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Fetal death

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Summary



Fetal death or stillbirth is a major obstetrical complication and a devastating experience for parents. Health care workers are responsible for investigating the cause of death. Unfortunately, the cause remains unexplained in up to two-thirds of fetal deaths. This is partly influenced by lack of consensus on classification of cause of fetal death and diagnostic investigations into causes.

Different aspects of classification systems for cause of perinatal mortality were investigated. In this thesis, the main focus is on optimal investigation of cause of intrauterine antepartum fetal death. Therefore, we studied the value of different diagnostics in allocating the underlying cause. The aim of this thesis was to propose an evidence based guideline for diagnostic work-up after fetal death to determine the cause of death.

Part I: Classification of perinatal mortality

In Part I we focused on diverse aspects of different classification systems for perinatal mortality. In **Chapter 1**, the pathophysiological Tulip classification system for underlying cause and mechanism of perinatal mortality is introduced based on clinical and pathological findings. This classification, consisting of groups of causes and mechanism of death was drawn up by a multidisciplinary panel through the causal analysis of events related to 411 studied perinatal mortalities. The underlying cause of death was defined as the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death. The classification system consists of six main causes: 1. congenital anomaly, 2. placenta, 3. prematurity, 4. infection, 5. other and 6. unknown. Mechanisms of death defined as the organ failure incompatible with life and the origins of the mechanism were also drawn up. In addition, contributing factors were defined as other known factors on the causal pathway to death. Clear definitions and guidelines for case allocation with case examples were developed. The largest cause of death group was congenital anomalies (35%). Cause of death was unknown in only 11%. Inter-rater agreement between five panel members expressed by kappa score was 0.81 for main cause of death (0.86 after excluding guideline misinterpretations), 0.67 for subclassification of cause of death and 0.72 for mechanism of death. The best agreement level for cause of death was observed for “congenital anomaly” and the lowest for “other”. Classifying perinatal mortality to compare performance over time and between centres is useful and necessary for different purposes. The Tulip classification seems consistent and allows unambiguous classification of a single underlying cause and mechanism of perinatal mortality. It is easily applicable in a team of clinicians when guidelines are followed.

Differences between perinatal mortality classification systems could have consequences for the validity of vital statistics, for targeting preventive strategies and also for counselling parents on recurrence risks. In **Chapter 2**, this was illustrated by comparing the use of the Tulip classification with other currently used international classification systems for cause of fetal death. We selected the extended Wigglesworth classification, modified Aberdeen, ReCoDe and the classifications by Hey, Hovatta, Galan-Roosen and Morrison and Olsen. Our multidisciplinary panel classified cause of 485 intrauterine antepartum fetal deaths according to the different systems after individual investigation of structured patient information. Distribution of cases into cause of death groups for the different systems varied. The proportion of cases in the placental groups varied from 0% (no placental category provided in those systems) to 65% in the Tulip classification, the largest cause of death group. In some systems, cases with an unexplained cause of death comprised the largest group such as in the extended Wigglesworth (86%), while in other systems no deaths were classified as unexplained because death groups consisted of clinical manifestations. The most frequent contributing factor was growth restriction. Systems that lack a placental category and systems that allocate most cases to the “unknown” categories or to categories that comprise only clinical manifestations are not discriminatory for the underlying cause of death. In the Tulip classification, mother, fetus and placenta are addressed together and the system has a clear defined sub classification of the placenta group.

There is not a universally accepted classification system for perinatal mortality. All systems have their own strengths and weaknesses. In **Chapter 3**, we compared all known international classification systems 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. We allocated these classification systems to one of three categories: ‘when’, ‘what’ or ‘why’. This was dependent on whether the allocation of the individual cases of perinatal mortality was based on the moment of death (‘when’), the clinical conditions associated with death: fetal, maternal or placental (‘what’), or the underlying cause of death: the event that initiated the chain of events that eventually resulted in death (‘why’). This led to proposal of a systematic multilayered approach for the analysis of perinatal mortality by using combinations of existing classification systems. Cross tables of the different systems can give insight into the relation between ‘when’, ‘what’ and ‘why’. If causes and conditions are mixed within a system, overlap in allocation is possible, information is then lost and comparison is unreliable. When cause and condition are used separately, they may add to each other. This approach is not only useful for in depth analysis of perinatal mortality in the developed world

but also for analysis of perinatal mortality in developing countries, with limited resources.

Part II: Value of diagnostic tests after intrauterine antepartum fetal death

In Part II of this thesis value of different diagnostic tests for allocation of causes of intrauterine antepartum deaths according to the Tulip classification by a multidisciplinary panel was evaluated. The results of the prospective ZOBAS study of couples and their singleton intrauterine fetal death after 20 weeks of gestation before the onset of labor are presented in the following chapters. **Chapter 4** describes different placental pathologies causing fetal death in 750 cases. Placental pathology was the most dominant cause of death group in 65%, becoming relatively more important at higher gestational age. Placental bed pathology was observed most of all; in 34% of all fetal deaths, with the highest occurrence between 24 and 32 weeks and a strong decline after 32 weeks. In contrast, contribution of developmental placental pathology (18%) increased after 32 weeks of gestation ($p < 0.001$), as did umbilical cord complications (5%) and combined placental pathology (6%). In the placental bed pathology group more hypertension-related disease and small for gestational age fetuses were observed compared to other cause of death groups. However, more than one third of cases with placental bed pathology did not present with these clinical manifestations. Diabetes-related disease was particularly observed in the group of deaths due to placental hypoplasia. We concluded that different placental pathologies were associated to different gestational age periods, and that clinical manifestations varied during pregnancy.

One of the placental causes of death we studied is the relatively unknown villus immaturity described in **Chapter 5**, causing unexpected antepartum fetal death after 36 weeks of gestation. In our complete ZOBAS cohort of 1025 intrauterine antepartum fetal deaths, 352 were beyond 36 weeks of gestation. These fetal deaths were divided into three cause of death groups: villus immaturity, other placental pathology and non-placental pathology. A placental cause of death was identified in almost 80%. The overall prevalence of villus immaturity was 23%, either solitary or in combination with other placental pathology. The prevalence of gestational diabetes in the villus immaturity group was 2.5 fold-higher than in the group caused by other placental pathology (14% versus 6%, $p = 0.03$) and 10 fold- higher than in the group caused by non-placental pathology (14% versus 1%, $p = 0.005$). Villus immaturity was also associated with placental

hypoplasia (developmental pathology) in comparison to the group of deaths with a non-placental cause. No associations were found for oligohydramnios although this occurred almost twice as often in the group with villus immaturity (23%) than in the group with non-placental causes (13%, $p=0.14$); hyper coiling of the umbilical cord; pre-existent diabetes mellitus; hypertensive-related disease; intoxications (smoking, alcohol, drugs); or fetal characteristics.

Chapter 6 describes chromosomal abnormalities causing fetal death. The aim of the study was to estimate success rates for cytogenetic analysis in different types of tissue after evaluation of 750 intrauterine antepartum fetal deaths. In addition, we studied selection criteria for and value of cytogenetic testing in determining cause of death. We observed chromosomal abnormalities in 13% of deaths. Cytogenetic success rates were significantly higher for invasive testing (85%) than for postpartum tissue analysis (28%, $p<0.001$). Success rates of tissues taken postpartum varied between 32% for umbilical cord and 0% for pericardium. A small for gestational age fetus or advanced maternal age (above 35 years) were not associated with more chromosomal abnormalities. Cytogenetic analysis was successful in 35% of severely macerated fetuses. There were more abnormal chromosomes (38%) in fetal deaths with morphologic abnormalities than in those without (5%, $p<0.001$). However, the posterior probability of a chromosomal abnormality in the absence of morphologic abnormalities was still 5%. Cytogenetic analysis was valuable in determining the cause in 19% of fetal deaths. The results of this study led to recommendations for a fetal death cytogenetic flowchart. We suggest counselling parents on different aspects of cytogenetic analysis and discussing their consequences, and performing non-selective invasive testing after fetal death and before labor for all intrauterine antepartum fetal deaths.

In **Chapter 7**, a retrospective family cohort study (Descartes study) is presented with absolute risks of fetal loss for women with hereditary deficiencies of either antithrombin, protein C and S compared to their non-deficient female relatives. Evaluable were 317 women, who had 987 pregnancies (582 in 185 deficient women). Total fetal loss rates were 47% (antithrombin deficient), 45% (protein C deficient), 21% (protein S type I deficient) and 30% (protein S type III deficient), compared to 32%, 28%, 29% and 27% in non-deficient women, respectively. Adjusted for clustering of pregnancies in women, and compared to all non-deficient women, relative risks for fetal death were 2.3 (95% CI, 0.9-6.1) in antithrombin deficient women, 2.1 (95% CI 0.9-4.7) in protein C deficient women, 0.7 (95% CI 0.2-1.8) in protein S type I deficient women and 1.1 (95% CI 0.6-2.0) in protein S type III deficient women. Early fetal death rates showed no statistically significant differences between deficient and non-deficient women. Differences

were mainly due to higher late fetal death rates in antithrombin (adjusted relative risk 11.3; 95% CI, 3.0-42.0) and protein C deficient women (adjusted relative risk 4.7; 95% CI, 1.3-17.4). An additional effect of cosegregation of other thrombophilic defects: factor V Leiden and/or prothrombin G20210A was not demonstrated in both groups. Beforehand however, we excluded pregnancies after prior venous thromboembolism because thromboprophylaxis may have influenced the outcome, which could explain our cosegregation findings. These women probably have a high risk of fetal loss.

In **Chapter 8**, we describe the prevalence of maternal thrombophilic defects, either inherited or acquired during pregnancy and paternal thrombophilic defects, tested at induction of labor in the ZOBAS cohort (n=750) compared to prevalence in the normal population. Prevalence of inherited thrombophilias was no higher in couples with fetal death than in the normal population. More women with fetal death had decreased antithrombin (16.8%) and protein C (4.0%) and increased von Willebrand factor (15.5%) plasma levels compared to healthy pregnant women (2.5%). However, compared to normal ranges in the non-pregnant population, only more women with fetal death were observed with increased von Willebrand factor (12.4%). More fathers with fetal death had decreased free protein S and elevated von Willebrand factor than healthy men. When comparing main causes of death, thrombophilia was not associated with a placental cause of death, presumed to express thrombosis in the uteroplacental circulation. After studying specific placental causes, abruption and infarction were associated with acquired maternal defects. In contrast with common clinical practice, our data provide no support for routine testing of inherited or acquired thrombophilic defects after fetal death, although acquired maternal defects may play a role in deaths caused by abruption or infarction.

Part III: Fetal death workup guideline

In the last part of this thesis we present recommendations for a basic and selective workup guideline for intrauterine antepartum fetal death. This workup is presented in **Chapter 9** by means of a flowchart for a diagnostic workup guideline based on the identification of valuable tests for determining the cause of death by a multidisciplinary evaluation of diagnostic procedures in the complete ZOBAS cohort of 1025 intrauterine antepartum fetal deaths. Beforehand an extensive non-selective diagnostic workup was performed for all deaths. Main causes of death were placental pathology (65.2%), congenital anomaly (4.8%), infection (1.8%) and other (5.0%) while in 23.2% cause remained unknown. The most

valuable tests for determination of cause of death were placental examination in 98%, autopsy in 73% and cytogenetic analysis in 29%. Fetal-maternal haemorrhage determined by a positive Kleihauer-Betke was observed in 12% of women. IgM antibodies against viruses and Toxoplasmosis were positive in 18%, but in only 1.8% placental examination and/or autopsy were able to support an intrauterine infection as cause of death. Testing for maternal diseases was regarded valuable if there was a suspect clinical history or suspect current pregnancy. Autopsy, placental examination and cytogenetic analysis are the base for diagnostic work-up for all fetal deaths. We recommend further individualised sequential testing on the base of these results or specific clinical characteristics to avoid unnecessary investigations and positive test results that do not identify the cause of fetal death.