. These definitions of causes of death are the first step to achieve uniformity regarding allocation of causes. While there is evidence for some conditions to rise to the level of probable causes of death, there is still varying certainty in establishing other causes because of our incomplete understanding of the underlying pathophysiology. The Tulip classification is designed in such a way that future knowledge allows expansion or amendment of cause of death categories. Based on the occurrence of our reported placental pathologies in the ZOBAS study (studying valuable tests after intrauterine antepartum fetal death) we proposed amending the subgroups of placental causes of death in the Tulip classification. Essential in this process is always to go back to the initial, demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death when allocating a cause. There will be an ongoing process of amendments of cause of death categories as these are currently based on the existing knowledge we have on these entities.

Guideline for investigation of fetal death
As described in this thesis, to optimize investigation into cause of fetal death a ‘golden standard’ guideline is essential. On the base of our findings, we proposed an
intrauterine antepartum fetal death work-up guideline for diagnostic investigation in order to classify underlying cause of death. This proposal included a basic and an additional workup after fetal death based on our multidisciplinary evaluation of diagnostic procedures in determining cause of fetal death. We concluded that autopsy, placental examination, cytogenetic analysis and testing for fetal-maternal haemorrhage are the base for diagnostic work-up for all fetal deaths. For further sequential testing, based on the results of these tests or clinical characteristics, serum for maternal virus serology and material for maternal, fetal and placental cultures or other microbiological diagnostic tests should be obtained and stored from all fetal deaths. The investigations for intrapartum deaths can be extracted from this protocol as the underlying causes are mostly the same. To implement these work-up findings nationally in daily patient care a national practice guideline will be extracted from our results in collaboration with the Dutch Society of Obstetrics and Gynaecology (NVOG). Earlier, fetal death workup protocols were based on expert opinion with controversies about what tests should be undertaken often resulting in hesitance of clinicians to adopt recommendations and a non-systematic approach to evaluation. The extent to which this suboptimal diagnostic approach is artificially inflating the number of unexplained stillbirths in the Netherlands is unknown. A side effect of implementation of our proposed evidence based work-up guideline could be an increase in deaths with a known cause, specially the group where important information was missing. Future studies should address this issue. With adequate implementation of this fetal death work-up guideline through publicity, education and training, optimal uptake of these findings should be ensured. In Australia and New Zealand, an educational program has been developed by the national Stillbirth Alliance Research Collaborative to assist with implementation of their stillbirth guidelines. The program is a small group, interactive, multi disciplinary skills training course, based on the SCORPIO model designed to address the educational needs of all health professionals involved with childbirth and early newborn care.

Placental pathology

In this thesis, we concluded that more than half of the intrauterine antepartum fetal deaths were caused by placental pathology. Concerning this cause of death group there are two main issues that require attention and further research. Firstly, assessment of published work on placental pathologies and stillbirth is impeded by a general absence of standard definitions and nomenclature between studies. For example, for the discussed placental pathology villus immaturity there is not yet a general accepted definition. International consensus on definitions of different placental pathologies causing death needs to be further accomplished. Secondly,
the pathophysiology underlying both acute and chronic placental dysfunction is mostly unclear. With further investigation into the origin of these pathologies, occurrence and clinical manifestations, the cause of death categories will change. Based on differences in clinical manifestations we found evidence for separation of the cause placental hypoplasia and placental bed pathology. We subdivided the large group of fetal deaths caused by placental hypoplasia in relative and absolute hypoplasia. These two sub causes could be an expression of two different underlying pathophysiological entities. With more insight into this cause, placental hypoplasia could even become a clinical manifestation comparable to fetal growth restriction that was regarded as a cause of death earlier.

Cytogenetic analysis

Our results indicated that cytogenetic analysis for all intrauterine antepartum fetal deaths is valuable, preferably by invasive testing before labor as analysis of tissue postpartum had a high rate of failure. This implies that health care workers involved with fetal death should be able to perform amniocentesis or chorionic villus biopsy. If they do not have the expertise, couples should be referred to centres that perform invasive testing. Advances in molecular genetic technology will hopefully improve our ability to identify more genetic causes of stillbirth. Additional molecular cytogenetic analyses, such as fluorescent in situ hybridization, multiplex ligation-dependent probe amplification, comparative genomic hybridization and quantitative fluorescent polymerase chain reaction, have been advised if cells do not grow in culture. Although the numbers of these tests in our study were small, these techniques seem promising. The feasibility of these techniques in common practice needs further evaluation.

Thrombophilia

In our retrospective thrombophilia family cohort study, hereditary antithrombin and protein C deficiencies were associated with a high absolute risk of fetal death. An additional effect of cosegregation of other thrombophilic defects was not demonstrated. We concluded that this may be due to the exclusion of women at highest risk of venous thromboembolism. The group of women we studied is a group with non-prevalent hereditary thrombophilic deficiencies. Women from these families have often been confronted with thrombophilia related problems in their families or by their own around the age of childbearing. Some women have therefore already been tested for thrombophilic deficiencies in family setting. We must keep in mind that this is a special non-prevalent group of women with thrombophilia related risks. Our results support those of others that advise thrombophilia testing in women with fetal death with a family history of hereditary thrombophilia or a personal history of venous thromboembolism, in whom testing could help prevent further maternal venous thromboembolism. In contrast to standard care in many hospitals, the need for routine testing of thrombophilic defects after intrauterine antepartum
fetal death was not supported by the results of the ZOBAS study. We showed that plasma levels of acquired thrombophilic defects changed during pregnancy. More women with fetal death had decreased antithrombin and protein C and increased von Willebrand factor plasma levels than pregnant women with uncomplicated pregnancies. However, compared to plasma levels in the normal population we only observed more women with fetal death with increased von Willebrand factor. Prevalence of inherited thrombophilias was not higher in couples with fetal death than in the normal population. Our results of main cause of death groups did not confirm the hypothesis that the pathophysiology of fetal death associated with thrombophilia is thrombosis in the uteroplacental circulation. Neither inherited nor acquired maternal or paternal thrombophilic defects were associated with main causes of death, but of placental causes abruption and infarction were associated with acquired maternal defects.

The clinical implications of these findings are yet unclear. Testing for abnormal levels of antithrombin, protein C, total protein S or von Willebrand factor may yield valuable predictors for a subgroup at risk for fetal death. However, thrombophilia screening should only be performed in cases where a proper management can be offered. As long as there are no randomized controlled trials proving the benefits of anticoagulant therapy in cases with known thrombophilic factors in relation to pregnancy outcome, we must be reserved about implementing a potentially harmful intervention in pregnant women.

Valuable tests

From our studies, we concluded that pathological examination consisting of autopsy and placental examination; and chromosomal analysis were valuable in the determination of cause of intrauterine antepartum fetal death. Parents should be informed about the reasons for and value of autopsy, placental examination and chromosomal analysis and their procedures. Health care workers involved in perinatal mortality should adequately counsel parents on these issues with respect to their background, religious and cultural aspects and wishes. Ideally, parents should also be given written information explaining these aspects. In order to better equip health care workers in confronting bereaved parents with these emotional matters more education is needed for professionals on this issue. The use of standard pathology guidelines ensures that informative gross description and diagnostic histologic features are not overlooked. It assures the reader of the report that all features and aspects of the fetus and placenta have been critically examined. Whereas if the report only states abnormal findings a reader may be left wondering whether such critical histologic examination has been performed.

At the start of the ZOBAS study there were no national pathological guidelines for autopsy and placental examination. In collaboration with the Dutch Working...
Party Paediatric Pathology (WKPLL) a pathological study protocol was prepared to
accomplish more uniformity in the ZOBAS study. A national autopsy and placental
examination guideline is now being extracted from this study protocol by the
WKPLL for use for national perinatal audit. Hopefully, this guideline will receive a
Dutch Institute for Healthcare Improvement (CBO) status in the near future. Such a
guideline deserves the same implementation strategies under pathologists as the
fetal death diagnostic work-up protocol for gynaecologists.

Performance of adequate autopsy and placental examination requires expertise
in this field. It is fundamental to provide the pathologist with essential clinical
information in guiding appropriate investigation into causes. Clinicians should
request autopsies from the service providing the highest quality. Therefore,
ideally a perinatal/paediatric pathologist should perform or supervise all perinatal
post-mortems and placental examinations. If needed transport to a centre with
appropriate expertise should be arranged to ensure that all examinations are
of sufficient quality. Elsewhere this is already standard patient care.13 A plain
language pathology report for parents could give them more insight into findings
and the value of pathological examination. Such a plain language report is already
used for Dutch genetic counselling.

Developing countries

Ideally the complete proposed fetal death diagnostic workup guideline should be
performed. However, this will not be feasible when resources are limited. While in
many developing countries the ability to undertake the most basic diagnostic tests
is extremely limited or even impossible, a systematic approach to collection and
review of basic information from clinical history and examination of mother and
baby should be achievable. Such data collection would constitute a major step
forward in addressing stillbirth prevention on a global scale. When considering
what investigations should be included in local stillbirth work-up in developing
countries, it makes sense as we discussed in our proposal for a work-up guideline to
focus on conditions suggested by the clinical history. In addition, there should be a
focus on those disorders with meaningful recurrence risks. Population attributable
risk (PAR) allows us to consider conditions that carry the largest burden in certain
populations aiding in focussing and rationalising the approach to investigation.14

Conditions with higher prevalence and higher risk have higher PAR. Malaria and
syphilis for example have high stillbirth PAR’s in developing countries. We proposed
a basic and an additional workup after fetal death in our guideline. In collaboration
with others, concerning diagnostic work-up internationally a four-tiered approach
was presented with two main levels based on resource availability, each with
additional testing dependent on the scenario. Level 1: Basic investigation. This
level should be achievable in all settings regardless of the economic setting. Level
Scenario specific investigation. These investigations may assist in identifying important contributing factors in specific situations where access to laboratory services and expertise is limited. Level 2: Optimal investigation for all stillbirths. In addition to Level 1, this approach is considered optimal and should be undertaken in all developed country settings. Level 2S: Optimal – scenario specific investigation. Additional testing based on clinical scenario which should be undertaken in all developed country settings.14

Psychological effects of fetal death
In addition to investigating the medical aspects of fetal death, it is important to consider the psychological effects on the family.15 Parent support should include emotional support. Referral to a bereavement counsellor, religious leader, peer support group, or medical social worker is advisable for management of grief and depression. In the University Medical Centre Groningen the importance of psychosocial aftercare following perinatal deaths through a multidisciplinary approach coordinated by medical social workers has been studied. It was concluded that the aftercare group counselling sessions met a strong patient need.16 Psychosocial problems in bereaved parents after perinatal loss need be further defined.

Prevention
This thesis gives more insight into occurrences of causes of intrauterine antepartum fetal death. With more insight into these causes, we can subsequently aim to bring down fetal death rates. This will also contribute to a decrease in perinatal morbidity. Bringing down fetal death rates can be achieved on different levels such as improving quality of care, studying risk factors and development of fetal testing during pregnancy for women at risk for fetal death.

Since the Peristat publications2,3 different measures have been taken in the Netherlands in order to improve the quality of perinatal care. The most important are the preparations for the national perinatal audit, better prenatal screening and the introduction of preconception care.17 Women at risk for adverse pregnancy outcome should be identified before pregnancy. The health care giver should perform a risk assessment for each individual patient and give realistic estimates of anticipated obstetric outcomes.

Risk factors
In developed countries, the most prevalent risk factors for stillbirth are obesity, socioeconomic factors, and advanced maternal age.18 The prevalence of maternal...
obesity is increasing steadily worldwide. Recent studies in the Netherlands indicated that women in the age group 20-39 years had the highest body-mass index (BMI) increase over the last years compared to other age groups. In the ZOBAS study prevalence of mothers with a BMI > 30.0 was more than twice as high as in the age and sex matched general Dutch population. During pregnancy, these women had more hypertension and diabetes-related diseases compared to women in the other BMI groups and more intrauterine antepartum fetal deaths due to placental causes of death, namely placenta-bed pathology. For these obese women preconception advice, risk analysis and accurate identification of pregnancy complications is needed. The fact that women with a previous stillbirth are at increased risk of stillbirth in future pregnancies is well known. We studied women with previous fetal death and evaluated pregnancy outcome. There seems to be an association between previous fetal death and subsequent unfavourable fetal outcome related to the cause of death, especially in early gestation. In terms of reducing potentially preventable stillbirths, the Confidential Inquiry into Stillbirths and Infant Death (CISID) of Northern Ireland found that the failure to adequately diagnose and manage fetal growth restriction was the most common error, followed by failure to recognize additional maternal medical risk factors. It is also known that pregnancies affected by decreased fetal movements are at an increased risk of fetal growth restriction and fetal death. Tveit et al. recently found, that combining improved guidelines for management of decreased fetal movements to health professionals and uniform information on fetal activity to expecting women, improved the quality of care and was associated with a reduction of stillbirth rates. With more insight into the association between stillbirth risk factors and different causes of fetal death, better strategies to prevent death can be developed.

Fetal testing during pregnancy

We demonstrated that diverse placental pathologies are the main causes of intrauterine antepartum fetal death and that they vary in their clinical manifestations and depend on gestational age. Clinically useful gauges for detecting progressive placental failure during pregnancy need to be developed. Future research into fetal death will focus on understanding the pathophysiology of impaired placentation to establish tests for assessing risk of fetal death, and assessment of interventions to prevent fetal death in women who test positive. Up to now, studied fetal tests include circulating concentrations of placently derived proteins in the mother’s blood PAPP-A, and α-fetoprotein (AFP), doppler flowvelocimetry of the uterine and umbilical arteries, and ultrasonic assessment of the appearance of the placenta. Combining the results of these studies, with our demonstrated differences in gestational age occurrence of placental cause of death subgroups
can give more insight into possible timing of testing. We concluded that placental bed pathology had the highest occurrence of early intrauterine fetal death between 24 and 32 weeks and a strong decline after 32 weeks. In contrast, contribution of developmental placental pathology increased after 32 weeks of gestation. In doppler flow velocimetry studies of the uterine arteries a high resistance pattern of flow at the end of the second trimester of pregnancy was observed and associated with an increased risk of growth restriction and stillbirth. Research on other fetal tests is still premature and has limited clinical use. Meta-analyses of methods of fetal monitoring do not suggest any methods of fetal assessment that reduce the risk of stillbirth when used in an unselected population. Some trials seem to show possible beneficial effects, such as assessment of placental maturity in the third trimester but this has not been confirmed (or refuted) by any further trials.

Given all of the potential factors that influence the risk of fetal death, it would be helpful to have an interactive model that would estimate the risk for an individual pregnancy. This model could then be used to decrease the risk of fetal death by monitoring of pregnancy and informing decisions about the timing of delivery to prevent fetal death. However, delivery of the fetus incurs the risk of maternal or neonatal morbidity or mortality. The current management of risk conditions such as diabetes mellitus requiring insulin, hypertension-related disease, and fetal growth restriction already includes various schedules for testing during pregnancy. This proactive, comprehensive approach has led to the reduction of the stillbirth risk, albeit at the cost of an increased risk of iatrogenic preterm birth.

An alternative approach to assessment of fetal wellbeing is to schedule delivery of women considered at high risk of stillbirth irrespective of the results of fetal tests. Villus immaturity, one of the placental causes of fetal death we studied, characterised by a reduced number of syncytiovascular membranes in the tertiary villi cannot yet be clinically diagnosed. In our study we observed an association with gestational diabetes. Up to now, no other markers seem to correlate with this histopathological finding. Stallmach et al. proposed that these fetuses can be rescued by birth as their placenta is required to function for only a few more days and suggested birth at 37 completed weeks of gestation. There are however no data from randomised controlled trials that directly support timing of delivery because of the difficulty in doing adequately powered studies for these women. Further studies are needed to design interventions for pregnant women at risk of fetal death that will reduce the incidence of fetal death and lead to the birth of a healthy newborn.
References


