On Perinatal Pathology

Aspects of the perinatal autopsy,
placental pathology and
classification of perinatal mortality

Sanne Gordijn

Publication of this thesis was generously sponsored by: SANDS, Stillbirth & neonatal death charity.

Further financial support by Medical Dynamics, Bayer Health Care BV, SHARE and the University of Groningen for the publication of this thesis is greatly acknowledged.

On Perinatal Pathology
Sanne J Gordijn
PhD thesis, University of Groningen – with summary in Dutch

Cover: Bernhard Siegfried Albinus, Leiden 1753
Cover design: Roeland Kuiper (www.koef.nl)
Lay out: Legatron Electronic Publishing, Rotterdam
Printing: Ipskamp drukkerijen, Enschede

ISBN: 978-90-367-3873-6

RIJKSUNIVERSITEIT GRONINGEN

On Perinatal Pathology

Aspects of the perinatal autopsy, placental pathology and classification of perinatal mortality

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 9 september 2009
om 14.45 uur

door

Sanne Jehanne Gordijn

geboren op 8 december 1978
te Enschede

Promotores:	Prof. dr. J.P. Holm
	Prof. dr. T.Y. Khong
Copromotores:	Dr. J.J.H.M. Erwich
	Dr. A. Timmer
Beoordelingscommissie:	Prof. dr. H. Hollema
	Prof. dr. G.H.A. Visser
	Prof. dr. P.P. van den Berg

Voor Bas en Guus

Contents

CHAPTER 1

INTRODUCTION AND OUTLINE OF THESIS

Introduction

Death of a baby is one of the most painful and traumatic life events parents can experience. Perinatal mortality not only affects the parents but their relatives and the healthworkers involved as well. In the period just after death many issues have to be dealt with. In this thesis we address several of these issues and provide suggestions for obtaining permission for autopsy, for the use of placental examination, for improvement of placental reports, for better communication between pathologists and clinicians and for use of perinatal mortality classification systems. With these suggestions we hope to improve knowledge and care concerning perinatal mortality. Better knowledge and care will result in better analysis and hopefully contribute to preventive strategies for future cases.

Definition of perinatal mortality

The perinatal period involves intrauterine life, the delivery and time after birth. In 1992 the World Health Organization (WHO) defined this perinatal period in the International Classification of Diseases version 10 (ICD 10) as: at least 22 completed weeks of gestation (154 days) or, if the gestational age is unknown, it includes infants with a birth weight of at least 500 grams or with a crown-heel length of at least 25 cm. This perinatal period lasts until 7 days after birth.[1] However, many different definitions have been used over time in- and between countries, thereby hampering (international) analysis of perinatal mortality figures.[2]

Perinatal mortality rates

Perinatal mortality is an important problem and the perinatal mortality rate is among the most commonly used indicators for the health status of a population and for quality of obstetrical care. The perinatal mortality rate in developed countries, such as the Netherlands, is relatively low. The impact for the parents, family and also health workers however is enormous. Perinatal mortality rates have greatly declined over the past decades. The stillbirth rate halved between 1970 and 1998 and much of this decrease has occurred in (near) term babies.[3] The rate of early neonatal deaths fell even more.

A shift in stillbirths and neonatal deaths occurred. Preterm babies are delivered at an earlier gestational age in the case of expected intrauterine problems. Those babies die now in the neonatal period. On the other hand, the preterm neonates can be kept alive longer due to better neonatal intensive care facilities. Some of these babies will die after the neonatal period of seven days and therefore will be lost to the statistics of the perinatal period. At present, stillbirths account for almost half of perinatal mortality cases with an estimated 4 million stillbirths occurring worldwide every year. More than 97% of these take place in developing countries.[4] The intrapartum death rate in developed countries is a maximum 10% of stillbirth cases, while in the developing countries this rate can be up to 50%.[5]

Perinatal mortality in the Netherlands

In 2003 the Peristat project revealed that the Netherlands is amongst the European countries with the highest perinatal mortality rates.[6] The Netherlands differ from other European countries because of the high percentage of home births. This, however, did not provide an explanation for the difference in mortality rates. Several other factors were considered responsible. First, in the Netherlands there is a reluctance to use

prenatal diagnosis and subsequent termination of pregnancy for congenital anomalies. These terminations of pregnancy usually occur before the perinatal period and accordingly would never appear in the perinatal statistics. Second, neonatologists are also more likely to refrain from treating very preterm newborns if their prospects are unfavourable. These untreated babies will die in the (early) neonatal period while treated babies may survive beyond the neonatal period. Third, the fact that more and more Dutch women have their first child when they are in their late twenties. The first time mothers in Holland are among the oldest mothers in the world, together with mothers in Greece and Spain.[7] This delay in childbearing also carries an increased risk of multiple pregnancies which forms an additional perinatal mortality risk. A fourth reason for the unfavourable mortality rates could be the relatively high percentage of non-western non-Dutch speaking women of low socio-economic background, from countries that carry relatively high risks of perinatal mortality, that have settled in the Netherlands. Consanguine relations are more frequent in some foreign groups, consanguinity results in more perinatal deaths caused by congenital anomalies. The final possible reason was a factor with unclear impact: the over-registration of perinatal deaths. The different registration systems (cause of death statistics and municipal population registration system) in the Netherlands are not linked with an unique linking key. The Peristat project used several registries, which can have resulted in double counting.[8] After publication of the Peristat a national feasibility study was initiated for audit of perinatal mortality (LPAS: Landelijke Perinatale Audit Studie) One of the elements of the perinatal audit is the determination of substandard factors in the care process and understanding its consequences for causality of mortality.

In 2008 the Peristat published results of the follow-up of the perinatal mortality rates in Europe and again the Netherlands was amongst the countries with the highest mortality rates in Europe.

Outline of the thesis

The causes of perinatal mortality can be found in the mother, in the foetus, in the placenta and in their interaction. In order to determine the cause of death the, sometimes complex, processes can be analysed by thorough evaluation of the chain of events that eventually resulted in death.

Autopsy

The analysis preferably involves an autopsy.[10,11] Perinatal autopsy rates however declined during the past decades for several reasons, the most recent being the "organ retention controversy" including the Alder Hey Scandal where pathologists retained organs without the consent or knowledge of the relatives.[12] The perinatal autopsy is the principal topic of the first chapters. In *Chapter 2* we assess the value of perinatal autopsy by reviewing the available literature on this subject. In *Chapter 3* we describe the topics concerning the autopsy that should be discussed with the parents, including differences in parental cultural and religious background.

Placenta

Until recently the placenta has been a neglected source of information for establishing the diagnosis in case of perinatal mortality. This organ however forms the link between mother and foetus, it has been called the "diary" of pregnancy and should therefore always be submitted fot pathological investigation in case of perinatal mortality. The next three chapters of this thesis focus on this special organ. In *Chapter 4* we address the quality of pathology reports of the placenta. We evaluate the reports for both their completeness and description of findings including the conclusion by the pathologist. For an estimation of the quality of the reports we use a selfdeveloped scoring system for evaluation of placental reports from four different hospitals. In *Chapter 5* we explain the rationale of evaluation of placentas. The importance of submission of placentas to the pathologist and communication between pathologist and obstetrician are illustrated. Some placental causes of foetal death are obvious and easy to diagnose by the clinician such as placental abruption (based mainly on the clinical diagnosis of vaginal bleeding and a "uterus en bois" resulting in foetal distress and death) other placental causes need to be diagnosed by the pathologist, for instance villous immaturity. This condition cannot be diagnosed on clinical history and macroscopic evaluation of the placenta alone, but requires histologic examination. We describe the evaluation of intrauterine foetal death cases caused by villous immaturity, either by villous immaturity alone or by villous immaturity in combination with other placental pathology, in our cohort of 1025 foetal deaths from the ZOBAS study (Zinnig Onderzoek bij Antepartum Sterfte) in C*hapter 6.*

Classification of perinatal mortality

In the Netherlands, as in many other countries, the clinician enters the cause of death on a death certificate (the CBS B-form is used in the Netherlands) shortly after birth, despite unavailability of the results of autopsy, placental examination and other investigations. Reliable classification of perinatal mortality based on information from this death certificate is therefore not possible. Classification of perinatal mortality is essential to enable comparison of mortality figures; for audit of prenatal care and for determination of future preventive options.

In the last three chapters the aspects and results of a search for the ideal classification system are described. We aimed to find a classification system for perinatal mortality that classifies the underlying cause of death but also identifies the mechanism of death and risk factors. In our opinion none of the existing classifications was useful for our purpose. In *Chapter 7* we develop and test a new classification system for detecting the cause, mechanism and contributing factors of perinatal mortality: the Tulip classification. In *Chapter 8* we assess several classifications for their use in intrauterine foetal deaths, especially considering the placental causes of death. In *Chapter 9* we propose a systematic multilayered approach for the analysis of perinatal mortality that uses one or more of the previously published systems for classification of perinatal mortality.

Reference list

1. World health organisation. International classifcation of diseases. 10th edition. 1992. Geneva.
2. Macfarlane A, Gissler M, Bolumar F, Rasmussen S. The availability of perinatal health indicators in Europe. Eur J Obstet Gynecol Reprod Biol 2003; 111 Suppl 1:S15-S32.
3. Goldenberg RL, Kirby R, Culhane JF. Stillbirth: a review. J Matern Fetal Neonatal Med 2004;16:79-94.
4. McClure EM, Nalubamba-Phiri M, Goldenberg RL. Stillbirth in developing countries. Int J Gynaecol Obstet 2006;94:82-90.
5. McClure EM, Goldenberg RL, Bann CM. Maternal mortality, stillbirth and measures of obstetric care in developing and developed countries. Int J Gynaecol Obstet 2007; 96:139-146.
6. Buitendijk S, Zeitlin J, Cuttini M, Langhoff-Roos J, Bottu J. Indicators of fetal and infant health outcomes. Eur J Obstet Gynecol Reprod Biol 2003; 111 Suppl 1:S66-S77.
7. Coleman D, Garssen J. The Netherlands: Paradigm or exception in Western Europe's demography? Demograhic Research 2002;7:433-468.
8. Garssen J, Meulen A van Perinatal mortality in the Netherlands. Background of a worsening International ranking. Demograhic Research 2004;13:357-394.
9. Eskes M, Diem MTh van Landelijke Perinatal Audit Studie (LPAS). 2005.
10. Bohra U, Regan C, O'Connell MP, Geary MP, Kelehan P, Keane DP. The role of investigations for term stillbirths. J Obstet Gynaecol 2004;24:133-134.
11. Incerpi MH, Miller DA, Samadi R, Settlage RH, Goodwin TM. Stillbirth evaluation: what tests are needed? Am J Obstet Gynecol 1998;178:1121-1125.
12. Khong TY, Tanner AR. Foetal and neonatal autopsy rates and use of tissue for research: the influence of 'organ retention' controversy and new consent process. J Paediatr Child Health 2006;42:366-369.

CHAPTER 2

VALUE OF THE PERINATAL AUTOPSY: CRITIQUE

Sanne J. Gordijn,
Jan Jaap H.M. Erwich,
T. Yee Khong

Pediatric and Developmental Pathology 2002; 5: 480-488

Abstract

In consenting to a perinatal autopsy, the primary motive of parents may be to find the exact cause of death. A critical review on the value of perinatal autopsies was performed to see whether parents could be counselled regarding their main motive. A literature search was performed in MEDLINE, EXCERPTA MEDICA, and the Cochrane library. We evaluated the value of the autopsy by comparing the clinical and autopsy diagnoses in stillbirths, neonatal deaths, and therapeutic terminations. Clinicopathologic concordance was divided into four categories: (1) change in diagnosis, (2) additional findings, (3) complete confirmation, and (4) inconclusive. We sought information on factors that may influence the value of perinatal autopsies: the type and definitions of perinatal loss; autopsy rate; level of hospital; expertise of pathologists; autopsy protocol used; whether patients were inborn or referred; and antenatal diagnosis. From the 27 articles that met our review criteria, the autopsy revealed a change in diagnosis or additional findings in 22% to 76% of cases. If confirmation of clinical findings is included, then the value of the perinatal autopsy was as high as up to 100%. Factors that could influence this rate were reported variably by investigators. When centers report their experience of the value of the perinatal autopsy, information on the factors that may influence their reports should be provided as well. Clinicians can confidently advise parents of the usefulness of the perinatal autopsy in ascertaining the cause of death or for counseling their future pregnancies.

Introduction

An unsuccessful outcome of pregnancy is a major catastrophe for parents. Seeking consent for performing an autopsy from the grieving parents can be difficult.[1] Positive effects that may be of direct benefit to the parents, the family, or to society can accrue from an autopsy.[2] These benefits may not be immediately evident to the parents, however. At the time of perinatal death, their only interest may be to have an accurate cause of death and counseling for the next pregnancy. Given the adverse publicity about the perinatal autopsy, the physician could use evidence to counsel the parents about this particular issue. While studies have shown that there is value in perinatal autopsies,[3-9] it is not clear whether particular factors that can influence those results have been looked at. The aims of this study were to perform a critical review of all papers published on the value of the perinatal autopsy, and to determine to what extent we can rely on published reports to confidently counsel a couple about the likelihood of determining a cause of death and, subsequently, the recurrence risks for a future pregnancy.

Methods

A literature search using MEDLINE, Cochrane library, and EXCERPTA MEDICA was performed to obtain all published papers on the value of perinatal autopsies. The search terms used were perinatal mortality and synonyms (perinatal deaths, neonatal mortality, neonatal deaths, infant mortality, infant deaths, stillbirths (SB), stillborn, fetal deaths, fetal mortality, intrapartum deaths); autopsy and synonyms (necropsy, autopsies, necropsies, post-mortem examination, postmortem examination, postmortem, post-mortem, PM); and value and synonyms (validity, use, usefulness, utility, useful, importance). Publications were limited to the period from 1980 until June 2001.

An attempt was made to separate stillbirths, neonatal deaths, terminations, and the total group of perinatal deaths from the papers. Each publication was assessed for the degree to which the autopsy findings differed from the premortem or clinical findings. Antenatal ultrasound diagnosis, sometimes in combination with amniocentesis or chorion villous biopsy, was considered a clinical diagnosis. Clinicopathological concordance or discordance was divided into four categories according to the information revealed at the autopsy: category 1 was change – the autopsy revealed a new diagnosis or made a change in the main diagnosis; 2, additional – the autopsy revealed additional diagnoses or findings, which were not suspected clinically, but did not change the main diagnosis;

3, confirmation – the autopsy revealed exactly the same main diagnosis and no additional findings were established; and 4, inconclusive – the autopsy demonstrated no obvious cause of death or other significant findings. Various factors that can influence the accuracy of the perinatal autopsy were analyzed, including the type of perinatal loss; autopsy rate; level of hospital; expertise of pathologists; autopsy protocol used; whether patients were inborn or referred; and availability of antenatal diagnosis.

Results

Sixty-seven papers meeting the search criteria were identified; 40 were excluded. Those that were excluded did not make a comparison between a clinical and postmortem diagnosis and only stated or tabulated the causes of death.[10-19] In others, the definitions of groups were not concordant with the criteria of age groups of the perinatal period, or the research was focused only on the quality of the autopsy.[20-24] Papers that were mainly descriptive[1,2,5,9,25-35] or in which only specific diagnoses were validated[36,37] were also excluded. One article that compared clinical and autopsy data focused only on the change in classifications and was excluded from this review.[38] Articles focusing on ultrasound diagnosis in which the autopsy diagnoses incorporated the opinion of the medical geneticist or results of other investigations, such as amniocentesis, were excluded as it was not obvious what the direct value of the autopsy alone was.[39-41] In other articles only a clinical diagnosis was compared to an ultrasound diagnosis.[42-45]

Twenty-seven papers were deemed suitable for critical review.[4,6-8,46-68] In 10 articles, determination of accuracy of the ultrasound diagnoses was the main objective and thus the ultrasound and autopsy diagnoses were compared.[59-68] In all papers comparisons of clinical and autopsy findings had been classified, but when the classification differed from that used for this review, the numbers and percentages were recalculated from the data in those papers.

Table 1 shows the percentage of autopsies for which there were additional findings, whether these findings changed the main diagnosis or not, and which may have led to change in management or counseling. Additional findings were found in 22%[46,48,67] to 76%[52] of all autopsies, but this varied with the type of perinatal loss. In the stillbirths group the range was from 28%[4] to 75%.[65] For neonatal deaths it ranged from 22%[48] to 81%[8] and for the therapeutical terminations it ranged from 22%[4,67] to 49%.[63] Two articles only mention a category 1 percentage and almost no other information.[50,55]

Table 1. Usefulness of the perinatal autopsy

Reference[a]	Stillbirth (%)	Neonatal death (%)	Therapeutic terminations (%)	All perinatal losses (%)
4	28	35	22	29[b]
6	Not stated	Not stated	–	26[c]
7	Not stated	Not stated	–	30[d]
8	60	81	–	70
46	Not stated	Not stated	–	22[e]
47	–	27	–	27[f]
48	–	22	–	22
49		58	–	58[b]
50	21	2	3	12[g]
51	–	44	–	44·
52	Not stated	Not stated	–	60[h]
53	34	34	–	34
54	–	27	–	27
55	Not stated	Not stated	–	14[i]
56	Not stated	Not stated	–	55[j]
57	Not stated	Not stated	–	57
58	Not stated	Not stated	Not stated	26
59	–	–	35	35
60	–	–	40	40
61	Not stated	Not stated	Not stated	39
62	-	-	30	30
63	Not stated	-	49	49
64	–	Not stated	Not stated	76[c]
65	75	38	39	46
66	–	–	40	40
67	–	–	22	22
68	Not stated	–	44	44

–, not investigated. [a] Articles [59–68] compare antenatal ultrasound findings with autopsy findings. [b] Estimations were taken from a graph or table. [c] Only recurrence risk change is seen as a significant finding. [d] There was no category 2. The actual value may be higher. [e] Article stated a potential value of 37%, the autopsy revealed a previously undiagnosed disorder that either caused or contributed to the death. This study did not contain a clear "additional findings" category (2). [f] There was no category 2. Article stated significant findings in 39%, but significant findings are not comparable to what is considered significant in this analysis. [g] It was impossible to extract overlap of categories 1 and 2. Article stated +50% of cases in category 2. [h] There was an extremely low autopsy rate for stillbirths; high maceration rates may indicate a selected population. [i] Very little information provided, only category 1. No calculations or estimations of category 2 were possible. Three time periods were studied;1981–1985 is the only period of interest for this review. [j] There was an uncertain degree of overlap between categories 1, 2, and 3 (32%, 23%, and 68%, respectively).

The descriptions of the types of perinatal loss were not readily available from many studies. In 10 articles the types of perinatal deaths were not defined.[7,8,49,50,55,60-62,64,65] Six articles defined the stillbirth group as 20 weeks gestational age or older,[4,6,53,57,58,60] while two articles each used definitions of older than 24 weeks and older than 28 weeks gestational age.[46,52] The definition of stillbirths was not mentioned or not extractable in seven papers.[7,8,50,55,56,61,65] Two articles that investigated the accuracy of the ultrasound diagnosis used the definition of 12 weeks gestational age as cut-off.[63,68] The definition of neonatal deaths differed among all these articles; eight articles did not state it.[7,8,49,55,60,61,64,65] Definitions of 48 h postnatal[6,53] and (within) 1 year were used in eight articles. [4,46-47,50,57,58] Neonatal deaths within 1 month were used in three articles.[48,52,54] Other studies defined neonatal deaths starting at a certain age, but no cut-off was stated for the end of this period.[51,56] The range of gestational age when therapeutic terminations were performed was not defined in nine articles.[4,50,58-62,64,65] Three other papers on terminations mentioned the gestational age range, which was different in all three.[63,66,67]

Reporting of the subject size ranged from full disclosure in each group of losses[4,7,47-54,58-63,65-68] to none mentioned.[6,8,46,55,64] The total numbers studied ranged from 45 to 601.[56,64] These numbers ranged from 5 to 300[56,61] in the stillbirth group; 16 to 301[56,65] in the neonatal death group and 19 to 357[50,59] in the termination group (Table 2).

The overall autopsy rate ranged from 16% to 100%[52,65] (mean 38%) but was sometimes stated either not accurately or not at all.[47,61,63,64,66,68] The autopsy rate ranged from 5% to 100% in the stillbirth group,[52,65] from 33% to 100% in the neonatal death group,[52,65] and from 79% to 100% in the termination group.[4,64,65]

The level of hospital was not stated in 10 papers.[8,50,52,55,60,61,63,64,66,67] In nine articles the research was performed in a level 3 hospital.[6,46-49,51,53,54,68] In three papers the research was performed in a level 2 hospital.[48,56,65] Five articles were reviews of regional practices and the levels of hospitals involved were not stated.[4,57-59,62] The degree of expertise of the pathologists who performed the autopsy was usually stated (Table 3) but was not specified in 11 reports.[8,47,48,50,51,55,56,61,65,66,67]

Macroscopic and histologic examinations were usually performed (Table 3). Supplementary investigations were standard in some centers but only performed when clinically indicated in others. Four papers evaluated the quality of the autopsy in some or all of their cases in regional audits by using a set protocol.[4,54,57,58] Placental evaluation was not performed because of non-availability in two reports.[47,48] Some

articles did not state what investigations had been performed in case of perinatal death.[48,55,56,60,61,64,66,68]

Table 2. Numbers studied (n) and autopsy rates (%) of stillbirths, neonatal deaths, therapeutic terminations, and total deaths.

Reference*	Stillbirth n (%)	Neonatal death n (%)	Therapeutic terminations n (%)	All perinatal losses n (%)
4	141 (61)	40 (42)	27 (79)	208 (57)
6	NS (NS)	NS (NS)	–	NS (33)
7	52 (81)	87 (81)	–	139 (81)
8	150 (NS)	150 (NS)	–	300 (NS)
46	NS (NS))	NS (NS)	–	91 (40)
47	–	71 (NS)	–	71 (NS)
48	–	221 (99)	–	221 (9)
49	–	338 (NS)	–	NS (62)
50	54 (55)	31 (~55)	19 (59)	104 (56)
51	–	296 (61)	–	296 (61)
52	46 (5)	215 (33)		261 (16)
53	77 (83)	47 (64)	–	124 (74)
54	–	102 (43)	–	102 (43)
55	NS (NS)	NS (NS)	–	114 (93)
56	300 (94)	301 (90)	–	601 (92)
57	88 (47)	143 (48)	–	231 (47)
58	173 (NS)	96 (NS)	40 (NS)	314 (62)
59	–	–	357 (97)	357 (97)
60	30 (NS)	25 NS)	78 (NS)	133 (NS)
61	5 (NS)	75 (NS)	116 (NS)	196 (NS)
62	–	–	158 (85)	158 (85)
63	52 (NS)	–	121 (NS)	163 (NS)
64	–	NS (NS)	NS (100)	45 (NS)
65	12 (100)	16 (100)	33 (100)	61 (100)
66	–	–	97 (NS)	97 (NS)
67	–	–	183 (NS)	183 (NS)
68	153 (NS)	–	–	153 (NS)

NS: not stated,-:not investigated. *:Articles (59-68) compare antenatal ultrasound with autopsy findings.

Discussion

The perinatal and pediatric autopsy has attracted considerable attention recently because of probity issues over ethics and legality. This has also called into question the usefulness of the autopsy.

This review showed that the perinatal autopsy could reveal a new diagnosis, make a change in diagnosis, or provide important additional information in between 22% and 76% of cases. We have not used the more liberal definition of usefulness, insofar as confirmation of a diagnosis or a syndrome is also useful; in this situation parents and physicians can rely on the clinical diagnosis and all the implications that accompany that specific diagnosis. In some of the reports, confirmation of clinical diagnoses was possible in up to 100% of autopsies. These important conclusions are tempered, however, by the fact that comparisons could not be made between institutions because information about local factors, which could influence the usefulness rate, often were not provided in the literature.

Limitations

Certain limitations are present in this critique. We confined the literature review to papers written in English only. We reviewed articles published after 1980 as we felt that comparison of data published before then would not be valid because of the very rapid evolution of diagnostic techniques, therapeutic procedures for problems during the perinatal period, and developments in fetomaternal medicine, obstetrics, and neonatal care.

Autopsy protocol

It is not possible to discern from the publications which indications triggered those tests that were performed only "when indicated". The thresholds for performing these tests may differ among centers, an example being that of placental examination, which ranged from being examined routinely[7,50,53] to specifically not being examined[47,48] or not being mentioned at all.[8,46,49,51,52] It is self-evident that a properly conducted autopsy will more likely reveal the pathologic process and allow for a meaningful clinicopathologic correlation. How the scope of investigations relates to usefulness of the autopsy is complex, however. In the three studies in which the usefulness of the autopsy in stillbirth and the extent of tests performed were known,[8,50,53] the center with the most investigations had a median level of usefulness[53] while the one with the least investigations had the highest level of usefulness.[8] This paradox could be explained by

including tests not adding to the "usefulness" of the autopsy, as they may only confirm a clinical premortem diagnosis.

Autopsy rates

Excluding groups of patients, such as macerated stillbirths,[25,26] or low autopsy rates through limiting the range of stillbirths or infants autopsied[17] can bias conclusions about the usefulness of the autopsy. Autopsies are more likely to be useful when no clear clinical cause of death is available or if there is a malformation, whether suspected or not; the tendency to request an autopsy or consent to one is higher in these cases.[16,49] The complexity of the relationship of various factors is illustrated by two centers with comparable high neonatal autopsy rates[8,48] in which the usefulness of the autopsy was markedly different.

The difference is probably due to the unstated protocol, which the authors said lacked sophistication because it was carried out in a developing country, and possibly the expertise of the pathologists, which also was not stated.[48]

Pathology expertise and level of hospital care

The level of care that a hospital provides is a complex factor in this review: referrals are likely to be the more complicated cases that tend to yield more additional information and changes in diagnosis than single malformations at autopsy[6,62,65] but may undergo a more detailed and sophisticated clinical evaluation prior to death.[58] Pediatric pathologists are more likely to practice in a tertiary hospital and tend to perform perinatal autopsies to a higher standard than that of other pathologists.[57,58] It is expected that the convergence of expertise and patients with complex problems in a level 3 hospital is likely to enhance the value of the autopsy, but unraveling the influence of each is difficult; the level of expertise was not stated in many publications, nor was the level of supervision of the registrars or residents performing the autopsies. For example, the usefulness of autopsies at the three non-level 3 hospitals[48,58,65] was comparable to that at others, being in the middle of the range, for all losses and for centers that focused on ultrasound diagnosis.

Table 3. Pathology expertise and autopsy protocols

Ref	Pathologyservice/seniority of pathologists	Autopsy protocols[b]
4	Local pathologists performed the autopsies, except terminations, which were carried out mainly by pediatric pathologists	Survey in a big area with quality evaluation by the Rushton protocol[c]
6	Single perinatal pathologist	MACRO, HISTO, RAD, PHOTO, MICRO, CYTO, meta, plac
7	First-year pathology residents under supervision, pediatric pathologist	MACRO, HISTO, PLAC, PHOTO, cyto, rad, bio, micro
8	NS	MACRO, HISTO, rad, cyto, bact
46	Pediatric pathologist and forensic pathologist	MACRO, HISTO, BACT
47	NS	MACRO, HISTO, BACT, vir, rad, cyto
48	NS	NS
49	Coroner and other (NS)	MACRO, HISTO, MICRO, RAD, CYTO
50	NS	MACRO, HISTO, PLAC, micro, cyto, bio
51	NS	MACRO, HISTO, micro
52	Pathologist or physician[a]	MACRO, HISTO, micro
53	Perinatal pathologist or resident supervised by a perinatal pathologist	MACRO, HISTO, RAD, BACT, PHOTO,PLAC, cyto, vir
54	Survey in a large area, thus more than one pathologist	Survey in a large area, scoring partly by Rushton protocol[c]
55	NS	NS
56	NS	NS
57	General and pediatric/perinatal pathologist	Survey in a large area with quality evaluation by the CESDI protocol[d]
58	Local pathologist or pediatric pathologist	Survey in a large areawith quality evaluation by the Rushton protocol[c]
59	Survey in a large area, thus more than one pathologist	Survey in a big area; more than one protocol
60	Pathology Resident under supervision (NS)	NS
61	NS	NS
62	Survey in a large area, thus more than one pathologist	MACRO, histo, cyto, rad, photo
63	One single pathologist (expertise NS)	MACRO, HISTO, plac, cyto, em, rad
64	Autopsies under direction of a pediatric pathologist	NS
65	NS	MACRO, HISTO, RAD, CHROM, PHOTO,cyto, bio
66	NS	NS

Table 3 (Continued)

Ref	Pathologyservice/seniority of pathologists	Autopsy protocols[b]
67	NS	MACRO, HISTO, CHROM, rad
68	One single pediatric pathologist	NS

BACT, bacterial cultures; BIO, biochemical studies; CHROM, chromosomal analyses; CYTO, cytogenetic studies; EM,electron microscopic examinations; HISTO, histological examination (microscopic); MACRO, macroscopic examination (which includes gross dissection); META, metabolic studies;MICRO, microbiology; NS, not stated; PLAC, placental evaluation; PHOTO, photo documentation; RAD, radiology; VIR, viral cultures.

[a] In a developing country with low autopsy rate.

[b] Lower-case letters denote investigations performed when there was indication.

[c] The Rushton protocol consists of clinical summary, body measurements, descriptive content of autopsy, organ weights, radiology, microbiology, histology, and other investigations such as metabolic investigations, chromosomal analyses, cytogenetic studies, biochemical studies, and electron microscopic examinations. For all of these investigations points are given and a minimal acceptable score is determined.

[d] The Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) protocol consists of internal and external descriptions, placental description and histology, organ histology, summary of findings and commentaries. Points are given for every investigation performed and description made.

Antenatal diagnosis

It is likely, but by no means certain, that hospitals offering antenatal diagnosis will offer therapeutic terminations as well. This group of terminations of pregnancy is helpful for testing new antenatal diagnostic techniques.[4,54] In this review, 35% and possibly up to 76% of antenatal ultrasound diagnoses were modified by additional findings,[63,64] comparable to the 40% and 37% rates of revised diagnosis, after antenatal (ultrasound) diagnoses were performed, in Manchester, UK[69] and Denver, CO, USA, respectively.[39] Having a therapeutic termination group among the autopsies can influence the value of the autopsy in the groups of stillbirths and neonatal deaths, as these terminated fetuses would otherwise likely die later in pregnancy or following delivery. Only two centers had a therapeutic termination group among their studied perinatal losses.[4,50] The usefulness of these groups was markedly lower than for the centers reporting on their ultrasound experience. Part of the reason for this may be that antenatal diagnosis in the therapeutic termination group was not limited to ultrasound but could also include chromosomal analysis, via chorionic villous sampling or amniocentesis. Another reason, which reiterates an earlier discussion about autopsy rate and numbers, is that those two centers had small numbers of therapeutic terminations in their studies, compared with the numbers reported for ultrasound centers.[4,50]

Summary

In summary, there is a great variation in the reporting of the various factors that can influence the usefulness of the perinatal autopsy, making it difficult to draw conclusions on the impact of these factors. Nevertheless, this review demonstrates that the perinatal autopsy consistently and persistently provides valuable clinical information. We recommend that (1) individual centers for perinatal pathology continue to report their clinicopathological concordance so that their clinicians can use local figures to advise parents, and (2) when centers report their experience of the value of the perinatal autopsy, they should provide information on the factors that may influence its usefulness and the definitions of the age group studied so that comparisons can be made among centers worldwide.

Reference list

1. Rushton DI. Prognostic role of the perinatal postmortem. Br J Hosp Med 1994;52:450–454.
2. Macpherson TA, Valdes-Dapena M, Kanbour A. Perinatal mortality and morbidity: the role of the anatomical pathologist. Semin Perinatal 1986;10:179–186.
3. Gau G. The ultimate audit. BMJ 1977;1:1580–1581.
4. Cartlidge PH, Dawson AT, Stewart JH, Vujanic GM. Value and quality of perinatal and infant postmortem examinations: cohort analysis of 400 consecutive deaths. BMJ 1995;310:155–158.
5. Beckwith JB. The value of the pediatric postmortem examination. Pediatr Clin North Am 1989;36:29–36.
6. Faye-Petersen OM, Guinn DA, Wenstrom KD. Value of perinatal autopsy. Obstet Gynecol 1999;94:915–920.
7. Meier PR, Manchester DK, Shikes RH, Clewell WH, Stewart M. Perinatal autopsy: its clinical value. Obstet Gynecol 1986;67:349–351.
8. Porter HJ, Keeling JW. Value of perinatal necropsy examination. J Clin Pathol 1987;40:180–184.
9. Sharma AK. The clinical value of a perinatal autopsy. Indian Pediatr 1994;31:5–7.
10. Agapitos E, Kouri E, Alexacos L, Bacoula C, Papacharalampous NX. Primary causes of perinatal deaths–an autopsy study of 556 cases in Greek infants. Pathol Res Pract 1986;181:733–738.
11. Autio-Harmainen H, Rapola J, Hoppu K, Osterlund K. Causes of neonatal deaths in a pediatric hospital neonatal unit–an autopsy study of a ten-year period. Acta Paediatr Scand 1983;72:333–337.
12. Huidi C, Dixian J. Analysis of 645 autopsy findings in fetuses and newborn infants from the clinical obstetric viewpoint. Chin Med J 1980;93:474–476.
13. Hovatta O, Lipasti A, Rapola J, Karjalainen O. Causes of stillbirth: a clinicopathological study of 243 patients. Br J Obstet Gynaecol 1983;90:691–696.
14. Husain AN, O'Conor GT. The perinatal autopsy: a neglected source of discovery. IARC Sci Publ 1991;310:151–162.
15. Nakamura Y, Hosokawa Y, Yano H, et al. Primary causes of perinatal death–an autopsy study of 1000 cases in Japanese infants. Hum Pathol 1982;13:54–61.
16. Settatree RS, Watkinson M. Classifying perinatal death: experience from a regional survey. Br J Obstet Gynaecol 1993;100:110–121.
17. Singh M, Deorari AK, Paul VK, Murali MV, Mathur M. Primary causes of neonatal deaths in a tertiary care hospital in Delhi: an autopsy study of 331 cases. Ann Trop Paediatr 1990;10:151–157.
18. Dandekar CP, Mysorekar VV, Rao SG, Anupama V. Perinatal autopsy–a six year study. Indian Pediatr 1998;35: 545–548.
19. Tettey Y, Wiredu EK. Autopsy studies on still births in Korle Bu Teaching Hospital: pathological findings in still births and their placentae. West Afr J Med 1997;16:12–19.
20. Maclaine GDH, MacArthur EB, Heathcote CR. A comparison on death certificates and autopsies in the Australian Capital Territory. Med J Aust 1992;156:462–464.
21. McKelvie PA, Rode J. Autopsy rate and clinicopathological audit in an Australian metropolitan hospital–cause for concern? Med J Aust 1992;156:456–460.

22. Cameron HM, McGoogan E, Watson H. Necropsy: a yardstick for clinical diagnoses. BMJ 1980; 985–988.
23. Cremin BJ, Draper R. The value of radiography in perinatal deaths. Pediatr Radiol 1981;11:143–146.
24. Wright C, Cameron H, Lamb W. A study of the quality of perinatal autopsy in the former northern region. The Northern Perinatal Mortality Survey Steering Group. Br J Obstet Gynaecol 1998;105:24–28.
25. Rushton DI. West Midlands perinatal mortality survey,1987. An audit of 300 perinatal autopsies. Br J Obstet Gynaecol 1991;98:624–627.
26. Curry CJR. Pregnancy loss, stillbirth, and neonatal deaths. Pediatr Clin North Am 1992;39:157–192.
27. Mueller RF, Sybert VP, Johnson J, Brown ZA, Chen WJ. Evaluation of a protocol for post-mortem examination of stillbirths. N Engl J Med 1983;309:586–590.
28. Chambers HM. The perinatal autopsy: a contemporary approach. Pathology 1992;24:45–55.
29. Sharma AK, Phadke SR, Kamboj M, Agarwal SS. The clinical value of a limited fetal autopsy' as illustrated by 2 cases. Aust N Z J Obstet Gynaecol 1994;34:111–113.
30. Wigglesworth JS. Investigation of perinatal death. Arch Dis Child 1987;62:1207–1208.
31. Favara BE, Cottreau C, McIntyre L, Valdes-Dapena M. Paediatric pathology and the autopsy. Pediatr Pathol 1989; 9:109–116.
32. Craven CM, Dempsey S, Carey JC, Kochenour NK. Evaluation of a perinatal autopsy protocol: influence of the Prenatal Diagnosis Conference Team. Obstet Gynecol 1990;76:684–688.
33. Buetow SA. The perinatal autopsy, its conduct and reporting in Australia. Med J Aust 1992;156:492–494.
34. Battle RM, Pathak D, Humble CG, et al. Factors influencing premortem and postmortem diagnoses. JAMA 1987; 258:339–344.
35. Robinson HB. Diseases of fetus and newborn. In: Reed GB, Claireaux AE, Cockburn F, eds. Fetal Autopsy. London: Chapman & Hall, 1995;381–388.
36. Russell GA, Berry PJ. Postmortem audit in a paediatric cardiology unit. J Clin Pathol 1989;42:912–918.
37. Duley LMM. A validation of underlying cause of death, as recorded by clinicians on stillbirth and neonatal death certificates. Br J Obstet Gynaecol 1986;93:1233–1235.
38. Keeling JW, MacGillivray I, Golding J, Wigglesworth J, Berry J, Dunn P. Classification of perinatal deaths. Arch Dis Child 1989;64:1345–1351.
39. Manchester DK, Pretorius DH, Avery C, et al. Accuracy of ultrasound diagnoses in pregnancies complicated by suspected fetal anomalies. Prenat Diagn 1988;8:109–117.
40. Medeira A, Norman A, Haslam J, Clayton Smith J, Donnai D. Examination of fetuses after induced abortion for fetal abnormality–a follow-up study. Prenat Diagn 1994;14: 381–385.
41. Wilson RD, Chitayat D, McGillivray BC. Fetal ultrasound abnormalities: correlation with fetal karyotype, autopsy findings, and postnatal outcome–five-year prospective study. Am J Med Genet 1992;44:586–590.
42. Anderson N, Boswell O, Duff G. Prenatal sonography for the detection of fetal anomalies: results of a prospective study and comparison with prior series. AJR Am J Roentgenol 1995;165:943–950.

43. Crane JP, LeFevre ML, Winborn RC, et al. A randomized trial of prenatal ultrasonographic screening: impact on the detection, management, and outcome of anomalous fetuses. The RADIUS Study Group. Am J Obstet Gynecol 1994;171:392–399.
44. Ewigman BG, Crane JP, Frigoletto FD, LeFevre ML, Bain RP, McNellis D. Effect of prenatal ultrasound screening on perinatal outcome. RADIUS Study Group. N Engl J Med 1993;329:821–827.
45. Group NRSS. Fetal abnormality: an audit of its recognition and management. Northern Regional Survey Steering Group. Arch Dis Child 1992;67:770–774.
46. Barr P, Hunt R. An evaluation of the autopsy following death in a level IV neonatal intensive care unit. J Paediatr Child Health 1999;35:185–189.
47. Craft H, Brazy JE. Autopsy. High yield in neonatal population. Am J Dis Child 1986;140:1260–1262.
48. D'Costa G, Khot S, Daga SR. The value of neonatal autopsies. J Trop Pediatr 1995;41:311–313.
49. Dhar V, Perlman M, Vilela MI, Hacque KN, Kirpalani H, Cutz E. Autopsy in a neonatal intensive care unit: utilisation patterns and associations of clinicopathological discordances. J Pediatr 1998;132:75–79.
50. Hägerstrand I, Lundberg LM. The importance of post-mortem examinations of abortions and perinatal deaths. Qual Assur Health Care 1993;5:295–297.
51. Kumar P, Angst DB, Taxy J, Mangurten HH. Neonatal autopsies: a 10-year experience. Arch Pediatr Adolesc Med 2000;154:38–42.
52. Rajashekar S, Bhat BV, Veliath AJ, Ratnakar C. Perinatal autopsy–a seven-year study. Indian J Pediatr 1996;63: 511–516.
53. Saller DN, Lesser KB, Harrel U, Rogers BB, Oyer CE. The clinical utility of the perinatal autopsy. JAMA 1995;273: 663–665.
54. Sutton L, Bajuk K. NICUS. Postmortem examinations in a statewide audit of neonatal intensive care unit admissions n Australia in 1992. Acta Paediatr 1996;85:865–869.
55. Tang M, Zhu Y, Xu H, Gai M, Ji X, Zhao S. Clinicopathological analysis of causes of perinatal death. Chin Med J 1989;102:672–678.
56. Tasdelen E, Aksoy F, Arvas A, et al. Causes of fetal and neonatal death. Turk J Pediatr 1995;37:201–207.
57. Thornton CM, O'Hara MD. A regional audit of perinatal and infant autopsies in Northern Ireland. Br J Obstet Gynaecol 1998;105:18–23.
58. Vujanic GM, Cartlidge PH, Stewart JH, Dawson AJ. Perinatal and infant postmortem examinations: how well are we doing? J Clin Pathol 1995;48:998–1001.
59. Brand IR, Kaminopetros P, Cave M, Irving HC, Lilford RJ. Specificity of antenatal ultrasound in the Yorkshire Region: a prospective study of 2261 ultrasound detected anomalies. Br J Obstet Gynaecol 1994;101:392–397.
60. Chescheir NC, Reitnauer PJ. A comparative study of prenatal diagnosis and perinatal autopsy. J Ultrasound Med 1994;13:451–456.
61. Grant HW, MacKinlay GA, Chambers SE, Keeling JW, Muir BB. Prenatal ultrasound diagnosis: a review of fetal outcome. Pediatr Surg Int 1993;8:469–471.
62. Julian-Reynier C, Macquart-Moulin G, Philip N, et al. Fetal abnormalities detected by sonography in low-risk pregnancies: discrepancies between pre- and post-termination findings. Fetal Diagn Ther 1994;9:310–320.
63. Kaiser L, Vizer M, Arany A, Veszpremi B. Correlation of prenatal clinical findings with those observed in fetal autopsies: pathological approach. Prenat Diagn 2000;20:970–975.

64. Rutledge JC, Weinberg AG, Friedman JM, Harrod MJ, Santos-Ramos R. Anatomic correlates of ultrasonographic prenatal diagnosis. Prenat Diagn 1986;6:51–61.
65. Shen-Schwarz S, Neish C, Hill LM. Antenatal ultrasound for fetal anomalies: importance of perinatal autopsy. Pediatr Pathol 1989;9:1–9.
66. Sun CCJ, Grumbach K, DeCosta DT, Meyers CM, Dungan JS. Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal anomalies. Pediatr Dev Pathol 1999;2:131–142.
67. Tennstedt C, Chaoui R, Bollmann R, Korner H, Dietel M. Correlation of prenatal ultrasound diagnosis and morphologicalfindings of fetal autopsy. Pathol Res Pract 1998; 194:721–724.
68. Weston MJ, Porter HJ, Andrews HS, Berry PJ. Correlation of antenatal ultrasonography and pathological examinations in 153 malformed fetuses. J Clin Ultrasound 1993; 21:387–392.
69. Clayton-Smith J, Farndon PA, McKeown C, Donnai D. Examination of fetuses after induced abortion for fetal abnormality. BMJ 1990;300:295–297.

CHAPTER 3

THE PERINATAL AUTOPSY: PERTINENT ISSUES IN MULTICULTURAL WESTERN EUROPE

Sanne J. Gordijn,
Jan Jaap H.M. Erwich,
T. Yee Khong

European Journal of Obstetrics and Gynecology and Reproductive Biology 2007; 132: 3-7

Abstract

Western Europe is in a demographic transition with increasing multicultural societies. Health professionals have to understand the background, religious and cultural aspects of parents to counsel them regarding an autopsy in the event of a perinatal loss. Autopsy rates have declined over the past decades, the major limiting factor being the granting of permission for an autopsy, possibly because of adverse publicity or reluctance of doctors to obtain consent. Autopsy has proved its value in revealing unsuspected findings. The public can be convinced of this utility by means of good information notwithstanding their religious or cultural background.

Introduction

Western Europe is in a demographic transition with migration and reproductive health choices influencing its population make up. Internal European migration and, particularly, an external migration into Europe from the Muslim world and from Asia and Africa have brought a multicultural diversity. Reproductive health and lifestyle choices have generally resulted in small family size in Europe in recent decades. Urbanisation has resulted in fracturing of the traditional nuclear family support and has contributed to the trend to smaller families. This demographic transition has meant that when there is a perinatal loss, health professionals have to understand the changed cultural aspects to counsel parents regarding an autopsy. Furthermore, health professionals have to counsel the parents against a background of recent adverse publicity about the autopsy that has also influenced the public perception of its usefulness.

One of the limiting factors for the autopsy is the granting of permission by a doctor who is insecure about the inquiries and procedures of the autopsy in relation to parental background or religion and who is not always convinced of its value.[1,2] The purpose of this paper is to provide all necessary information for health professionals who counsel parents for a perinatal autopsy. In the following sections, we will discuss the reasons for declining autopsy rates, the quality of autopsies, the role of autopsy in the subgroups of perinatal mortality, the procedures of autopsy and its alternatives, the issue of organ retention and the religious and cultural proscriptions to the autopsy.

Perinatal autopsy rates and the quality of the autopsy

Perinatal autopsy rates were stable in comparison to the (low) adult autopsy rate until the 1990s.[3] However, a drop in the perinatal autopsy rate was found over the past decades.[4] The major rate-limiting factor is the granting of permission from the parents to a postmortem examination.[5,6] Adverse publicity could have contributed to this decrease. It can also be due to the reluctance of some doctors to ask permission for the autopsy because of personal reasons or due to the assumption of clinicians that current techniques can replace the autopsy.[1] The autopsy rates for perinatal deaths vary between 16 and 100% (mean 38%), for stillbirths between 5 and 100%, for neonatal deaths between 33 and 100% and for terminations of pregnancy between 79 and 100%.[7]

Another limiting factor for granting permission to the autopsy may be the finding that a high percentage of the autopsies in the perinatal period did not reach the arbitrary minimum quality.[8,9] Poorly performed autopsies or substandard autopsy reports are likely to dissuade clinicians from vigorously requesting permission. Despite the fact

that the perinatal autopsy is important for many reasons, approximately 25-50% of the autopsy reports fail to reach the minimum standard.[8,10-12] It has been suggested that the perinatal autopsy should be performed by a trained perinatal pathologist or should be referred to a regional perinatal/paediatric pathology Center.[8,12,13] Following publication of an updated *Guidelines for Postmortem Reports*, Vujanic et al. evaluated the implementation of these recommendations and guidelines and found that autopsies then failed to reach the minimum quality in 7%.[13]

Why perform a perinatal autopsy?

The primary reason for performing a perinatal autopsy is to ascertain the cause of death or, in the case of (therapeutic) terminations, to confirm the indications for the termination.[14] A review of contemporary studies on the value of perinatal autopsy showed that the autopsy could reveal a previously undiscovered diagnosis, a change in the diagnosis or additional information in 22-76% of cases.[7] The cause of death is important for counseling the parents and family about recurrence risks in future pregnancies and to allay any fears, guilt or doubts that the family may have.[7,14-17]

Secondarily, the autopsy aids the audit of perinatal deaths. It may uncover causes of death or may suggest substandard care. The autopsy also provides information for audit of medical treatment.[8,14,18] Another reason to perform autopsies, and one which transcends religious or cultural boundaries, is the role of the perinatal autopsy in research and education. However, unless these benefits are explained properly, compliance with legal and bureaucratic consent forms may deter parents from consenting to the use of the tissue from the autopsy for research or education purposes.[6]

The use of autopsy in different subgroups of perinatal mortality

Different definitions for subgroups of perinatal mortality have been used over time and between countries.[19,20] The autopsy has proved to be useful in these separate groups. Generally, perinatal losses can be divided in three subgroups.

The first group consists of (therapeutic) terminations. This group would comprise mainly fetuses terminated for anomalies, but may also comprise terminations for maternal reasons in case of illness or for psychosocial reasons. Antenatal ultrasound diagnoses of anomalies can be evaluated by performing an autopsy. In confirming the anomalies, they reassure parents that their, often difficult, choice of terminating the pregnancy was not inappropriate. The autopsy serves in clinical audit, especially in the field of antenatal diagnosis for fetal malformations. When pregnancies are terminated

for maternal reasons, important pathophysiological mechanisms can be revealed, as demonstrated, for example, by a study on isotretinoin (Roaccutane) embryopathy.[15]

The second group consists of intrauterine fetal deaths. Autopsies may not always demonstrate an anatomic demonstrable cause of death, but in combination with clinical history and additional laboratory investigations, associated factors may often be revealed. For example, extensive avascular placental villi may bring about investigations of parental thrombophilias and suggest a likely cause of placental failure.[21]

The third group comprises neonatal deaths. Autopsies in this group of perinatal losses have declined compared with the other two groups but, in recent years, have increased again.[22] Iatrogenic disease, so often a side-effect of neonatal intensive care, can be revealed by the neonatal autopsy but this needs to be distinguished from endogenous disease. For example, tracheomalacia may be a rare acquired complication in the chronically ventilated preterm infant, but it may also be found with other congenital abnormalities, such as the charge association.

How to perform the autopsy, what are the alternatives?

The autopsy in general involves an incision into the body. The autopsy should consist of a thorough macroscopic examination of the body and the internal organs. Tissue samples can be taken for microscopy, but no more tissue than necessary for establishing the diagnosis. In certain cases, additional laboratory tests for virology, bacteriology, cytogenetics and molecular studies are desirable.[14]

Some parents may not give permission for a complete autopsy. They may, however, permit a limited autopsy or needle biopsy where examination is confined to a body cavity or specified organ(s).[23] Frequently this occurs when parents of infants who died of a suspected cardiac cause may allow only the heart or the thoracic cavity organs to be examined. While this is less conclusive than a complete autopsy, at least it allows suspected pathology to be confirmed. Other parents may wish to have an external examination only; the value here may be even more limited, but may be sufficient for certain syndromes and some skeletal dysplasias that may have a characteristic phenotype.[23]

The placenta has been a neglected source of information. The value of placental autopsy is proven and it should therefore thoroughly be investigated as well, particularly where parents do not consent to autopsy of the fetus.[24]

Besides limited autopsy and needle biopsy, imaging techniques form other alternatives for the perinatal autopsy. Radiography showed abnormalities in 30% and is of

vital importance in 0.9% for finding the cause of death in a population-based study.[25] Other non-population-based studies showed radiographic abnormalities in 18.2-68% of cases.[26-28] It is not recommended to perform radiography as routine examination in non-deformed perinatal deaths, but it can serve as an alternative in cases where the parents do not consent to an autopsy.[25,26,29] The autopsies have been useful in the audit for alternatives to the autopsy itself; for example, magnetic imaging studies have shown a good complement to the autopsy for cranial anomalies and central nervous system anomalies but less so for other organ systems.[29,20]

Tissue and organ retention

The "organ retention" controversy in the wake of tissue retained following paediatric autopsy in United Kingdom has had a profound effect on the granting of consent for autopsy.[6] Parents are likely to ask and wish to know their choices with regard to this topic and may find it useful to discuss this directly with the pathologist. Practices may differ between institutions but, in general, portions of tissue are taken to be fixed before trimming for histopathological processing.

A contentious issue arises with examination of the brain. Ideally, brains need to be fixed for 3-4 weeks before being sliced and sampled, especially fetal and infant brains which are soft. Furthermore, they should be retained until microscopic examination as further sampling may be required; this whole process may take up to 3 months.[31] Alternatives include fixing the brain in high strength formalin for about 1 week or, for smaller brains, in a modified Bouin's solution for 1-2 days. Lungs may be perfused-fixed for morphometric analysis, but this inflating-perfusion could be accomplished in about 1 h. Generally, other organs do not need to be retained for diagnostic purposes.

There is an argument that the slides, tissue blocks from which the histological slides were cut and any residual tissues from the trimmings should be retained as they are of potential value to the families as well as for research.[31,32] Retention of whole organs or of additional tissue for educational or research purposes would rightly warrant discussion with the parents.

Religion and autopsy in multicultural societies

In the Netherlands in 2005, approximately 10% of the inhabitants were migrants and the percentage of immigrants is still increasing in the Dutch population. The religious distribution in 2002-2003 in the Netherlands is: Roman Catholic: 31%, protestant: 21%, Islam: 5%, other (Buddhist, Jewish, Hindu): 3% and non-religious: 40%.[33] In

Germany, approximately 9% of the inhabitants are migrants. The German religious distribution is: Roman Catholic: 32%, protestants: 32%, Islam: 4%, other (Buddhist, Jewish, Hindu): 2%, non-religious: 30%.[34] Approximately 7% of the French are migrants. The religious distribution in France is: Roman Catholic: 70-80%, Islam: 5-7%, protestant: 2%, non-religious: 10-20%.[35] This religious distribution and percentage of migrants will vary in other Western European countries but it serves to illustrate the ethnic and religious diversity now current in Western Europe. This presents a challenge to the perinatal autopsy as "religious objections to the autopsies are as old as the autopsies themselves".[36] Earlier we discussed some aspects of religious backgrounds and the autopsy.[37] There is actually no real proscription against the performance of an autopsy amongst the major religions (Table 1). However, it has been shown that even in communities where there is a perceived religious proscription against autopsies, with appropriate counselling and explanation of the autopsy, it is possible to obtain consent for different clinical situations.[38]

Devout Hindus always cremate their dead and burial is not allowed by tradition. The ashes are ceremoniously committed to a river or ocean. In Hinduism it is believed that autopsies are disturbing to the still-aware soul which has just separated from the body. Death is not viewed as a finite event and it is therefore important to provide a smooth transition from life to death with altering the body as little as possible. Autopsy should therefore be avoided unless required by law. Similarly, embalming, which replaces the blood with a preservative fluid, is not permitted.[39]

Buddhists believe that the body, which is a temporary shell for the spirit, should be treated with great respect and care so the mind can concentrate on pursuing enlightenment. They also cremate their dead. According to the Buddhist belief, the body should be left undisturbed until three days after death so that the soul can make its transition. However, an autopsy may be permitted after a religious teacher determines that the soul has left the body.[40]

Table 1. Major religions and conditions

Religion	Generally	Exceptions	In practice
Hinduism	Cremation and not burial; reincarnation. Funeral should be celebration and remembrance service.	Autopsy avoided. Autopsy if required by law.	Imaging techniques, macroscopic examination, placenta investigations and maybe needle biopsy.
Buddhism	Cremation and not burial. Body should be left undisturbed for three days as the soul makes its transition.	Autopsy permitted when soul pronounced to have left body.	Autopsy after permission of a religious teacher. Alternatives if autopsy not permitted
Judaism	Burial as soon as possible.	Autopsy permitted for public or family benefit. Also permitted if three doctors cannot ascertain the cause of death.	Good counseling of benefits of the autopsy. Perform the autopsy as soon as possible after death and make sure the body is as complete as possible after the autopsy.
Islam	Burial before sunset the next day (within 24 h). Cremation is forbidden.	Autopsy permitted where there is public benefit or required by law.	If required by law and by means of explanation of the (public) benefits. Autopsy during the day/night after death.
Roman Catholicism	Either burial or cremation preferably burial.	Autopsy (scientific research) permitted with family consent.	Good counseling
Protestants	Either burial or cremation permitted.	Autopsy permitted with family consent.	Good counseling
Eastern Church	Burial not cremation	Autopsy permitted (with the utmost respect to the earthly remains of the body.)	Good counseling

Jewish law requires immediate burial, including all internal organs and the blood. It is believed that while the soul or spirit leaves the body upon death, it is nevertheless aware and conscious of its surroundings, until after its return to the earth. Any invasive procedure is seen as a desecration.[36,41] Burial should be as soon as possible in consecrated ground and any delay is seen as unnecessary painful. Permission for autopsy can be granted when there is a benefit for public health, in case of unclear cause of death, or when a hereditary cause is possible and the family can benefit from this diagnosis.[42] The autopsy should be performed in a body pouch and the samples for pathologic investigations should be as small as possible. All instruments should be buried with the body as well as all the blood stained material and clothing. The sutures should be as tight as possible and leak-proof.[43]

The teaching of Islam does not allow for voluntary autopsy because it is considered a "disfigurement" of a person. In certain subdivisions of the Islam, the body should be buried before sunset on the day of death. The benefits of the autopsy outweigh the drawbacks if public health profits by an autopsy (for example, by unexpected death or contagious disease) and the autopsy can be performed. If the autopsy is required by law (for example, in criminal death), the autopsy can be performed as well.[36,41,44,45,46]

In the Roman Catholic tradition, there is no law or edict that forbids autopsy.[41,42,45,47,48] Pope Sixtus IV allowed in the 15th century the dissection of bodies in Bologna and Padua.[41] Pope Pius XII declared in the 20th century that autopsy can be morally permitted as long as the family has consented to the autopsy and the body is treated with respect. It is justified for legal inquests but also for scientific research.[42,27]

The Eastern Church includes the Orthodox Church, Greek (Orthodox), the Russian Orthodox Church and others. Although the term Greek Orthodox is often used as a name for the Eastern Church, it is used most accurately for the Patriarch of Constantinople, the Church of Greece and related churches that use the Byzantine rite. The Ethiopian, Coptic, Armenian, Syrian and Indian Churches are considered by some in the Eastern Church to be heretical. The Eastern Church believes that an autopsy may lead to finding the cause of death or to enlightenment for physicians in treating similar cases in future and, as such, is not opposed to the autopsy.[49] The religion insists on the utmost respect to the earthly remains of the body. Donation of the entire body for medical research is seen as not in keeping with traditional orthodox practice nor is dismemberment of the body during an autopsy.

In perinatal autopsy, there is the aspect of the religious discussion on investigations of human bodily tissue in relation to therapeutic terminations of pregnancy. Whether

the fetus is considered a human being or not is outside the scope of this review, but it should be treated with the same respect as other human beings.[42]

Conclusions

The perinatal autopsy is an integral part of perinatal care and management in cases of perinatal mortality. Contemporary studies have demonstrated the value of the perinatal autopsy in revealing unsuspected findings.[4,7,16,18] Convincing the public of this utility by means of good information has already been demonstrated to reverse falling neonatal autopsy rates.[22] This process can be further enhanced by understanding possible religious or cultural sensitivities to the autopsy as clinicians and paramedical staff have a role to play in requesting an autopsy or to persuade parents to allow use of tissue for research and educational purposes.[2]

Reference list

1. D. Newton, C.M. Coffin, E.B. Clark and A. Lowichik, How the pediatric autopsy yields valuable information in a vertically integrated health care system?, Arch Pathol Lab Med 128 (2004) (11), pp. 1239-1246.
2. T.Y. Khong, D. Turnbull and A. Staples, Provider attitudes about gaining consent for perinatal autopsy, Obstet Gynecol 97 (2001) (6), pp. 994-998
3. T.Y. Khong, A review of perinatal autopsy rates worldwide, 1960-1990s, Paediatr Perinat Epidemiol 10 (1996) (1), pp. 97-105.
4. M. Brodlie, I.A. Laing, J.W. Keeling and K.J. McKenzie, Ten years of neonatal autopsies in tertiary referral Center: retrospective study, BMJ 324 (2002) (7340), pp. 761-763.
5. R. Adappa, S. Paranjothy, Z. Roberts and P. Cartlidge, Perinatal and infant autopsy in Wales, Arch Dis Child Fetal Neonatal Ed (2006).
6. T.Y. Khong and A.R. Tanner, Foetal and neonatal autopsy rates and use of tissue for research: the influence of 'organ retention' controversy and new consent process, J Paediatr Child Health 426 (2006), pp. 366-369.
7. S.J. Gordijn, J.J. Erwich and T.Y. Khong, Value of the perinatal autopsy: critique, Pediatr Dev Pathol 5 (2002) (5), pp. 480-488.
8. P.H. Cartlidge, A.T. Dawson, J.H. Stewart and G.M. Vujanic, Value and quality of perinatal and infant postmortem examinations: cohort analysis of 400 consecutive deaths, BMJ 310 (1995) (6973), pp. 155-158.
9. D.I. Rushton, West Midlands perinatal mortality survey, 1987. An audit of 300 perinatal autopsies, Br J Obstet Gynaecol 98 (1991) (7), pp. 624-627.
10. C.M. Thornton and M.D. O'Hara, A regional audit of perinatal and infant autopsies in Northern Ireland, Br J Obstet Gynaecol 105 (1998) (1), pp. 18–23.
11. R. Bjugn and J. Berland, Quality of fetal, perinatal and infant autopsy reports. An audit of all reports of postmortem examinations following fetal, perinatal and infant death in Rogaland County, Western Norway, 1997–1999, APMIS 110 (2002) (10), pp. 746–752.
12. Confidential enquiry into stillbirths and deaths in infancy. Annual Report 1993. London: Department of Child Health; 1995.
13. G.M. Vujanic, P.H. Cartlidge and J.H. Stewart, Improving the quality of perinatal and infant necropsy examinations: a follow up study, J Clin Pathol 51 (1998) (11), pp. 850–853.
14. T.Y. Khong, The contribution of the pathologist after a perinatal loss: what we should be telling the parents, Aust N Z J Obstet Gynaecol 36 (1996) (1), pp. 15–17. [15]
15. S. Coberly, E. Lammer and M. Alashari, Retinoic acid embryopathy: case report and review of literature, Pediatr Pathol Lab Med 16 (1996) (5), pp. 823–836.
16. O.G. Killeen, C. Burke, D. Devaney and T.A. Clarke, The value of the perinatal and neonatal autopsy, Ir Med J 97 (2004) (8), pp. 241–244
17. O.M. Faye-Petersen, D.A. Guinn and K.D. Wenstrom, Value of perinatal autopsy, Obstet Gynecol 94 (1999) (6), pp. 915–920.
18. P.A. Boyd, F. Tondi, N.R. Hicks and P.F. Chamberlain, Autopsy after termination of pregnancy for fetal anomaly: retrospective cohort study, BMJ 328 (2004) (7432), p. 137.
19. World Health Organisation, International classification of diseases (10th ed.), World Health Organisation, Geneva (1992).

20. World Health Organisation. Definition of stillbirth. Technical Report Series no. 25; 1950.
21. T.Y. Khong, Placental vascular development and neonatal outcome, Semin Neonatol 9 (2004) (4), pp. 255-263.
22. J.C. Becher, I.A. Laing, J.W. Keeling and N. McIntosh, Restoring high neonatal autopsy rates, Lancet 364 (2004) (9450), pp. 2019-2020.
23. C. Wright and R.E. Lee, Investigating perinatal death: a review of the options when autopsy consent is refused, Arch Dis Child Fetal Neonatal Ed 89 (2004) (4), pp. F285-F288.
24. F.T. Kraus, Perinatal pathology, the placenta, and litigation, Hum Pathol 34 (2003) (6), pp. 517-521.
25. O.E. Olsen E, A. Espeland, H. Maartmann-Moe, R.S. Lachman and K. Rosendahl, Diagnostic value of radiography in cases of perinatal death: a population based study, Arch Dis Child Fetal Neonatal Ed 88 (2003) (6), pp. F521-F524.
26. U. Seppanen, The value of perinatal post-mortem radiography. Experience of 514 cases, Ann Clin Res 17 (1985) (Suppl. 44), pp. 1–59.
27. B.J. Cremin and R. Draper, The value of radiography in perinatal deaths, Pediatr Radiol 11 (1981) (3), pp. 143–146.
28. J. Gronvall and N. Graem, Radiography in post-mortem examinations of fetuses and neonates. Findings on plain films and at arteriography, APMIS 97 (1989) (3), pp. 274–280.
29. T.A. Huisman, Magnetic resonance imaging: an alternative to autopsy in neonatal death?, Semin Neonatol 9 (2004) (4), pp. 347-353.
30. P.J. Woodward, R. Sohaey and D.P. Harris et al., Postmortem fetal MR imaging: comparison with findings at autopsy, AJR Am J Roentgenol 168 (1997) (1), pp. 41-46.
31. W. Squier, Neuropathology and the new laws: will we survive?, Bull Roy Coll Pathol 131 (2005), pp. 32-35.
32. J. Savulescu, No consent should be needed for using leftover body material for scientific purposes, BMJ 325 (2002) (7365), pp. 648-651.
33. CBS Statline. CBS annual report integration. The Hague; 2005. www.cbs.nl.
34. Federal statistical office Germany; 2005. www.destatis.de.
35. INED. Institut National d'Etudes Demographiques (INED); 2005. www.ined.fr.
36. G.J. Davis and B.R. Peterson, Dilemmas and solutions for the pathologist and clinician encountering religious views of the autopsy, South Med J 89 (1996) (11), pp. 1041-1044.
37. S.J. Gordijn, J.J.H.M. Erwich and T.Y. Khong, Aspects of perinatal autopsy, Perinatology 7 (2005) (5), pp. 215-219.
38. O. Abudu and A. Akinkugbe, Clinical causes and classification of perinatal mortality in Lagos, Int J Gynaecol Obstet 20 (1982) (6), pp. 443-447.
39. Insight in Medical Ethics; July-September 2002. www.ayush.com/articles/jul.htm.
40. RIGPA Australia for the human rights and equal opportunity commission workshop on religion and human rights. Buddhist beliefs on death and dying and practical implications for policy; 28-4-1998.
41. S.A. Geller, Religious attitudes and the autopsy, Arch Pathol Lab Med 108 (1984) (6), pp. 494-496.
42. C.S. Campbell, Religion and the body in medical research, Kennedy Inst Ethics J 8 (1998) (3), pp. 275-305.

43. Torah Network. International Burial Society. The schema Yisrael, www.shemayisrael.com.
44. V. Rispler-Chaim, The ethics of postmortem examinations in contemporary Islam, J Med Ethics 19 (1993) (3), pp. 164-168.
45. E. Souder and J.Q. Trojanowski, Autopsy: cutting away the myths, J Neurosci Nurs 24 (1992) (3), pp. 134-139.
46. E. Svendsen and R.B. Hill, Autopsy legislation and practice in various countries, Arch Pathol Lab Med 111 (1987) (9), pp. 846-850.
47. L.R. Boglioli and M.L. Taff, Religious objection to autopsy. An ethical dilemma for medical examiners, Am J Forensic Med Pathol 11 (1990) (1), pp. 1-8.
48. S.A. Geller, To see or not to see: the status of the autopsy at The Mount Sinai Medical Center, Mt Sinai J Med 46 (1979) (1), pp. 33-38.
49. American Carpatho-Russian Orthodox Dioces of the USA. Insights into contemporary moral issues; 2006. http://www.acrod.org/orthodox6.html.

CHAPTER 4

QUALITY OF PLACENTAL PATHOLOGY REPORTS

T. Yee Khong,
Sanne J. Gordijn

Pediatric and Developmental Pathology 2002; 6: 54-58

Abstract

The surgical report is an important means of documenting normal and abnormal findings, and for distilling such information into a meaningful clinico-pathologic correlation. An audit of the quality of placental reports from four laboratories was performed using an arbitrary numerical scoring scheme that examined the gross, histologic, and commentary components of each report. The mean scores from the four laboratories were not statistically different from each other. Three (2%) and 48 (33%) of the 147 singleton placentas scored less than 50 and 75%, respectively, on this scoring scheme. None and 14 (41%) of the placentas from 34 multiple pregnancies scored less than 50 and 75%, respectively. Different aspects of the gross and histologic examination were reported variably by the laboratories. Commentaries on gross or histologic abnormalities, and in relation to clinical indications, were inconsistently reported. The standards of placental surgical reporting can be improved. The use of templates and checklists for reporting of placentas may be considered.

Introduction

Pathological examination of the placenta may clarify the pathophysiology of a pregnancy, assist in the medico-legal assessment of an adverse outcome, help in the management of the mother's subsequent pregnancies, and provide possible clues to adult-onset diseases.[1-3] No matter how careful and meticulous the examination, those important objectives will not be fulfilled unless the placental pathology report communicates the findings and clinical implications of that specimen. The practices of pathologists in reporting different variables was studied as part of a survey of members of the American Society of Clinical Pathologists,[4] but the actual quality of each placental surgical pathology report has not been investigated. The purpose of this study was to evaluate the quality of the placental pathology reports from four laboratories.

Methods

Four private pathology laboratories, three pathology laboratories from general public hospitals, and one pathology laboratory from a maternity hospital in Australia were invited to submit all their pathology reports for placentas accessioned during 1 calendar month, or, if fewer than 50, then 50 consecutive cases from May 1, 2000. Placentas from singleton and multiple pregnancy were included in the study but "products of conception" and placentas from pregnancies less than 20 weeks' gestation were excluded. Reports were submitted without patient or physician identifiers. The reports were scored for components of the gross and histologic descriptions, commentary on gross and/or histologic findings, and commentary on absence or presence of lesions in relation to the clinical details. The maximum score for gross description was 12, allocated as umbilical cord (length, diameter, insertion, and number of vessels: 1 point each), extraplacental membranes (completeness, rupture: 1 point each), and the disc (untrimmed or trimmed weight: 1 point; or trimmed and untrimmed weight: 2 points; dimensions- one diameter: 1 point; or two diameters: 2 points; or two diameters and thickness: 3 points; completeness: 1 point). Description of gross abnormalities of the cord, extraplacental membranes, and placental disc, or specific mention of no abnormalities attracted 8 points each, resulting in a maximum for the gross description of 24 points. Histologic description of any abnormality or specific mention of no abnormalities of the cord, extraplacental membranes, and disc were allocated 8 points each, resulting in a maximum for the histologic description of 24 points. Five points were given for a final diagnosis in the report. One point each was deducted if (i) there

was no commentary where there were gross or histologic abnormal findings, (ii) no commentary correlating the placental examination with the clinical history, and (iii) no commentary on recurrence risks if a diagnosis of villitis, massive chronic intervillositis, abruption placentae, placenta accreta, fetal or maternal thrombotic vasculopathy, maternal floor infarction, or massive perivillous fibrin deposition was made. Thus, a maximum score for a singleton placenta is 65 points with a maximum deduction of 3 points. For a multiple pregnancy, an additional 24 points are given for each pregnancy by allocating 8 points each for description of degree of fusion of the discs, type of chorionicity, and comment on the birth order. Thus, the maximum score was 154 (65 x 2 x 24) for a twin pregnancy, and 219 (65 x 3 x 24) for a triplet pregnancy, both with a maximum deduction of 3 points for lack of commentaries or final diagnosis. The score for each multiple pregnancy was derived by adding the scores for all placentas and dividing by the order of multiples of that pregnancy. Reports were assessed also for the inclusion of a block code; although this recommendation was not in the College of American Pathologists' guideline,[2] it was advocated in the American Society of Clinical Pathologists' survey.[4] Mean and median scores for each laboratory were calculated, and statistical analysis used paired t-test.

Results

None of the private laboratories provided placental reports for evaluation as they examined fewer than 50 placentas in a year. The remaining laboratories provided reports from 44, 53, 50, and 54 pregnancies of which 8, 4, 0, and 8, respectively, were not assessed because they were from pregnancies less than 20 weeks of gestation. As a result of multiple pregnancy, 48, 55, 59, and 56 placentas, respectively, were available for assessment from those laboratories.

The median scores from the four laboratories did not differ statistically significantly from each other for examination of placentas from singleton or from multiple pregnancies (Table 1). Three (2%) of the 147 singleton placental reports failed to score more than 50% (one report from laboratory A and two from laboratory B) and 48 (33%) failed to achieve higher than 75% (20, 9, 14, and 5 reports from laboratories A, B, C, and D, respectively). None of the placentas from multiple pregnancies scored less than 50% but 14 (41%) scored less than 75% (6, 1, 4, and 3 reports from laboratories A, B, C, and D, respectively).

Table 1. Median scores for reporting of placentas from individual laboratories[a]

Laboratory	Singleton	Multiple
A	45 (42, 47) (n=26)	57 (n=10)
B	54 (50, 54) (n=43)	59 (n=6)
C	54 (42, 60) (n=41)	64 (n=9)
D	52 (51, 53) (n=37)	61 (n=9)
All	52 (46, 54) (n=147)	58 (52, 64) (n=34)

[a]Median score (inter quartile range).

Analysis of the individual components of the report showed that some items were reported or performed well, such as the number of cord vessels, cord diameter and length, dimensions of the disc, or either a trimmed or untrimmed weight (Table 2). Other items, such as site of membrane rupture and completeness of the membranes, were reported poorly by all laboratories. Trimmed weights were provided in 19 of 181 reports. Laboratory B tended to report untrimmed weights (45 of 49 reports), while it was unclear whether trimmed or untrimmed weights were recorded by laboratories C and D (48 of 49, and all 37 reports, respectively, where weights were recorded). Completeness of the maternal surface of the disc were reported poorly by laboratories B, C, and D. Gross description of the cord was performed well only by laboratory C, and gross description of the membranes was performed poorly by laboratory A. In the 33 placentas from multiple pregnancy, there were 3 omissions of degree of fusion of discs, 3 of type of chorionicity or placentation, and 15 specifications of the birth order. Commentary on an abnormal gross or histologic finding was done poorly in laboratory D. All four laboratories infrequently commented on zygosity in multiple pregnancies or on possible recurrence risks. A final diagnosis was not provided in 27% of reports from laboratory C (Table 2).

Block codes were provided in all but three reports (from laboratory A); in these three reports, no abnormal areas were described grossly. Where abnormal areas were described grossly, block codes for sections from normal and abnormal areas were given in 69 reports but, in a further three reports, the block codes provided did not indicate whether the blocks were from normal or abnormal areas of the placenta.

Table 2. Data included from descriptions in placental reports[a]

	A	B	C	D
No of cord vessels	29 (60)	54 (98)	55 (93)	53 (95)
Cord length	46 (96)	55 (100)	58 (98)	56 (100)
Cord diameter	37 (77)	53 (96)	54 (92)	56 (100)
Cord insertion	39 (81)	45 (81)	51 (86)	51 (91)
Membrane completeness	33 (69)	28 (51)	26 (44)	7 (12)
Either trimmer or untrimmed weight	0	24 (44)	13 (22)	1 (2)
Disc dimensions	31 (65)	55 (100)	58 (98)	44 (79)
One diameter	0	0	0	0
Two diameters	3 (6)	0	0	0
Two diameter and thickness	36 (75)	47 (85)	59 (100)	56 (100)
Completeness of maternal surface	40 (84)	30 (55)	24 (41)	27 (48)
Gross description of cord	10 (21)	5 (9)	44 (75)	7 (12)
Gross description of membrane	8 (17)	52 (95)	56 (95)	56 (100)
Gross description of disc	42 (87)	55 (100)	56 (95)	56 (100)
Histologic description of cord	46 (96)	48 (87)	43 (73)	49 (82)
Histologic description of membrane	45 (94)	55 (100)	44 (75)	55 (98)
Histologic description of disc	48 (100)	55 (100)	56 (95)	56 (100)
Commentary on gross or histologic abnormality[b]	14/18 (78)	19/35 (54)	31/36 (86)	15/36 (42)
Commentary relating to clinical details[c]	33/35 (94)	26/48 (54)	19/44 (43)	27/44 (61)
Commentary on zygosity in multiple pregnancy[d]	0	0	1/9 (11)	4/9 (44)
Commentary on recurrence risk[e]	2/4 (50)	0	0	2/9 (22)
Diagnosis[f]	36 (100)	49 (100)	36 (72)	46 (100)

[a]Percentages are indicated in parentheses. Denominator is number of placentas, unless indicated otherwise

[b]Denominator is number of placentas with normal findings

[c]Denominator is number of pregnancies where clinical information was provided on request form.

[d]Denominator is number of multiple pregnancies

[e]Denominator is number of cases where recurrence risk should be commented; see text.

[f] Denominator is number of pregnancies

Discussion

The American Society of Clinical Pathologists' survey was important in ascertaining the practices of pathologists but, unfortunately, did not investigate whether those practices and descriptions of findings were translated onto individual reports.[4] We are only aware of one previous attempt to assess the quality of placental reports. The 6th Confidential Enquiry into Stillbirths and Deaths in Infancy arbitrarily scored them as missing, poor, adequate, and good without any numerical description as part of their audit of post-mortem examination reports.[5] While others may find it idiosyncratic, we tried to remove the subjectivity regarding the quality by allocating points to various components of the report and the coverage of the topographical parts of the organ; the last we could do only for the gross but not for the microscopic examination. Using a numerical scoring system, we found that while only three reports from 181 failed to achieve 50% of the maximal score, 33% of reports of singleton pregnancies and 41% of multiple pregnancies failed to reach a 75% mark. It can be argued that these performances may be worse, as penalties were minimal for a lack of commentary on abnormal gross or histologic findings or a clinico-pathological correlation. On the other hand, more points were awarded for any description of normality or abnormality of components of the gross or histologic assessments of the cord, extraplacental membranes, and disc.

The scoring did not test the quality or interpretative skills of the pathologist, a task that selfevidently we could not perform unless we had access to the sliced placental gross specimens to assess block selection or the histologic slides to compare with the reports. In this respect, appropriate block-taking with an accompanying block code is important as subsequent review by another pathologist is possible.[6] Although the recording of a block code is not in the College of American Pathologists' guideline, our review indicates that this is accomplished in the majority of cases.

There was an interlaboratory variance in the standard of reporting of the different components of the report. What is particularly alarming, though, is that some simple descriptive or mensuration items were poorly performed. For example, the number of cord vessels is easily assessed grossly but one laboratory poorly documented that in comparison with the other three laboratories in this study (range 93-98%) or with the pathologists in the American Society of Clinical Pathologists' survey (98%); admittedly, the finding of a single umbilical artery can be confirmed histologically and the gross finding is of less import. Standard placental weight charts are based on trimmed placental weights and yet only about 10% of the reports provided trimmed weights;

furthermore, in many reports, it was unclear whether the weight of the placenta was untrimmed or trimmed of cord and extraplacental membranes.

A model template for a placental report is provided in the College of American Pathologists' guideline[2] while others are widely available.[7-10] The use of such templates or checklists should ensure that informative gross description or diagnostic histologic features that should be included in every report are not overlooked. It assures the reader of the report that all features and aspects of placenta have been critically examined,[2,11] whereas a reader may be left wondering whether such critical histologic examination has been performed if the report only stated abnormal findings. For that reason, while we awarded marks for stating normal findings in our scoring scheme, we could not finesse the microscopic part of the reporting further because we could not be reasonably sure that all topographical components had been assessed when merely a statement of normality was given. Indeed, the College of American Pathologists' guideline recommends that specific statements regarding the placenta, membranes, and umbilical cord should be made.[2] The inconsistent reporting of commentaries on abnormal findings and specific commentaries relating to clinical details suggests that opportunities to use the report as a means of communicating with the clinicians are lost.

The goal of recommendations for the reporting of numerous specimens, specifically common malignancies, is to attain consistency and thoroughness of included information relevant to the management of patients.[12–15] Given that placental findings often carry significant information for the index pregnancy in explaining pathophysiologic events, for future pregnancies and the well- being of the infant through adult life,[1-3] similar emphasis on the quality of the placental report is warranted. We would have liked to have performed an educational feedback and re-audit process, but the absence of any prior audit on the quality of placental pathology reports warrants reporting the findings of this audit now.

Reference list

1. Benirschke K. The placenta in the litigation process. Am J Obstet Gynecol 1990;162:1145-1450.
2. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997;121:449-476.
3. Barker DJP. Fetal and infant origins of adult disease. London: BMJ Publishing Group, 1992.
4. Gersell DJ. ASCP survey on placental examination. Am J Clin Pathol 1998;109:127-143.
5. Gould S, Keeling J, Thornton CM. Perinatal pathology. In: Shaw R, Hamilton P, Gould S, et al., eds. 6th Annual Report of the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI). London: Maternal and Child Health Research Consortium, 1999;48-55.
6. Grether JK, Eaton A, Redline R, Bendon R, Benirschke K, Nelson K. Reliability of placental histology using archived specimens. Paediatr Perinat Epidemiol 1999;13:489-495.
7. Sander CH. The surgical pathologist examines the placenta. Pathol Annu 1985;20:235-288.
8. Kaplan C. Placental pathology for the nineties. Pathol Annu 1993;28:15-72.
9. Lage JM. The placenta. In: Gompel C, Silverberg SC, eds. Pathology in Gynecology and Obstetrics, 4th ed. Philadelphia: J.B. Lippincott, 1994;448-514.
10. Lewis SH, Benirschke K. Overview of placental pathology and justification for examination of the placenta. In: Lewis SH, Perrin E, eds. Pathology of the Placenta, 2nd ed. New York: Churchill Livingstone, 1999;1-26.
11. Khong TY. A topographical and clinical approach to examination of the placenta. Pathology 2001;33:174-186.
12. Kempson RL. The time is now. Checklists for surgical pathology reports. Arch Pathol Lab Med 1992;116:1107- 1108.
13. Rosai J. Standardized reporting of surgical pathology diagnoses for the major tumor types. A proposal. Am J Clin Pathol 1993;100:240-255.
14. Leslie KO, Rosai J. Standardization of the surgical pathology report: formats, templates, and synoptic reports. Semin Diagn Pathol 1994;11:253-257.
15. Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of surgical specimens containing uterine cervical neoplasms. Hum Pathol 2000;31:1194-1198.

CHAPTER 5

HISTOPATHOLOGICAL EXAMINATION OF THE PLACENTA: KEY ISSUES FOR PATHOLOGISTS AND OBSTETRICIANS

Sanne J. Gordijn,
Jane E. Dahlstrom,
T. Yee Khong,
David A. Ellwood

Pathology 2008; 2: 176-179

Abstract

The placenta is often not submitted for histopathological examination and obstetricians may be sceptical of the value of the examination. This article looks at the reasons for histopathological assessment of the placenta, examines what clinical information should be provided to pathologists and reviews what information can be gained from this 'diary of the pregnancy', especially for explaining adverse outcomes and potentially guiding the management of future pregnancies.

Introduction

Until recently, most maternity units would practise a rather strange ritual with the placenta. After birth it would be examined closely by the midwife, weighed (this was recorded for posterity in the birth register) and then be put in the fridge for a few days, in case someone wanted to look at it prior to being discarded. Rarely was it thought to be of value to send this remarkable organ to an expert for histopathological examination. It is now more commonplace for placentas to be presented for further studies, although many obstetricians may still be sceptical about the value of this investigation. This article looks at the reasons for histopathological assessment of the placenta, examines what clinical information should be provided to pathologists, and discusses lesions that should be recognised and commented upon by the pathologist in the report. It reviews what information can be gained from this 'diary of the pregnancy', especially for explaining adverse outcomes and potentially guiding the management of future pregnancies.

Which placentas require histopathological assessment?

The placenta remains a neglected source of discovery, although in 30-64% of placentas an indication for the cause of adverse pregnancy outcome can be found in the placenta.[1-3] The College of American Pathologists (CAP) published guidelines in 1997 for pathological assessment of the placenta.[4] Despite this, Badawi et al. found only 11.2% of placentas were examined, although according to the guidelines developed by CAP 43.3% had an indication for examination.[5] Spencer et al. found that only 32% of placentas with an indication (following the CAP guidelines) were examined.[6] Similar figures have been reported from the USA.[7] While there are no Australian guidelines for placental examination, many obstetric departments adopt modified forms of these CAP guidelines.

From recent medicolegal cases in Australia it is surprising how often placental examination is not requested in cases when a baby has been born unexpectedly 'flat' and with a putative diagnosis of perinatal asphyxia. Although placental abnormalities do not necessarily mean that there has not been any negligence in treatment around the time of birth, it can help to provide a more complete picture of what may have happened earlier in the pregnancy before the obstetrician had a reasonable chance to intervene. Placental pathology may point to a pre-labour cause of fetal hypoxia and neurological damage[8] and is particularly valuable in cases of stillbirth due to congenital infection when parents do not agree to perinatal autopsy.

Standardised clinical information

For the pathologist to interpret the placental pathology it is important to be adequately informed about the circumstances of the patient's pregnancy and relevant medical history. It is known that, in general, medical history details are usually not well provided on pathology request forms.[9] Because the placenta is dynamically growing during the short period of gestation and the responses to various insults may appear similar, this information is vital for the pathologist to interpret in line with the pathology findings. No studies are available regarding the results of histological assessments by pathologists either provided with or blinded for clinical history or information of current pregnancy; however, clinical information is necessary for complete assessment and the potential to draw conclusions regarding the pathophysiological pathways. These pathways could lead to adverse maternal or fetal outcomes, including death, and may also help in determining recurrence risks.

How much information should be provided on the request form? Uniformly presented relevant medical and obstetric history provides clarity and use of a standard format for this is helpful[1]. The presented data should include maternal age, gravidity, parity, fetal losses, vascular disease, uterine abnormalities, systemic diseases such as hypertension, infections, caesarean(s), and also relevant family history regarding congenital anomalies and systemic diseases. Secondly, information on the current pregnancy should include: gestational age, medication, smoking and drug or alcohol use, bleeding or infection, abnormalities discovered at ultrasonographic examination, diseases in pregnancy such as infections, trauma or antepartum haemorrhages, pregnancy related diseases such as preeclampsia or gestational diabetes. Finally, information of circumstances around birth should be recorded: estimated weight (expected or unexpected intra-uterine growth restriction/macrosomia), interval of rupture of membranes, meconium-stained amniotic fluid or not, duration of labour, signs of infection, cardio-tocographic abnormalities, mode of delivery, APGAR scores, congenital abnormalities of the baby (gross examination), fetal sex and birth weight, and abnormalities of placenta. Developing a standard form for placenta examination request, with the items mentioned above, can facilitate this type of communication between obstetrician and pathologist. Standardised request forms have been shown to improvensubmission rates for placental examination.[1]

What common placental lesions have recurrence risks?

There have been several recent reviews and monographs on the examination of the placenta.[10-16] It does appear that some placental lesions have a recurrence risk, although it is unclear to what extent obstetricians are aware of these risks. Some of the more common lesions are discussed below.

Chronic villitis is defined as a lympho-histiocytic inflammation of the terminal villi (Figure 1). Chronic villitis may be associated with some viral infections but most are nonspecific and not associated with known pathogens; hence the term 'villitis of unknown aetiology'. A bacterial aetiology has not been found for chronic villitis.[17] The exact pathogenesis remains unclear: it could be due to pathogens that are as yet unrecognised or due to a maternal-fetal immunological reaction. Support for the latter comes from the finding that approximately 50% of the inflammatory infiltrate in the villous stroma is maternal in origin[18,19] and also that non-specific chronic villitis is associated with maternal autoimmune disease and with oocyte donor pregnancies.[20] Non-specific villitis may be associated with intrauterine growth restriction, preterm labour and fetal death and may be recurrent in up to 17% of cases.[11]

Thrombophilia effects on the placenta are being increasingly recognised and reported. Although the association of adverse obstetric and fetal outcomes with various thrombophilias have been questioned, there is potential of recurrence because of the heritability of the haematological condition.[21] Thrombosed fetal vessels can sometimes be discerned on the chorionic plate. Thrombotic or occlusive lesions in the placenta can be seen as white plaques grossly on the placental slices or as avascular villi on microscopy (Figure 2). The term 'fetal thrombotic vasculopathy' has been used to describe this and other lesions, such as fibromuscular sclerosis of stem villous vessels, haemorrhagic endovasculitis, and fetal artery thromobosis.[22] The tracts of avascular villi are seen more often than frank thrombosis and there is usually a clear demarcation between the vascular and avascular portions of the placenta. Upstream from these avascular villi is the likely location of a thrombosed stem artery (Figure 3). It is evident that dislodged fragments of the thrombus can easily embolise to the fetal brain through the paradoxical fetal circulation and cause perinatal stroke, leading to subsequent neurological impairment.[23]

The finding of acute chorioamnionitis or evidence of amniotic fluid infection may affect management of future pregnancies. Bacterial vaginosis has serious implications during pregnancy, as it has been associated with adverse outcomes such as chorioamnionitis, late miscarriage, premature rupture of membranes and preterm birth.

The organisms implicated include Gardnerella vaginalis and Mycoplasma hominis. The infection recurrence rate is high, even in treated women, due to relapse and reinfection.[24] and the value in placental examination would be more for documenting the role of the infection in the index pregnancy than in screening in the next pregnancy. Group B streptococcus infection is associated with preterm labour and can be recurrent.[25] Most obstetricians would modify their management of the next pregnancy if the index pregnancy was affected by Group B streptococcus.

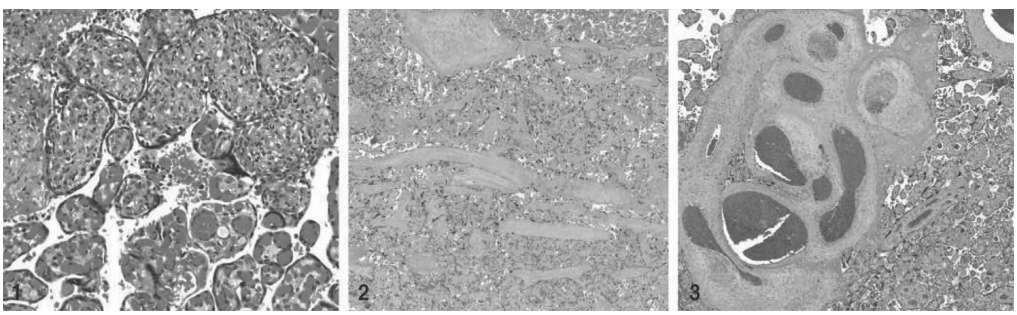

Figure 1. Chronic villitis showing infiltration of villous stroma by lymphocytes and histiocytes (H&E, high power). Figure 2. Fetal thrombotic vasculopathy. Tracts of avascular villi are clearly demarcated from the vascular villi (H&E, low power). Figure 3. Thrombosed fetal vessel in the chorionic plate in a case with fetal thrombotic vasculopathy (H&E, medium power).

Inherited metabolic disorders may sometimes be diagnosed at placental examination, especially in cases of fetal hydrops and stillbirths. Some may have recurrence risks.

Documentation of various pathologies is not merely an exercise for pathologists. It has relevance for obstetricians, although interventions and treatments for those pathological processes that may be recurrent are still quite limited. Perhaps the most important is increased fetal surveillance with chorionic villous sampling, ultrasound biometry and Doppler assessment of umbilical and uterine artery blood flows in future pregnancies. Early delivery is often advocated for such things as severe placental abruption or unexplained stillbirth. If the placental pathology has pointed to a thrombophilia or similar process then lowdose aspirin or low molecular weight heparin might be used. Whether or not there is a place for immunosuppressive treatments such as corticosteroids for conditions such as villitis of unknown origin is unclear and must

await the outcome of future clinical trials. The detection of infection, such as group B streptococcus, can be managed with peripartum antibiotics.

The placental report as information for the obstetrician

New placental abnormalities are still being defined or their definitions refined. Recently, attention has been drawn to the coiling index of the umbilical cord as this has been related to an adverse pregnancy outcome.[26,27] An umbilical cord without any coiling was described as raising the risk of intrauterine fetal death for the first time in 1993.[28] A year later abnormalities in umbilical coiling were related to meconium stained amniotic fluid, intrauterine death, preterm delivery, intrapartum heart rate abnormalities, operative delivery for fetal distress and karyotypical abnormalies.[29] It has been advised that any placenta with abnormal coiling should be sent to the pathologist for evaluation. The clinical consequences, such as antenatal ultrasound measurements of the coiling index, are not clear yet as the exact mechanism that eventually determines the coiling index at different gestational ages is still under debate (is it the first step in the causal pathway or a consequence of something else?).[30] The abnormal coiling index remains an unknown or unrecognised abnormality for many clinicians and it may be an important lesion for the pathologist to document when examining the placenta. Pathologists and clinicians should educate one another on topics such as coiling indexes, for better research and follow-up, with potential consequences for future pregnancies. For example, the antenatal ultrasound finding of a diminution of coiling from the fetal to umbilical end of the cord may be confirmed post-delivery but the correlation with gestational age cannot.[31,32] Pathologists often receive only part of the cord for examination and this may hamper comparative studies.

In clinical practice, preterm birth may result from either ischaemic or infectious lesions which can be confirmed by placental examination.[33] The clinical diagnosis of infection can be difficult for several reasons: maternal fever and fetal tachycardia could be due to epidural analgesia, which can also mask abdominal pain.[34] In clinically suspected chorioamnionitis, evidence is brought by histopathological evaluation in approximately 60% of cases. Histological evidence better correlates with fetal signs than maternal signs for infection.[35] If chorioamnionitis is seen, approximately 70% of cultures or PCR will be positive.[36,37] However, chorioamnionitis does not necessarily equate to fetal infection.[38] Besides these difficulties in diagnosis of chorioamnionitis and infection, the placentas of suspected infections are often not even presented for pathology examination.

Several placentation disorders and placental abnormalities that can be discovered by ultrasound examination have been described. These abnormalities may not have much significance in daily practice, as in case of echolucencies or calcifications in the term pregnancy, but these abnormalities are easily detected at pathology examination.[39] The same abnormalities in a preterm placenta, however, may be a cause for concern as placental function can be impaired.[40] How well the ultrasound recognition of placental pathology correlates with what is found on placental histopathology is unclear and requires much more systematic research. Unlike studies that have examined correlation between ultrasound and pathological findings in fetuses, no clear data are available on ultrasound detection rates and their correlation with pathology results. It is not always possible to confirm ultrasound diagnosis by placental examination, for example in the case of vasa praevia, as the exact location of the velamentous vessels remain unknown.[41] Other ultrasound diagnoses, such as twin-to-twin transfusion syndrome and chorangioma, can be confirmed by pathology. Although demonstration of vascular anastomoses does not necessarily equate with a twin-twin transfusion syndrome, nevertheless such examination should be performed in all monochorionic twin placentas. Parenthetically, the identification of two yolk sac remnants on placental examination or the finding of a fetus papyraceous would indicate a twin pregnancy, the former being a vanishing twin; this has effects on the surviving twin.[42] Some placental abnormalities with clinical consequences are obvious at placental examination but hard to observe at ultrasonography, such as (recent) infarctions and placental abruptions.[40,43] Other abnormalities can be detected by ultrasound but many false positive cases can be expected, such as with placenta circumvallata.[41]

What does the obstetrician require from the pathology report?

Placental reports should provide the necessary information for the clinician to be able to counsel the parents and provide an explanation of possible pathophysiological pathways leading to the adverse outcome, their recurrence risks and possible interventions in future pregnancies. In an assessment of the quality of placental reports, the pathologist commented on gross histopathological abnormalities in 42-86%, on relation with clinical situation in 43-94%, and on recurrence risks in 0-50% (and in case of twin pregnancy on zygosity in 0-44%).[44] Communication is very important between pathology and other specialties; both parties should make sure that the other is well informed with understandable language and explanations on their part.[45-47] In surgery it has been described to be useful to organise multidisciplinary meetings including

a pathologist for early refining of diagnosis.[48] The involvement of the pathologist in similar meetings with obstetricians and neonatologists may be equally as informative, particularly in the case of apparent unexplained stillbirth or serious adverse outcome.

This is perhaps one area of clinical obstetric practice where the clinician would really welcome the pathologist to be as directive as possible and to provide as much information as possible about the significance of the placental lesions identified, the likely causality with any adverse outcome, and the possibility of recurrence in future pregnancies. For most obstetricians, adverse outcomes are encountered relatively infrequently in their obstetric practice and the pathologist should not assume that there is any more than a basic knowledge of the significance of placental pathology. A description of what is seen down the microscope, using unfamiliar histopathological terms, without any discussion of the significance is of little value to all but the most informed and educated subspecialist with a special interest in placental pathology. Most obstetricians would agree with the statement 'Tell us what you see, and tell us what it might mean!' As with all medicine, optimal patient care requires good communication.

Reference list

1. Kent AL, Dahlstrom JE. Placental assessment: Simple techniques to enhance best practice. Aust NZ J Obstet Gynaecol 2006; 46: 32-7.
2. Horn LC, Langner A, Stiehl P, Wittekind C, Faber R. Identification of the causes of intrauterine death during 310 consecutive autopsies. Eur J Obstet Gynecol Reprod Biol 2004; 113: 134-8.
3. Incerpi MH, Miller DA, Samadi R, Settlage RH, Goodwin TM. Stillbirth evaluation: what tests are needed? Am J Obstet Gynecol 1998; 178: 1121-5.
4. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997; 121: 449-76.
5. Badawi N, Kurinczuk JJ, Keogh JM, Chambers HM, Stanley FJ. Why is the placenta being ignored? Aust NZ J Obstet Gynaecol 2000; 40: 343-6.
6. Spencer MK, Khong TY. Conformity to guidelines for pathologic examination of the placenta. Arch Pathol Lab Med 2003; 127: 205-7.
7. Curtin WM, Krauss S, Metlay LA, Katzman PJ. Pathologic examination of the placenta and observed practice. Obstet Gynecol 2007; 109: 35-41.
8. Kraus FT. Perinatal pathology, the placenta, and litigation. Hum Pathol 2003; 34: 517-21; discussion 522–7.
9. Burton JL, Stephenson TJ. Are clinicians failing to supply adequate information when requesting a histopathological investigation? J Clin Pathol 2001; 54: 806-8.
10. Vogler C, Petterchak J, Sotelo-Avila C, Thorpe C. Placental pathology for the surgical pathologist. Adv Anat Pathol 2000; 7: 214-29.
11. Benirschke K, Kaufmann P. Pathology of the Human Placenta. 4th ed. New York: Springer-Verlag, 2000.
12. Khong TY. A topographical and clinical approach to examination of the placenta. Pathology 2001; 33: 174-86.
13. Kraus FT, Redline RW, Gersell DJ, Nelson DM, Dicke JM. Placental Pathology. Washington, DC: American Registry of Pathology, 2004.
14. Hargitai B, Marton T, Cox PM. Best practice no 178. Examination of the human placenta. J Clin Pathol 2004; 57: 785-92.
15. Faye-Petersen O, Heller D, Joshi V. Handbook of Placental Pathology. London: Taylor and Francis, 2005.
16. Fox H, Sebire N. Pathology of the Placenta. 3rd ed. London: Saunders, 2007.
17. Ernst LM, Crouch J, Rinder H, Howe JG. Bacterial etiology for chronic villitis is not supported by polymerase chain reaction for 16S rRNA DNA. Pediatr Dev Pathol 2005; 8: 647-53.
18. Labarrere CA, Faulk WP. Maternal cells in chorionic villi from placentae of normal and abnormal human pregnancies. Am J Reprod Immunol 1995; 33: 54-9.
19. Redline RW, Patterson P. Villitis of unknown etiology is associated with major infiltration of fetal tissue by maternal inflammatory cells. Am J Pathol 1993; 143: 473-9.
20. Styer AK, Parker HJ, Roberts DJ, Palmer-Toy D, Toth TL, Ecker JL. Placental villitis of unclear etiology during ovum donor in vitro fertilization pregnancy. Am J Obstet Gynecol 2003; 189: 1184-6.
21. Khong TY. Placental vascular development and neonatal outcome. Semin Neonatol 2004; 9: 255-63.

22. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004; 7: 443-52.
23. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. Am J Obstet Gynecol 2005; 192: 452-7.
24. Jeffery H, Lahra MM. The impact of infection during pregnancy in the mother and baby. In: Keeling JW, Khong TY, editors. Fetal and Neonatal Pathology. London: Springer, 2007: 379-423.
25. Marinoff DN, Chinn MA. Preventing recurrent second trimester group B streptococcus chorioamnionitis by intermittent prophylactic ampicillin. Obstet Gynecol 2001; 98: 918-9.
26. De Laat MW, Franx A, Nikkels PG, Visser GH. Prenatal ultrasonographic prediction of the umbilical coiling index at birth and adverse pregnancy outcome. Ultrasound Obstet Gynecol 2006; 28: 704-9.
27. Kashanian M, Akbarian A, Kouhpayehzadeh J. The umbilical coiling index and adverse perinatal outcome. Int J Gynaecol Obstet 2006; 95: 8-13.
28. Strong TH Jr, Elliott JP, Radin TG. Non-coiled umbilical blood vessels: a new marker for the fetus at risk. Obstet Gynecol 1993; 81: 409-11.
29. Strong TH Jr, Jarles DL, Vega JS, Feldman DB. The umbilical coiling index. Am J Obstet Gynecol 1994; 170: 29-32.
30. De Laat MW, Franx A, van Alderen ED, Nikkels PG, Visser GH. The umbilical coiling index, a review of the literature. J Matern Fetal Neonatal Med 2005; 17: 93-100.
31. Qin Y, Lau TK, Rogers MS. Second-trimester ultrasonographic assessment of the umbilical coiling index. Ultrasound Obstet Gynecol 2002; 20: 458-63.
32. van Diik CC, Franx A, De Laat MW, Bruinse HW, Visser GH, Nikkels PG. The umbilical coiling index in normal pregnancy. J Matern Fetal Neonatal Med 2002; 11: 280-3.
33. Ghidini A, Salafia CM. Histologic placental lesions in women with recurrent preterm delivery. Acta Obstet Gynecol Scand 2005; 84: 547-50.
34. Smulian JC, Shen-Schwarz S, Vintzileos AM, Lake MF, Ananth CV. Clinical chorioamnionitis and histologic placental inflammation. Obstet Gynecol 1999; 94: 1000-5.
35. Rhone SA, Magee F, Remple V, Money D. The association of placental abnormalities with maternal and neonatal clinical findings: a retrospective cohort study. J Obstet Gynaecol Can 2003; 25: 123-8.
36. Miralles R, Hodge R, McParland PC, et al. Relationship between antenatal inflammation and antenatal infection identified by detection of microbial genes by polymerase chain reaction. Pediatr Res 2005; 57: 570-7.
37. Svensson L, Ingemarsson I, Mardh PA. Chorioamnionitis and the isolation of microorganisms from the placenta. Obstet Gynecol 1986; 67: 403-9.
38. de Araujo MC, Schultz R, Vaz FA, Massad E, Feferbaum R, Ramos JL. A case-control study of histological chorioamnionitis and neonatal infection. Early Hum Dev 1994; 40: 51-8.
39. Kanne JP, Lalani TA, Fligner CL. The placenta revisited: radiologicpathologic correlation. Curr Probl Diagn Radiol 2005; 34: 238-55.
40. Harris RD, Cho C, Wells WA. Sonography of the placenta with emphasis on pathological correlation. Semin Ultrasound CT MR 1996; 17: 66-89.
41. Harris RD, Wells WA, Black WC, et al. Accuracy of prenatal sonography for detecting circumvallate placenta. Am J Roentgenol 1997; 168: 1603-8.
42. Pinborg A, Lidegaard O, la Cour Freiesleben N, Andersen AN. Consequences of vanishing twins in IVF/ICSI pregnancies. Hum Reprod 2005; 20: 2821-9.

43. Oyelese Y, Ananth CV. Placental abruption. Obstet Gynecol 2006; 108: 1005-16.
44. Khong TY, Gordijn SJ. Quality of placental pathology reports. Pediatr Dev Pathol 2003; 6: 54-8.
45. Attanoos RL, Bull AD, Douglas-Jones AG, Fligelstone LJ, Semararo D. Phraseology in pathology reports. A comparative study of interpretation among pathologists and surgeons. J Clin Pathol 1996; 49: 79-81.
46. Farias-Eisner R, Shapter A, Fu YS. The importance of communication between the pathologist and the clinician in caring for patients receiving gynecologic treatment. Am J Clin Pathol 1995; 103: S13-6.
47. Powsner SM, Costa J, Homer RJ. Clinicians are from Mars and pathologists are from Venus. Arch Pathol Lab Med 2000; 124: 1040-6.
48. Wong K, Birks D. Surgical risk management: the value of a weekly surgical radio-pathological meeting. ANZ J Surg 2004; 74: 205-9.

CHAPTER 6

PLACENTAL VILLOUS IMMATURITY AS AN IMPORTANT CAUSE OF TERM FOETAL DEATH

Sanne J. Gordijn,
Fleurisca J. Korteweg,
Jan Jaap H.M. Erwich,
Jozien P. Holm,
Joke M. Ravisé,
Peter G.J. Nikkels,
Nic J.G.M. Veeger,
T. Yee Khong,
Albertus Timmer

Submitted

Abstract

Objective: Little is known about intrauterine foetal deaths caused by placental villous immaturity. Our objective was to describe the prevalence and clinico-pathological associations of intrauterine foetal deaths caused by placental villous immaturity.

Study design: In a prospective study of 1025 couples with singleton intrauterine foetal deaths beyond 20 weeks of gestation we studied all cases beyond 36 weeks of gestation (n = 352). The Tulip classification was used for allocation of the cause of death. Based on these causes of death the IUFD were divided in three groups: villous immaturity, other placental pathology and non-placental pathology.

Results: The overall prevalence of villous immaturity was 23% (81/352). Twenty nine percent (81/280) of the placental causes of death represented villous immaturity. Absolute placental hypoplasia, also a developmental pathology of the placenta, was found twice more often in foetal deaths caused by villous immaturity (43.4%) compared to non-placental causes (19.7%) (p = 0.006). Comparable differences were found for relative placental hypoplasia. Oligohydramnios occurred almost twice as often in the group with villous immaturity (23.1%) than in the group with by non-placental causes (12.5%) (p = 0.139). The prevalence of gestational diabetes was 2.5 fold-higher in the villous immaturity group than in the group caused by other placental pathology (13.9% vs. 5.5%) (p = 0.029) and 10 fold-higher than in the group caused by non-placental pathology (13.9% vs. 1.4%) (p = 0.005). Foetuses with villous immaturity as the cause of death were small for gestational age in 14.8% and large for gestational age in 16%, statistically not different in comparison to other placental causes and non-placental causes, neither in comparison to the general population.

Conclusions: Villous immaturity is an important cause of term foetal death and is associated with gestational diabetes and placental hypoplasia.

Introduction

Over 60% of intrauterine foetal deaths (IUFD) are reported to have a placental cause of death.[1-5] Different placental pathologies occur in different gestational periods of pregnancy. In mid-trimester pregnancy (24-32 weeks of gestation) placental bed pathology, characterised by inadequate spiral artery remodelling and/or spiral artery pathology, causes death in more than half of IUFD. In term pregnancy developmental pathology of the placenta characterised by morphologic abnormalities due to abnormal development, causes IUFD in 40%.[5]

Foetal development and wellbeing are dependent on placental function and maturation. Placental maturation is a gradual process that proceeds throughout pregnancy. During the last months of pregnancy foetal oxygen and nutrient requirements increase. The placenta compensates for the increased needs by an expansion of the maternal-foetal exchange surface, forming the so-called syncytiovascular membranes (SVM) in the tertiary villi. SVM are very thin membranes with a maternal to foetal diffusion distance of only about 3.7µm that allow efficient transport.[6]

Stallmach et al. have described immaturity of the tertiary villi with a reduced number of SVM as a cause of foetal death in their population survey of 17,415 consecutive unselected singleton placentas (beyond 32 weeks of gestation).[7] They concluded that defective maturation of the placenta results in a 70 fold risk of foetal death, but that few affected foetuses actually die. They reported a prevalence of 5.7% including 2.3% associated with foetal death and a tenfold risk of recurrent foetal death.[7] De Laat et al confirmed an association between foetal death and villous immaturity. In their study the odds ratio for foetal death was 132 (95% CI: 13.2-1315) in the presence of a mean number of SVM under the 10th percentile. They found a trend towards the combination of hypercoiling of the umbilical cord and villous immaturity.[8]

Until now no attempts have been undertaken to analyse a cohort of term foetal deaths for the prevalence of villous immaturity. Our aim is to describe the prevalence and clinico-pathological associations of term IUFD caused by villous immaturity alone, or villous immaturity in combination with other placental pathologies in our cohort of 1025 IUFD beyond 20 weeks of gestation.

Materials and Methods

In 2002 we initiated a Dutch prospective IUFD cohort study in 50 secondary and tertiary referral hospitals, serving a rural as well as an urban population. Inclusion criteria were singleton foetal death diagnosed ante partum (heart beat ceased before labour) after 20 weeks of gestation calculated from the last menstrual period and confirmed by ultrasonography. Pregnancy terminations and intrapartum foetal deaths were excluded.

The study was approved by the institutional review boards of all participating hospitals. Written informed consent was obtained from all participants. Collected data included medical and obstetric history; maternal and foetal characteristics; and pregnancy and birth details. Our diagnostic workup protocol included: extensive maternal blood tests including full blood count, chemistry and viral serology, and coagulation tests performed by a central laboratory; foetal blood tests including viral serology; microbiological cultures from mother, foetus and placenta; autopsy; placental examination; and cytogenetic analysis.

Autopsy and placental examination were performed by the consulting surgical and perinatal pathologists in the participating hospitals in accordance with guidelines published by The Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists [9] and the College of American Pathologists. [10,11] All examined placentas were studied histopathologically.

Foetal growth percentiles for birthweight by gestational age at time of diagnosis of foetal death were calculated according to the Kloosterman growth charts.[12] Small for gestational age (SGA) was defined as birth weight below the 10^{th} percentile, large for gestational age (LGA) was defined as birth weight > 90^{th} percentile. Definitions for hypertension related disease (chronic hypertension, pregnancy induced hypertension (PIH), preeclampsia, HELLP syndrome and superimposed conditions) were based on recommendations by the International Society for the Study of Hypertension in Pregnancy (ISSHP).[13] Placental hypoplasia was defined as an absolute too low placental weight < 10^{th} percentile (absolute placental hypoplasia) and/or a too low placenta/birth weight ratio (relative placental hypoplasia).[14] Villous immaturity was defined as a placental maturation defect after 36 weeks of gestation with deficient formation of syncytiovascular membranes as interpreted by the consulting pathologist.[5,7,14] The umbilical cord coiling index (UCI) was calculated as the number of coils in the umbilical cord divided by the cord length in meters. Normal range: 0.1-0.3 based on previously published normal values of the UCI.[15-17]

All cases were classified in the Tulip classification for perinatal mortality (Table 1) by a panel of two consulting obstetricians, one registrar in Obstetrics and Gynaecology and one perinatal pathologist for determination of the cause of death.[2] Cause of death was defined as the initial, demonstrable pathophysiological entity initiating the chain of events that had irreversibly led to death. Risk factors such as smoking or hypertension, defined as other known contributing factors to death, were identified. Only one underlying cause of death could be allocated. Subgroups of a placental cause of death were defined as described previously.[2,14]

Table 1. Tulip classification, placental categories.

Cause	Subclassification	
1. Congenital anomaly		
2. Placenta	1. Placental bed pathology	
	2. Placental pathology	1. Developmental
		2. Parenchyma
		3. Localisation
	3. Umbilical cord complication	
	4. Not otherwise specified	
3. Prematurity/immaturity		
4. Infection		
5. Other		
6. Unknown		

Villous immaturity

Villous immaturity is a subcategory of placental developmental pathology in the Tulip classification (Table 1).[2,5,14] We evaluated the presence of villous immaturity alone (Tulip: placenta, placental pathology, developmental) or villous immaturity in combination with other placental pathologies (Tulip: placenta not otherwise specified), as a cause of death in all term IUFD over 36 completed weeks. IUFD was caused either by villous immaturity alone or by villous immaturity in combination with other placental pathology. For comparison of characteristics and clinico-pathological associations we used two groups. The first group consisted of foetal deaths caused by placental pathology other than villous immaturity ('other placental'). The second group consisted of foetal deaths with a non- placental cause of death, including 'unknown' and 'other' causes of death ('non-placental'). Furthermore, maternal conditions that contributed to death, such as

hypertension and diabetes, as well as known risk factors for death were selected as possible variables for analysis.

Statistics

Categorical variables were expressed as counts and percentages and continuous data as median and ranges. Differences between groups for categorical data were evaluated by Fisher exact test or Chi Square test. For continuous variables the Mann-Whitney U test was used. A two-tailed p-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SAS software, version 9.1 (SAS-Institute Inc., Cary, NC, USA).

Results

In our national IUFD study, 1025 couples and their IUFD were analysed. In this cohort 352 IUFD occurred after 36 completed weeks of gestation and were included in our analysis. A placental cause of death was identified in 280 of these 352 cases (80%). The overall prevalence of villous immaturity was 23% (81/352). Twenty-nine percent (81/280) of the placental causes of death represented villous immaturity, either villous immaturity alone or villous immaturity in combination with other placental pathologies. In the case of combined pathologies, placental hypoplasia and foetal thrombotic vasculopathy were most often present (Table 2). The prevalence of IUFD with a placental cause other than villous immaturity was 57% (199/352). In 20% of the IUFD the cause of death was non-placental (72/352).

Absolute placental hypoplasia was found twice more often in placentas of foetal deaths caused by villous immaturity (43.4%) than in placentas with non-placental causes (19.7%) ($p = 0.006$). The difference between other placental causes (62.1%) and non placental causes (19.7%) was even higher. ($p = 0.004$) Comparable differences were found for relative placental hypoplasia although statistically no difference was reached between IUFD with villous immaturity and IUFD with other placental causes (Table 3).

Oligohydramnios occurred almost twice as often in deaths caused by villous immaturity (23.1%) than in deaths with a non-placental cause of death (12.5%) ($p = 0.139$). The prevalence of oligohydramnios did not differ between villous immaturity as the cause of foetal death (23.1%) and the other placental causes of foetal death (22.2%) ($p = 1.0$).

Table 2. Villous immaturity and possible combinations with other placental pathologies as a cause of intrauterine foetal deaths.

	n (%)	**n(%)**[a]
Villous immaturity[c]	39 (48.1%)	
Villous immaturity and combined placental pathology[d]	42 (51.9%)	
Hypoplasia		31 (75.6%)
Foetal thrombotic vasculopathy		15 (36.6%)
Villitis of unknown origin		7 (17.1%)
Abruption		4 (9.8%)
Infarction		4 (9.8%)
Umbilical cord occlusion		4 (9.8%)
Chromosomal		1 (2.4%)
Excessive bleeding		1 (2.4%)
Total	81 (100%)	

[a]Overlap between different form of pathology exists, therefore the number is not equal to 42 and the percentage exceeds 100.
[c]Villous immaturity as classified in the Tulip: placental pathology, developmental.
[d]Combined placental pathologies as classified in the Tulip: placental not otherwise specified.

The umbilical cord coiling-index (UCI) in deaths caused by villous immaturity was statistically not different from the UCI found in deaths with other placental causes of death other than villous immaturity ($p = 0.15$) or non-placental causes of death ($p = 0.17$). The UCI was most often within the normal range in the villous immaturity group (58.8%). The lowest percentage of hypercoiling was found in the group with villous immaturity (11.8%). Unfortunately the UCI could not be determined in 59% of cases (Table 3). Umbilical cord insertion was similar between the groups.

The prevalence of gestational diabetes was 2.5 fold-higher in the villous immaturity group than in the group caused by other placental pathology (13.9% vs. 5.5%) ($p = 0.029$) and 10 fold-higher than in the group caused by non-placental pathology (13.9% vs. 1.4%) ($p = 0.005$). Other risk factors and maternal conditions, including BMI, did not differ between the groups (Table 3).

In IUFD caused by villous immaturity foetuses were SGA in 14.8% and LGA in 16%, which is statistically not different compared to the general population (respectively $p = 0.22$ and $p = 0.12$). In almost a quarter of IUFD with a placental cause of death other than villous immaturity and in 20.8% of the IUFD with a non placental cause of

death foetuses were SGA, which was statistically not different from the prevalence of SGA in foetuses with villous immaturity as the cause of death. The prevalence of LGA was neither different between the groups (Table 3). Foetal gender was equally represented in all groups (Table 3).

Only one case of villous immaturity coincided with an abnormal foetal chromosomal pattern: 45X/46XY (Table 2).

Table 3. Clinico-pathological associations of IUFD

Cause of death	**Villous immaturity n = 81**	**Other placental n = 199**	**p value**	**Non placental n = 72**	**p value**
1. Placental characteristics					
Absolute placental[a] hypoplasia	43.4% (76)	62.1% (195)	0.006	19.7% (61)	0.004
Relative placental[a] hypoplasia	66.7% (78)	77.6% (196)	0.067	30.6% (62)	<0.001
Coiling index[a]					
<0.1	29.4% (51)	24.0% (75)	0.15	33.3% (21)	0.17
0.1-0.3	58.8%	50.7%		38.1%	
>0.3	11.8%	25.3%		28.6%	
Umbilical cord insertion[a,c]					
(Para)central	79.2% (72)	80.5% (174)	0.61	79.3% (58)	0.91
Velamentous/marginal	14.0%	15.5%		12.1%	
Not known	6.9%	4.0%		8.6%	
2. Amniotic fluid characetristics					
Oligohydramnios	22.2% (81)	23.1% (199)		12.5% (72)	
3. Maternal characteristics					
Maternal age					
Median	31.4 (81)	31.4 (199)	0.73	32.0 (72)	0.98
Range	17.5-42.6	21.1-45.2		20.8-38.9	
BMI					
Median	26.8 (64)	25.16 (155)	0.12	25.24 (48)	0.20
Range	20.0-47.8	17.0-46.7		15.8-38.2	
Parity					
Nulliparous	45.7%(81)	56.3% (199)	0.11	55. 6% (72)	0.26
Multiparous	54.3%	43.3%		44.4%	

Table 3 (Continued)

Cause of death	Villous immaturity n = 81	Other placental n = 199	p value	Non placental n = 72	p value
3. Maternal characteristics					
Diseases					
Pre-existent hypertension	1.2% (81)	2.5% (199)	0.68	0% (72)	1.00
Pregnancy induced hypertension	8.6%	10.6%	0.82	4.2%	0.33
Pre eclampsia	1.23%	3.0%	0.68	1.4%	1.00
HELLP	0.0%	0.5%	1.00	0.0%	–
Diabetes	2.5%	2.0%	1.00	0.0%	0.50
Gestational diabetes	13.6%	5.5%	0.029	1.4%	0.005
Intoxications[a]					
Smoking	18.5% (79)	23.1% (198)	0.40	18.1% (70)	0.27
Alcohol	3.8% (81)	3.1% (199)	0.72	5.8% (72)	0.71
Other drugs	2.5% (81)	1.5% (199)	0.50	0.0% (72)	0.63
4. Foetal characteristics					
Sex					
Boy	54.3% (81)	51.8% (199)	0.79	55.6% (72)	1.00
Girl	45.7%	48.2%		44.4%	
Foetal weight[b]					
<p10	14.8% (81)	24.1% (199)	0.11	20.8% (72)	0.40
>p90	16.0%	12.1%	0.44	15.3%	0.85

[a]The percentage calculated as percentage of cases over those with known data ()

[b]Foetal growth of the villous immaturity group in comparison to the general population based on the Kloosterman centiles: growth below the 10th percentile: p = 0.22, growth above the 90th percentile: p = 0.12.

[C]P value for coiling index > 0.3 between villous immaturity and other placental causes: p = 0.071 and villous immaturity and non placental causes:p = 0.096

Discussion

Placental villous immaturity is an important cause of term IUFD. This is the first cohort study describing the prevalence and clinico-pathological associations of villous immaturity in 352 IUFD of at least 36 completed weeks of gestation. A placental cause of death was identified in almost 80%. Twenty-nine percent of these placental causes of foetal death represented villous immaturity, either by villous immaturity alone or by villous immaturity in combination with other placental pathologies causing death. Villous immaturity was associated with gestational diabetes. Villous immaturity was also associated with placental hypoplasia in comparison to non placental causes. A trend was found towards oligohydramnios in comparison to non-placental causes.

In our study we primarily focused on IUFD, while others initiated their analysis from a placental point of view.[7,8] Differences in study groups might explain the much higher prevalence of villous immaturity in our IUFD cohort than the previously reported prevalences.[7,18] Two types of villous immaturity at term have been described.[19] In term placentas scattered small groups of immature chorionic villi can be seen in up to 97% of uncomplicated pregnancies. These immature villi are freshly formed and arise directly from the stem villi.[18,20,21] Groups of these immature villi are found in areas of placental growth and are not indicative of placental pathology. In the other pattern almost all chorionic villi are markedly immature for the duration of pregnancy with inadequate formation of SVM due to abnormal developmental processes, which is the pattern we have focused on.[19] However, in the international literature no uniform definition for villous immaturity have been established yet. Some base their definition of villous immaturity on the percentage of villi with SVM or on the number of SVM per terminal villous or per histological sample.[7,8,18,22] Data on the normal quantity of SVM are limited and the mean numbers differ.[7,8,18,19,22] Others use abnormalities in morphology and angiogenesis of the villi to define villous immaturity.[6,18,19,23,24] Akin studies on the nosology and reproducibility of placental reaction patterns[25-27] further studies are needed to review, define, and test the reproducibility of diagnostic criteria for villous immaturity.

Gestational diabetes and pre-existent diabetes have been associated with villous immaturity.[18,19,22-24,28-30] Calderon et al. reported that the size and number of terminal villi as well as villous total area in diabetes was similar to their control group. However, total and mean villous vessel surfaces were smaller in diabetes, resulting in a lower capillarisation index.[28] Evers et al also reported an increase in villous immaturity in placentas of diabetic mothers. They found that the appropriate for gestation (AGA) babies of diabetic women had a relatively high placental weight, which they suggested as possibly compensating for villous immaturity as a protection against hypoxaemia. Their LGA babies had a relatively lower placental weight, which may explain the increased incidence of foetal death in that category. Also in our study villous immaturity was associated with placental hypoplasia and gestational diabetes. The association of villous immaturity and gestational diabetes, but not with pre-existent diabetes between groups is remarkable. The reason for this difference is speculative, but may be related to differences in glycemic control.

Placental pathology can lead to decreased placental function, resulting in intrauterine growth restriction and oligohydramnios. In these cases the mode of foetal death

is chronic. Villous immaturity is a parenchymal disease characterised by inadequate development of SVM in tertiary villi. The absence of SVM is thought to cause placental dysfunction in a period of pregnancy when demands on placental function are increased. Signs of hypoxaemia in these cases of late foetal death support placental dysfunction as a mechanism of death in these cases.[8] In deaths caused by villous immaturity the mode of death is unknown and can only be speculated on. In appropriately grown foetuses a chronic mode of death seems less likely. A sub-acute mode of death is suggested by a trend towards increased prevalence of oligohydramnios in IUFD with villous immaturity as a sign of redistribution of foetal blood to vital organs at expense of renal blood flow. In the foetal deaths caused by villous immaturity the prevalence of SGA was found to be 50% higher than in the general population. Based on this trend towards a lower foetal weight one might suggest that at least in some of the SGA foetuses the mode of death is chronic as these foetuses might have grown less than their potential and are growth restricted. Use of customised growth charts to detect growth restricted foetuses[31,32] and correlation of clinical signs and symptoms with data on the mode of death obtained from autopsy studies could corroborate the mode of death further.[33]

In conclusion placental villous immaturity is an important cause of term IUFD. In pregnancy villous immaturity may only present with few clinical signs and symptoms which hinders intervention to prevent death. Recurrent disease has been described and only in these cases pregnancy may be rescued by birth.[7]

Reference list

1. Galan-Roosen AE, Kuijpers JC, van der Straaten PJ, Merkus JM. Evaluation of 239 cases of perinatal death using a fundamental classification system. Eur J Obstet Gynecol Reprod Biol 2002; 103(1):37-42.
2. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. BJOG 2006; 113(4):393-401.
3. Incerpi MH, Miller DA, Samadi R, Settlage RH, Goodwin TM. Stillbirth evaluation: what tests are needed? Am J Obstet Gynecol 1998; 178(6):1121-1125.
4. Rayburn W, Sander C, Barr M, Jr., Rygiel R. The stillborn fetus: placental histologic examination in determining a cause. Obstet Gynecol 1985; 65(5):637-641.
5. 5. Korteweg F.J., Erwich J.J.H.M., Holm J.P., Ravise J., Meer J.vd, Veeger N.J.G.M. Different placental pathologies are the main causes of fetal death; classification of 750 cases. 2009. Ref Type: Unpublished Work
6. Benirschke K, Kaufmann P. Pathology of the Human Placenta. 4th ed. New York: Springer-Verlag; 2000.
7. Stallmach T, Hebisch G, Meier K, Dudenhausen JW, Vogel M. Rescue by birth: defective placental maturation and late fetal mortality. Obstet Gynecol 2001; 97(4):505-509.
8. de Laat MW, van der Meij JJ, Visser GH, Franx A, Nikkels PG. Hypercoiling of the umbilical cord and placental maturation defect: associated pathology? Pediatr Dev Pathol 2007; 10(4):293-299.
9. RCOG. Fetal and perinatal pathology. Report of a joint working party. RCOG, editor. 2001. London. Ref Type: Report
10. Bove KE. Practice guidelines for autopsy pathology: the perinatal and pediatric autopsy. Autopsy Committee of the College of American Pathologists. Arch Pathol Lab Med 1997; 121(4):368-376.
11. Langston C, Kaplan C, Macpherson T, Manci E, Peevy K, Clark B et al. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997; 121(5):449-476.
12. Kloosterman GJ. [Intrauterine growth and intrauterine growth curves]. Ned Tijdschr Verloskd Gynaecol 1969; 69(5):349-365.
13. Brown MA LMSMdea. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Association for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 20, IX-XIV. 2001. Ref Type: Report
14. Korteweg FJ, Gordijn SJ, Timmer A, Holm JP, Ravise JM, Erwich JJ. A placental cause of intra-uterine fetal death depends on the perinatal mortality classification system used. Placenta 2008; 29(1):71-80.
15. Machin GA, Ackerman J, Gilbert-Barness E. Abnormal umbilical cord coiling is associated with adverse perinatal outcomes. Pediatr Dev Pathol 2000; 3(5):462-471.
16. van Diik CC, Franx A, de Laat MW, Bruinse HW, Visser GH, Nikkels PG. The umbilical coiling index in normal pregnancy. J Matern Fetal Neonatal Med 2002; 11(4):280-283.
17. Strong TH, Jr., Jarles DL, Vega JS, Feldman DB. The umbilical coiling index. Am J Obstet Gynecol 1994; 170(1 Pt 1):29-32.

18. Fox H. Villous immaturity in the term placenta. Obstet Gynecol 1968; 31(1):9-12.
19. Fox H, Sebire N. Histological Abnormalities of the Placenta. Pathology of the Placenta. 3rd ed. Philadelphia: Saunders Elsevier; 2007. 95-146.
20. Stallmach T, Hebisch G. Placental pathology: its impact on explaining prenatal and perinatal death. Virchows Arch 2004; 445(1):9-16.
21. Bleyl U, Stefek E. [On the morphology and diagnostic evaluation of loose immature villi in mature human placenta]. Beitr Pathol Anat 1965; 131(2):162-183.
22. Faye Petersen OM, Heller DS, Joshi VV. Histologic lesions of the placenta. Handbook of Placental Pathology. 2nd ed. London, New York: Taylor & Francis; 2006. 53-79.
23. Daskalakis G, Marinopoulos S, Krielesi V, Papapanagiotou A, Papantoniou N, Mesogitis S et al. Placental pathology in women with gestational diabetes. Acta Obstet Gynecol Scand 2008; 87(4):403-407.
24. Evers IM, Nikkels PG, Sikkema JM, Visser GH. Placental pathology in women with type 1 diabetes and in a control group with normal and large-for-gestational-age infants. Placenta 2003; 24(8-9):819-825.
25. Redline RW, Ariel I, Baergen RN, Desa DJ, Kraus FT, Roberts DJ et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004; 7(5):443-452.
26. Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2003; 6(5):435-448.
27. Redline RW, Boyd T, Campbell V, Hyde S, Kaplan C, Khong TY et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004; 7(3):237-249.
28. Calderon IM, Damasceno DC, Amorin RL, Costa RA, Brasil MA, Rudge MV. Morphometric study of placental villi and vessels in women with mild hyperglycemia or gestational or overt diabetes. Diabetes Res Clin Pract 2007; 78(1):65-71.
29. Laurini RN, Visser GH, van BE, Schoots CJ. Morphological findings in placentae of insulin-dependent diabetic patients treated with continuous subcutaneous insulin infusion (CSII). Placenta 1987; 8(2):153-165.
30. Teasdale F. Histomorphometry of the placenta of the diabetic women: class A diabetes mellitus. Placenta 1981; 2(3):241-251.
31. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992; 339(8788):283-287.
32. Gardosi J. The application of individualised fetal growth curves. J Perinat Med 1998; 26(4):333-338.
33. Becker MJ, Becker AE. Fat distribution in the adrenal cortex as an indication of the mode of intrauterine death. Hum Pathol 1976; 7(5):495-504.

CHAPTER 7

THE TULIP CLASSIFICATION OF PERINATAL MORTALITY: INTRODUCTION AND MULTIDISCIPLINARY INTER-RATER AGREEMENT

Fleurisca J. Korteweg,
Sanne J. Gordijn,
Albertus Timmer,
Jan Jaap H.M. Erwich,
Klasien A. Bergman,
Katelijne Bouman,
Joke M. Ravisé,
Martijn P. Heringa,
Jozien P. Holm

BJOG 2006; 113: 393-401

Abstract

Objective: To introduce the pathophysiological Tulip classification system for underlying cause and mechanism of perinatal mortality based on clinical and pathological findings for the purpose of counselling and prevention.

Design: Descriptive.

Setting: Tertiary referral teaching hospital.

Population: Perinatally related deaths.

Methods: A classification consisting of groups of cause and mechanism of death was drawn up by a panel through the causal analysis of the events related to death. Individual classification of cause and mechanism was performed by assessors. Panel discussions were held for cases without consensus.

Main outcome measures: Inter-rater agreement for cause and mechanism of death.

Results: The classification consists of six main causes with subclassifications: (1) congenital anomaly (chromosomal, syndrome and single- or multiple-organ system), (2) placenta (placental bed, placental pathology, umbilical cord complication and not otherwise specified [NOS]), (3) prematurity (preterm prelabour rupture of membranes, preterm labour, cervical dysfunction, iatrogenous and NOS), (4) infection (transplacental, ascending, neonatal and NOS), (5) other (fetal hydrops of unknown origin, maternal disease, trauma and out of the ordinary) and (6) unknown. Overall kappa coefficient for agreement for cause was 0.81 (95% CI 0.80-0.83). Six mechanisms were drawn up: cardio/circulatory insufficiency, multi-organ failure, respiratory insufficiency, cerebral insufficiency, placental insufficiency and unknown. Overall kappa for mechanism was 0.72 (95% CI 0.70-0.74).

Conclusions: Classifying perinatal mortality to compare performance over time and between Centers is useful and necessary. Interpretation of classifications demands consistency. The Tulip classification allows unambiguous classification of underlying cause and mechanism of perinatal mortality, gives a good inter-rater agreement, with a low percentage of unknown causes, and is easily applicable in a team of clinicians when guidelines are followed.

Introduction

There are intensified demands on medical, political and epidemiological grounds for proper determination and classification of cause of perinatal mortality.[1-4] Such classification is complex due to the complicated pathophysiological processes encountered in the mother, fetus and placenta, and as a result of their interaction.[5] The multiplicity of contributing factors and the different background of the clinicians involved add to the confusion.

Thirty classification systems for perinatal mortality have been introduced since 1954.[6-34] Systems have been designed for different reasons with different approaches, definitions and levels of complexity. Twenty systems focus on either pathological information or clinical details,[6,7,9-12,14-16,18,21,23,24,29-34] whereas in our opinion, both should be considered for classification. Half the systems aim at classifying the underlying cause of death.[6-8,10,13,15,18,20,29-32,34] Systems should not confuse this underlying cause of death with mechanism of death and risk factors.[3] Some systems are brief and easy to use, others are more detailed. Preferably, classification systems should contain a structure that allows unambiguous allocation to representative cause-of-death groups to ensure a high percentage of cases classified with a known cause of death.[20] It should be possible to amend a system to allow for future scientific developments without disturbing the system.[4]

Clear uniform definitions and classification guidelines make a model easy to use and uni-interpretable.[20,32] However, definitions of cause-of-death categories and guidelines are incomplete or not described in more than half of the articles.[6-9,15,16,19,21,22,24-26,29-31,33,34] Definitions of the perinatal period change over time and are not always unanimous between Centers.[21,35-37] There is need for a system that permits classification of cases occurring during the complete perinatal period independent of the used definitions.

Classification of cause of death must be independent of the specialty of the clinician.[23] It is important that there be a good inter-rater agreement and that classifications used are reproducible.[18,21,23,38] Only some systems test their level of agreement. This inter-rater agreement varies from 0.50-0.59 measured by independent raters[38] to 0.85-0.90 determined by the original assessors themselves.[15] The mother, the fetus and the placenta are all involved in the complex process of perinatal mortality; they should be addressed together. Only two systems consider these three factors together.[20,22] However, de Galan-Roosen et al.[20] have minimal subclassification of the placenta group, and the classification of Hovatta et al.[22] is designed for the stillbirth

group only. Our view was that existing classification systems for perinatal mortality did not fulfil our needs.

Our objective was to develop a new classification system that separates cause and mechanism of perinatal mortality for the purpose of counselling and prevention. Our 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. We describe here and assess the inter-rater agreement of the pathophysiological Tulip classification for cause and mechanism of perinatal mortality in a multidisciplinary setting.

Methods

To design a pathophysiological classification system for perinatal mortality, a panel of three obstetricians, a pathologist, a neonatologist, a clinical geneticist and two obstetrical residents organised panel meetings. The system was named Tulip as this is a well-known Dutch association. First, cause of death was defined as the initial, demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death. The mechanism of death was defined as the organ failure that is not compatible with life, initiated by the cause of death that has directly led to death. Origin of mechanism was defined as the explanation of the mechanism of death. This third step of the classification was proposed to make the pathway of death more clear and to prevent confusion with cause of death. The system was designed to include late fetal losses, stillbirths, early neonatal deaths, late neonatal deaths and perinatally related infant deaths during hospital admission from birth onwards.

Then we decided whether a strict hierarchy would be preferable for the system as hierarchy makes use easier. During multidisciplinary panel sessions, we proposed the concept that the cognitive process involved in making explicit the complex process of integrating all possible information to allocate the underlying cause and mechanism of death is comparable with diagnostic reasoning in clinical medicine, which has been described by other disciplines.[39] Since diagnostic reasoning is differential diagnosis and pattern recognition driven rather than hierarchical, we concluded that our classification system for underlying cause of death could not be strictly hierarchical.

The six main groups of causes of death with subclassifications, and the mechanisms of death were developed by the panel according to the causal analysis of 109 perinatally related deaths during a 1-year period. Case notes and results of complete diagnostic work-up (as current at that time in our institution) were available. Discussions between panel members on the basis of information from existing classifications and current obstetrical, pathologic, neonatologic and genetic literature on causes of perinatal mortality led us to the Tulip system. As congenital anomalies and placental pathology represent major causes of perinatal mortality, we decided to design detailed subclassifications for these groups.

Table 1. Tulip classification of perinatal mortality: causes

Cause	n (%)	Subclassification		n
1 Congenital anomaly	142 (35)	1 Chromosomal defect	1 Numerical	42
			2 Structural	8
			3 Microdeletion/ unipa-rental disomy	-
		2 Syndrome	1 Monogenic	15
			2 Other	2
		3 Central nervous system		22
		4 Heart and circulatory system		9
		5 Respiratory system		1
		6 Digestive system		2
		7 Urogenital system		13
		8 Musculoskeletal system		-
		9 Endocrine/metabolic system		-
		10 Neoplasm		2
		11 Other	1 Single organ	-
			2 Multiple organ	26
2 Placenta	111 (27)	1 Placental bed pathology		72
		2 Placental pathology	1 Development	28
			2 Parenchyma	6
			3 Localisation	2
		3 Umbilical cord complication		1
		4 NOS		2

Table 1 (Continued)

Cause	n (%)	Subclassification		n
3 Prematurity immaturity	95 (23)	1 PPROM		52
		2 Preterm labour		30
		3 Cervical dysfunction		12
		4 Iatrogenous		-
		5 NOS		1
4 Infection	6 (1)	1 Transplacental		2
		2 Ascending		4
		3 Neonatal		-
		4 NOS		-
5 Other	13 (3)	1 Fetal hydrops of unknown origin		4
		2 Maternal disease		5
		3 Trauma	1 Maternal	-
			2 Fetal	-
		4 Out of the ordinary		4
6 Unknown	44 (11)	1 Despite thorough investigation		16
		2 Important information missing		28
Total				411

Table 1 shows the categories for cause of death, and Table 2 shows the categories for mechanism of death. Definitions for the terms used and allocation to a certain category, as well as examples of clinical and pathological entities, were drawn up in a guideline.

Tulip guideline

1 *Congenital anomaly*: the cause of death is explained by a genetic or a structural defect incompatible with life or potentially treatable but causing death. Assignment to this group is justified if the congenital anomaly is the actual cause of death and no other major category of causes of death has initiated the causal pathway leading to death. Termination of pregnancy because of a congenital anomaly is also classified in this group; subclassification is dependent on the defect. These include;

1.1 *chromosomal defects*: with subclassification by type,

1.2 *syndromal*: with subclassification by whether monogenic or not and organ-specific abnormalities such as,

1.3 *central nervous system* or,

1.4 *heart and circulatory system*. Examples are shown in Table 1.

2 *Placenta*: the cause of death is explained by a placental pathological abnormality supported by the clinical findings.

2.1 *Placental bed pathology*: inadequate spiral artery remodelling and/or spiral artery pathology leading to uteroplacental vascular insufficiency such as placental infarction.

2.2 *Placental pathology*: pathology originated during development of the placenta itself, abnormalities in the parenchyma or localisation of the placenta.

2.2.1 *Development*: morphologic abnormalities that arise because of abnormal developmental processes such as placenta circumvallata, villous immaturity and placenta hypoplasia.

2.2.2 *Parenchyma*: acquired placenta parenchyma disorders of the villi or intervillous space. Examples are villitis of un-known origin, massive perivillous fibrin deposition and fetomaternal haemorrhage without obvious cause.

2.2.3 *Abnormal localisation*: example is praevia.

2.3 *Umbilical cord complication*: acquired umbilical cord complications supported by clinical findings. Example is umbilical cord prolapse, with occlusion of the vessels.

2.4 *Not otherwise specified (NOS)*: the cause of death falls into the group placenta, but because of the existence of different placenta subclassifications, a choice cannot be made as to what was first in the chain of events leading to death.

3 *Prematurity/immaturity*: the cause of death is explained by the initiation of preterm delivery only and in the case of neonatal death also, with the associated problems of prematurity/immaturity.

3.1 *Preterm prelabour rupture of membranes (PPROM):* initiates preterm delivery,

3.2 *Preterm labour:* where uterus contractions initiate preterm delivery.

3.3 *Cervical dysfunction:* initiates preterm delivery,

3.4 *Iatrogenic:* procedure initiates preterm delivery on maternal non-obstetrical indication only, for example caesarean section on maternal indication for carcinoma,

3.5 *NOS:* where prematurity/immaturity is the cause of death but it is not clear how preterm delivery was initiated.

4 *Infection*: the cause of death is explained by an infection resulting in sepsis and stillbirth or neonatal death. There is a clear microbiological evidence of infection with matching clinical and pathological findings.

4.1 *Transplacental:* where there is a haematogenous infection through the spiral arteries, the placenta and the umbilical cord to the fetus such as Parvovirus infection.

4.2 *Ascending:* where there is an ascending infection from colonisation of the birth canal such as Streptococci group B infection.

4.3 *Neonatal:* where there is infection acquired after birth such as *Escherichia coli* sepsis-meningitis.

4.4 *NOS:* where there is infection, but it cannot be discerned whether the infection was transplacental, ascending or acquired after birth.

5 *Other*: the cause of death is explained by another specific cause not mentioned in the previous groups of cause of death.

5.1 *Fetal hydrops of unknown origin,*

5.2 *Maternal disease:* is severe enough to jeopardise the fetus or the neonate, initiating death. Examples might be severe maternal sepsis or alloimmunisation. For most maternal medical conditions, this classification, (5.2) will only apply when the disease leads directly to perinatal death, as in diabetic ketoacidosis. Otherwise, the condition is a risk factor,

5.3 *Trauma.*

5.3.1 *Maternal:* such as severe road traffic accidents,

5.3.2 *Fetal:* such as birth trauma.

5.4 *Out of the ordinary*: a specific event or condition initiating the causal pathway to fetal or neonatal death such as rupture of the uterus.

6 *Unknown.*

6.1 *Despite thorough investigation*,

6.2 *Important information missing*.

To register more information about each case of perinatally related mortality, it is also possible to describe *contributing factors*, defined as other known factors on the causal pathway to death, e.g. risk factors such as obesity and smoking, and *co-morbidity*, defined as an event or a condition relevant for the clinical situation or the care given but not part of the causal pathway to death. Case examples illustrating the use of the Tulip classification are shown in the Appendix.

Table 2. Tulip classification of perinatal mortality: mechanisms

Mechanisms	*n* **(%)**
1 Cardiocirculatory insufficiency	44 11)
2 Multi-organ failure	30 (7)
3 Respiratory insufficiency	130 (32)
4 Cerebral insufficiency	7 (2)
5 Placental insufficiency	123 (30)
6 Unknown	77 (19)
Total	411 (100)

Agreements on cause, mechanism of death and origin of mechanism

Because certain case situations led to discussions, an additional list of agreements for cause, mechanism of death and origin of mechanism for use in our Center were prepared beforehand.

1 If a pregnancy was terminated with prostaglandins for a congenital anomaly, the congenital anomaly was considered the cause of death, placental insufficiency the mechanism of death and induction the origin of mechanism. If a fetus was born alive after this procedure and died within hours, respiratory insufficiency was considered as the mechanism of death and induction the origin of mechanism.

2 In the case of a sequence of recurrent vaginal blood loss, PPROM and a placenta circumvallata, we considered developmental placental pathology (2.2.1) as the cause of death.

3 If the cause of intrauterine death was developmental placental pathology (2.2.1) due to a twin-to-twin transfusion syndrome, cardiocirculatory insufficiency was considered as the mechanism of death for both the donor and the recipient fetus.

4 If a fetus died due to umbilical cord prolapse, the mechanism of death was cardiocirculatory insufficiency.

5 If a treatment was not initiated after birth for a nonviable, very early preterm neonate, respiratory insufficiency was considered as the mechanism of death and prematurity as the origin of mechanism.
6 If intrauterine fetal death was attributable to infection, multi-organ failure was considered the mechanism of death and intrauterine infection the origin of mechanism. In the case of neonatal death due to infection, multi-organ failure was considered the mechanism of death and sepsis the origin of mechanism.
7 If intrauterine fetal death was due to fetal hydrops of any cause, cardiocirculatory insufficiency could only be considered as mechanism of death if a hyperdynamic circulation existed.
8 Important information missing was defined as two out of three diagnostic investigations missing regarding pathological examination; autopsy and placental examination, chromosomal or microbiological investigation.

Origin of mechanism

Cessation of treatment for origin of mechanism is eligible when there is a medical prognosis of either early death (for example, Potters syndrome) or severe impairment associated with a very poor quality of life (for example, neurological damage due to severe asphyxia and congenital anomalies).[40] Cessation of treatment is not the origin of mechanism if the death was imminent. In the case of cessation of treatment of the neonate by reason of very poor prognosis, mechanism of death allocated was respiratory insufficiency.

Inter-rater agreement

After design of the Tulip classification system, a panel consisting of the original assessors who developed the system assessed the inter-rater agreement of the system for cases of perinatal mortality occurring during the 4-year period of 1999-2002. During this period, there were 7389 total births (stillborn and liveborn > 16 weeks of gestation) at our institution. A retrospective analysis was performed on all perinatally related deaths occurring during this period. These deaths comprised late fetal losses (spontaneous fetal loss and termination of pregnancy from 16 completed weeks of gestation until 22 weeks of gestation). Perinatally related deaths beyond 22 weeks of gestation were defined as stillbirths, early neonatal deaths, death up to seven completed days after birth; late neonatal deaths, death from 8 up to 28 completed days after birth and perinatally related infant deaths, death from 29 days up to six completed months after birth during hospital admission from birth onwards.

Table 3. Tulip classification of perinatal mortality: examples of origin of mechanism

Origin of mechanism	***n***
Cardiocirculatory	
Congenital heart malformation	2
Fetal hydrops	1
Myocardial ischaemia	2
Pneumopericard	1
Supraventriculary tachycardia	1
Twin to twin transfusion	5
Umbilical cord occlusion	14
Pulmonary	
Airway obstruction	2
Bronchopneumonia	1
Chronic lung disease/broncho pulmonary dysplasia	9
IRDS/hyaline membrane disease	11
Lunghypoplasia	25
Placental	
Placental abruption	16
Infarction	24
Villous immaturity/terminal villous deficiency	4
Hypoplasia	12
Partial mola	2
Fetal thrombotic vasculopathy	3
Massive perivillous fibrin deposition	3
Ectopic placentation	1
Other	
Sepsis	14
Infection intrauterine	12
Prematurity/immaturity	40
Excessive bleeding	6
Complication after medical procedure	11
Ceasure of treatment	31
Induction	63
Selective feticide	2
None of the above	12
Unknown	81
Total	411

IRDS, idiopathic respiratory distress syndrome.

Two independent researchers compiled narratives for each mortality case, describing chronologically the most important events. Narratives were based upon medical and obstetrical history, information about the pregnancy, diagnostic test results including pathological findings concerning autopsy and placental investigation and obstetrical and neonatology discharge letters. No other information sources was consulted.

The panel consisted of two obstetricians, an obstetrical resident, a neonatologist and a pathologist, each of whom individually classified cause and mechanism of death for all cases. Procedures were agreed upon in advance. Only one underlying cause and one mechanism of death could be allocated. Assessors were unaware of the results of classification from other panel members. Second, panel discussions were held for cases without initial consensus on cause or mechanism of death, and after a debate, a panel consensus was agreed upon. A panel judgement for origin of mechanism was also allocated. Cases, in which panel members failed to comply with the definitions for allocation to a certain category, stated in the guidelines, were registered as misinterpretation.

Statistical methods

Classification of the cause and mechanism of death was performed individually by different assessors. Inter-rater agreement beyond chance between the assessors was calculated using Cohen's kappa. Our qualitative interpretation of the kappa statistic for inter-rater agreement corresponding with others was: poor, < 0.4; fair, 0.40 to < 0.55; good, 0.55 to < 0.70; very good, 0.70 to < 0.85 and excellent, ≥ 0.85.[41] Kappa values and 95% CI were calculated for five assessors.

Results

During the 4-year period of 1999-2002, there were 411 perinatally related losses, comprising 104 late fetal losses, 153 stillbirths, 108 early neonatal deaths, 25 late neonatal deaths and 21 perinatally related infant deaths. The perinatal mortality rate (stillborn and liveborn > 500 g, death up to seven completed days after birth) was 30.7/1000. Clinical records were available for all deaths. An autopsy was performed in 199 (48%) cases and placental examination in 379 (92%). The mean time to individually classify one perinatal death was 15 minutes (range 10-25 minutes). Mean time for panel discussions for cases for which there was no consensus was 10 minutes (range 5-20 minutes). Due to experience, discussion time was shortened during the study.

Table 1 shows the distribution of classification of cause of death in the six primary groups of our classification, with further subclassification for the 411 perinatally related deaths. The largest cause-of-death group was *congenital anomalies* and contained 142 cases (35%). A total of 42 (30%) pregnancies were terminated for fetal congenital abnormalities. All terminations were performed before 24 weeks of gestation. Four deaths were classified in the groups *other* and *out of the ordinary*. The first death consisted of a termination of pregnancy at 17 weeks of gestation for an increased risk of congenital anomalies detected with serum screening. The second death was of a neonate who died 3 days after birth. The child was situated intraabdominal after a uterus rupture, originating during induction of labour at 42 weeks of gestation. The third case was a neonatal death occurring a few hours after immature labour at 24 weeks of gestation, after recurrent vaginal blood loss due to a cervical polyp. The fourth death was a case of recurrent blood loss after a transcervical chorion villous biopsy performed at 10 weeks of gestation. The membranes ruptured at 19 weeks of gestation, whereafter the umbilical cord prolapsed and the fetus died *in utero*. In 44 cases (11%), the cause of death remained unknown. In 28 (64%) of these deaths, important information was missing.

Table 4. Inter-rater agreement over six causes and mechanisms of death by five assessors

	Kappa	**95% CI**
Causes		
1 Congenital anomaly	0.92	0.89-0.95
2 Placenta	0.83	0.80-0.86
3 Prematurity/immaturity	0.83	0.80-0.86
4 Infection	0.47	0.44-0.50
5 Other	0.46	0.43-0.49
6 Unknown	0.70	0.67-0.73
Mechanisms		
1 Cardiocirculatory insufficiency	0.58	0.55-0.61
2 Multi-organ failure	0.61	0.58-0.65
3 Respiratory insufficiency	0.83	0.80-0.86
4 Cerebral insufficiency	0.40	0.37-0.43
5 Placental insufficiency	0.78	0.75-0.81
6 Unknown	0.66	0.63-0.69

The perinatally related deaths were distributed among the six different groups of mechanisms (Table 2). Examples of origin of mechanism are presented in Table 3, together with the number of deaths for which we allocated this origin. This table is in contrast to Tables 1 and 2, not exhaustive and can be modified depending on the pathology involved in the cases being classified.

Inter-rater agreement

All the 411 deaths were included to calculate the inter-rater agreement for the Tulip classification. In 47% of cases, consensus was achieved for cause of death after individual classification and in 69% of cases after excluding guideline misinterpretations. For mechanism of death, this was in 58% of cases and after excluding guideline misinterpretation, it was in 68% of cases. For the remaining cases, a panel consensus was achieved for cause and mechanism of death. Overall kappa coefficient for main cause of death for multiple observers and multiple test results was 0.81 (95% CI 0.80-0.83) and after excluding guideline misinterpretations, it was 0.86 (95% CI 0.84-0.87). Overall kappa coefficient for subclassification of cause of death was 0.67 (95% CI 0.66-0.68) and after excluding guideline misinterpretation, it was 0.79 (95% CI 0.79-0.80). For mechanism of death, overall kappa coefficient was 0.72 (95% CI 0.70-0.74) and after excluding guideline misinterpretation, it was 0.78 (95% CI 0.76-0.79). Over each main category of cause of death and each category of mechanism, a kappa correlation coefficient with lower-upper CI was calculated. Table 4 shows the distribution of inter-rater agreement over these categories by the five assessors. The best agreement level for cause of death was observed for congenital anomaly. The categories placenta, prematurity/immaturity and unknown showed very good agreement. Repro-ducibility of the causes infection and other was fair.

Discussion

We describe the development of a new classification system for cause and mechanism of perinatal mortality initiated by the audit of perinatal mortality and the problems we faced using existing systems. A pathophysiological background was the basis for this system, and our purpose was to identify the unique initial demonstrable entity on the causal pathway to death for the purpose of counselling and prevention. We assessed the inter-rater agreement for underlying cause and mechanism of perinatal mortality and found this system to be unambiguous and reproducible.

Confusion between mechanism of death and risk factors with cause of death is a problem when classifying.[3] Morrison and Olsen[30] used placental insufficiency and postmaturity as cause of death in their classification. In our system, placental insufficiency is a mechanism of death and postmaturity a contributing factor (risk factor) because these are not the first step on the causal pathway to death. Whitfield et al.[32] used intrauterine growth restriction (IUGR) as the cause of death in their classification; in our system, this would be considered a contributing factor since cause of death may differ in different cases with IUGR. In accordance to Hanzlick,[3] we defined the mechanism of death as the organ failure through which the underlying cause of death ultimately exerts its lethal effect. Fetuses or neonates dying from the same underlying cause may do so because of different mechanisms of death. In the case of a pregnant mother with pre-eclampsia, with a fetus, who died *in utero* due to placental insufficiency, the cause of death is placental bed pathology. In another mother with pre-eclampsia, who delivered by caesarean section and the child died due to respiratory insufficiency, the cause of death is also placental bed pathology. Information about the mechanism of death may be as valuable as the underlying cause of death itself, to evaluate and predict institutional needs for the care of such women. Although risk factors influence the causal pathway to death, they should not be considered as the cause of death.

If the aim of classification of death is to go back to the initial step on the causal pathway because of interest in prevention, it becomes vital that cause-of-death groups consist of pathophysiological entities and not clinical manifestations of these entities. Many classification systems consist of cause-of-death groups that encompass clinical conditions such as pre-eclampsia,[29] antepartum haemorrhage,[13] breech presentation[18] and intraventricular haemorrhage of the neonate.[21] In this respect, it does not seem appropriate to retain separate categories for deaths, with evidence of asphyxia.[6,11,14,17,21,22,32,33,42] Asphyxia is a clinical condition of an underlying cause of death and can be defined in most cases. If for other reasons, one is interested in the number of women with a perinatal death and clinical conditions such as pre-eclampsia or pre-existent hypertension, it is possible to record these as contributing factors in the Tulip classification.

Simple, short and easy to use classification systems may seem preferable.[17,23,33,38] However, the difficulty when focusing on aetiology of death if using a classification system such as the Wigglesworth classification[33] is that it remains very general. For example, all nonmalformed stillbirths are classified in the group: unexplained death prior to the onset of labour. Nevertheless, for many stillbirths, the cause of death is

evident. While the Tulip system is more complex than some, the advantages more than outweigh the complexity in application. Systems without subclassification of main causes can be too crude as is seen in a descriptive classification of underlying cause of death by de Galan-Roosen et al.[2] This system has been validated with good reproducibility (kappa = 0.7) and a low percentage (7%) of unclassifiable cases, both important requirements for a good classification. Yet, 53% of cases are classified in the group placenta pathology, 32% in the subgroup acute and 21% in the subgroup chronic, without further subclassification. We divided the group placenta into four subgroups and divided the subgroup placental pathology into three further subgroups. This subclassification may prove useful when counselling parents, since different placental pathologies differ in recurrence risk.

It should be preferable to allocate every mortality case to one cause-of-death category in a system only,[6,43] independent of the clinician and his or her specialty.[23] Clear guidelines are necessary with criteria for categorisation, definition of terms and case examples.[32] Often these are missing or stated very briefly in other systems.[6-9,15,16,19,21,22,24–26,29–31,33,34] However, in certain cases, differences in opinion between panel members regarding allocation of underlying cause of death in our system occurred. One of these was the debate about the start of the chain of events to death regarding prematurity. Pathways to preterm delivery are multifactorial.[44] Infection is often regarded as an important factor in PPROM or preterm labour but cannot always be assigned as the first step on the causal pathway to death. After debate, we considered infection as cause of death if there was clear microbiological evidence of infection with matching clinical and pathological infectious findings, concluding that the infection initiated the chain of events to death. For cases in which it is not possible to go back further in the chain of events than PPROM or preterm labour because of lack of clear evidence of an earlier step on the pathway, prematurity should be assigned as cause of death in the Tulip classification. A secondary infection will be expressed in an 'infectious' mechanism of death: *multi-organ failure* or origin of mechanism such as *sepsis*. This partly explains why our cause-of-death group *infection* (*n*= 6) consists of far less deaths than our *prematurity/immaturity* group (*n*= 95).

It is unsatisfactory to classify a high percentage of cases as unknown. In 11% of our cases, a cause of death could not be allocated. Due to differences in definition, it is difficult to compare this percentage with the percentages of 'unknown' or 'unclassifiable' in other studies. In one-third of these deaths, the cause remained unknown despite thorough investigation, and in two-thirds of deaths, the cause remained unknown

because important information was missing. This was most often because of missing diagnostic test results, such as results of chromosomal examination (because of either failure to perform the test or failure of cultures) and microbiological or pathological investigation. This suggests that many of these deaths may be underinvestigated rather than truly unexplained and that a decrease in the percentage of *unknown* causes can be achieved by adequate diagnostic procedures after perinatal death.

Inter-rater agreements were calculated for the assessors who originally developed the system. However, these kappas illustrate good multidisciplinary agreement. In other studies, kappa scores vary. Low scores of 0.45-0.62 were observed for the validation study of Cole's classification, 0.50-0.59 for Hey's classification and 0.50-0.68 for the 'New Wiggelsworth' classification.[38] These kappa scores were for external assessors. In the study of de Galan-Roosen et al.,[20] an overall kappa for main causes of death of 0.70 (95% CI 0.68-0.72) was calculated. The highest kappa scores of 0.85-0.90 were observed for the classification by Chan et al.[15]. Both inter-rater agreements were calculated for the original assessors who developed the system. Disagreement in our panel was partly because of failure to comply with the definitions and working rules and partly because of differences in the interpretation of the sequence to death, minimal information available or an unsatisfactory narrative. The importance of individual assessors following guidance is exemplified by the rise in the kappa scores for cause of death and subclassification after removal of cases where the guideline rules had been violated.

Due to increased knowledge, newly developed techniques and methods of investigation, the patterns of causes of death have changed during time.[21,37] Therefore, a classification system must be designed in such a way that future knowledge allows expansion.[4] The Tulip system allows adaptation to medical advances. To illustrate this, deaths defined as congenital anomaly, other, multiple-organ systems in the Tulip classification may be allocated as syndrome, monogenic in the future.

In conclusion, use of a large dataset of perinatally related deaths has allowed our multidisciplinary team to construct groups of cause and mechanism of death into a functional pathophysiological classification that directs attention towards initial causation and mechanism in order to focus on prevention of perinatal deaths. The unambiguous Tulip classification is a well-defined, single-cause system, with clear guidelines and case examples. The Tulip gives a good multidisciplinary inter-rater agreement, with a low percentage of unknown causes and is easily applied by a team of clinicians when Tulip guidelines are followed. The classification is currently in use in the Netherlands for national audit studies.

Reference list

1. Buitendijk S, Zeitlin J, Cuttini M, Langhoff-Roos J, Bottu J. Indicators of fetal and infant health outcomes. Eur J Obstet Gynecol Reprod Biol 2003;111(Suppl 1):S66-77.
2. de Galan-Roosen AE, Kuijpers JC, van der Straaten PJ, Merkus JM. Evaluation of 239 cases of perinatal death using a fundamental classification system. Eur J Obstet Gynecol Reprod Biol 2002;103: 37-42.
3. Hanzlick R. Principles for including or excluding 'mechanisms' of death when writing cause-of-death statements. Arch Pathol Lab Med 1997;121: 377-80.
4. Kramer MS, Liu S, Luo Z, Yuan H, Platt RW, Joseph KS. Analysis of perinatal mortality and its components: time for a change? Am J Epidemiol 2002;156: 493-7.
5. Wigglesworth JS. Causes and Classification of Fetal and Perinatal Death. Fetal and Perinatal Pathology. London: Blackwell Science; 1998. p. 75-86.
6. Alberman E, Botting B, Blatchley N, Twidell A. A new hierarchical classification of causes of infant deaths in England and Wales. Arch Dis Child 1994;70: 403-9.
7. Alberman E, Blatchley N, Botting B, Schuman J, Dunn A. Medical causes on stillbirth certificates in England and Wales: distribution and results of hierarchical classifications tested by the Office for National Statistics. Br J Obstet Gynaecol 1997;104: 1043-9.
8. Alessandri LM, Chambers HM, Blair EM, Read AW. Perinatal and postneonatal mortality among Indigenous and non-Indigenous infants born in Western Australia, 1980–1998. Med J Aust 2001;175: 185-9.
9. Autio-Harmainen H, Rapola J, Hoppu K, Osterlund K. Causes of neonatal deaths in a pediatric hospital neonatal unit. An autopsy study of a ten-year period. Acta Paediatr Scand 1983;72: 333-7.
10. Baird D, Walker J, Thomson AM. The causes and prevention of stillbirths and first week deaths. III. A classification of deaths by clinical cause; the effect of age, parity and length of gestation on death rates by cause. J Obstet Gynaecol Br Emp 1954;61: 433-48.
11. Bound JP, Butler NR, Spector WG. Classification and causes of perinatal mortality. BMJ 1956;12: 1191-6.
12. Bound JP, Butler NR, Spector WG. Classification and causes of perinatal mortality. II. BMJ 1956;44: 1260-5.
13. Butler NR, Alberman ED. Perinatal Problems: The Second Report of the 1958 British Perinatal Mortality Survey. Edinburgh, UK: E & S Livingstone Ltd, 1969.
14. Butler NR, Bonham DG. Perinatal Mortality: The First Report of the 1958 British Perinatal Mortality Survey. Edinburgh, UK: E & S Livingstone Ltd, 1963.
15. Chan A, King JF, Flenady V, Haslam RH, Tudehope DI. Classification of perinatal deaths: development of the Australian and New Zealand classifications. J Paediatr Child Health 2004;40: 340-7.
16. Chang A, Keeping JD, Morrison J, Esler EJ. Perinatal death: audit and classification. Aust N Z J Obstet Gynaecol 1979;19: 207-11.
17. Cole S, Hartford RB, Bergsjo P, McCarthy B. International collaborative effort (ICE) on birth weight, plurality, perinatal, and infant mortality. III: a method of grouping underlying causes of infant death to aid international comparisons. Acta Obstet Gynecol Scand 1989;68: 113-17.
18. Cole SK, Hey EN, Thomson AM. Classifying perinatal death: an obstetric approach. Br J Obstet Gynaecol 1986;93: 1204-12.

19. Fairweather DV, Russell JK, Anderson GS, Bird T, Millar DG, Pearcy PA. Perinatal mortality in Newcastle upon Tyne 1960–62. Lancet 1966;1: 140-2.
20. de Galan-Roosen AE, Kuijpers JC, van der Straaten PJ, Merkus JM. Fundamental classification of perinatal death. Validation of a new classification system of perinatal death. Eur J Obstet Gynecol Reprod Biol 2002;103: 30-6.
21. Hey EN, Lloyd DJ, Wigglesworth JS. Classifying perinatal death: fetal and neonatal factors. Br J Obstet Gynaecol 1986;93: 1213-23.
22. Hovatta O, Lipasti A, Rapola J, Karjalainen O. Causes of stillbirth: a clinicopathological study of 243 patients. Br J Obstet Gynaecol 1983;90: 691-6.
23. 23 Keeling JW, MacGillivray I, Golding J, Wigglesworth J, Berry J, Dunn PM. Classification of perinatal death. Arch Dis Child 1989;64: 1345-51.
24. Knutzen VK, Baillie P, Malan AF. Clinical classification of perinatal deaths. S Afr Med J 1975;49: 1434-6.
25. 25 Lammer EJ, Brown LE, Anderka MT, Guyer B. Classification and analysis of fetal deaths in Massachusetts. JAMA 1989;261: 1757-62.
26. Langhoff-Roos J, Borch-Christensen H, Larsen S, Lindberg B, Wennergren M. Potentially avoidable perinatal deaths in Denmark and Sweden 1991. Acta Obstet Gynecol Scand 1996;75: 820-5.
27. Low JA, Boston RW, Cervenko FW. A clinical classification of the mechanisms of perinatal wastage. Can Med Assoc J 1970;102: 365-8.
28. Low JA, Boston RW, Crussi FG. Classification of perinatal mortality. Can Med Assoc J 1971;105: 1044-6.
29. McIlwaine GM, Howat RC, Dunn F, Macnaughton MC. The Scottish perinatal mortality survey. BMJ 1979;2: 1103-6.
30. Morrison I, Olsen J. Weight-specific stillbirths and associated causes of death: an analysis of 765 stillbirths. Am J Obstet Gynecol 1985;152: 975-80.
31. Naeye RL. Causes of perinatal mortality in the U.S. Collaborative Perinatal Project. JAMA 1977;238: 228-9.
32. Whitfield CR, Smith NC, Cockburn F, Gibson AA. Perinatally related wastage–a proposed classification of primary obstetric factors. Br J Obstet Gynaecol 1986;93: 694-703.
33. Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. Lancet 1980;2: 684-6.
34. Winbo IG, Serenius FH, Dahlquist GG, Kallen BA. NICE, a new cause of death classification for stillbirths and neonatal deaths. Neonatal and Intrauterine Death Classification according to Etiology. Int J Epidemiol 1998;27: 499-504.
35. Campbell MK, Webster KM. Age at neonatal death in Ontario, 1979-1987: implications for the interpretation of mortality markers. Paediatr Perinat Epidemiol 1993;7: 426-33.
36. Cartlidge PH, Stewart JH. Effect of changing the stillbirth definition on evaluation of perinatal mortality rates. Lancet 1995;346: 486-8.
37. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961–1988. Obstet Gynecol 1992;79: 35-9.
38. Settatree RS, Watkinson M. Classifying perinatal death: experience from a regional survey. Br J Obstet Gynaecol 1993;100: 110-21.
39. Elstein AS, Schwarz A. Clinical problem solving and diagnostic decision making: selective review of the cognitive literature. BMJ 2002;324: 729-32.
40. Pearson GA, Stickley J, Shann F. Calibration of the paediatric index of mortality in UK paediatric intensive care units. Arch Dis Child 2001;84: 125-8.

41. Fleiss JL. Statistical Methods for Rates and Proportions, 2nd edn. New York: Wiley, 1981.
42. Winbo IG, Serenius FH, Dahlquist GG, Kallen BA. A computer-based method for cause of death classification in stillbirths and neonatal deaths. Int J Epidemiol 1997;26: 1298-306.
43. Elamin S, Langhoff-Roos J, Boedker B, Ibrahim SA, Ashmeig AL, Lindmark G. Classification of perinatal death in a developing country. Int J Gynaecol Obstet 2003;80: 327-33.
44. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342: 1500-7.

Appendix. Case examples

Example 1 Mother: 40 years old, G3P1A1, born at 20 weeks of gestation, girl, 260 g, termination of pregnancy with prostaglandines	
Cause of death	Congenital anomaly, chromosomal defect, numerical: trisomy 13 (1.1.1)
Mechanism	Placental insufficiency (5)
Origin of mechanism	Induction
Contributing factor	None
Co-morbidity	Psoriasis
Example 2 Mother: 38 years old, G2P1, 29 weeks of gestation, boy, 1500 g, died *in utero*	
Cause of death	Placental bed pathology (2.1.0)
Mechanism	Placental insufficiency (5)
Origin of mechanism	Placental infarction
Contributing factor	Pre-existing hypertension, factor II mutation
Co-morbidity	None
Example 3 Mother: 27 years old, G2P0, born at 26 weeks of gestation, girl, 505 g, died 8 weeks after birth	
Cause of death	Placental bed pathology (2.1.0)
Mechanism	Respiratory insufficiency (3)
Origin of mechanism	Chronic lung disease
Contributing factor	Pre-eclampsia with antihypertensive treatment, hyperhomocysteinemia, smoking, IUGR, prematurity
Co-morbidity	Alfa-thalassaemie
Example 4 Mother: 22 years old, G2P1, 26 weeks of gestation, boy, 835 g, died during labour	
Cause of death	Prematurity; PPROM (3.1.0)
Mechanism	Cardiocirculatory insufficiency (1)
Origin of mechanism	Umbilical cord occlusion
Contributing factor	Breech presentation, chorioamnionitis, small placental infarction
Co-morbidity	None
Example 5 Mother: 35 years old, G4P3, 37 weeks of gestation, boy, 3430 g, died *in utero*	
Cause of death	Infection ascending (4.2)
Mechanism	Multi-organ failure (2)
Origin of mechanism	Intrauterine infection
Contributing factor	None
Co-morbidity	Asthma

Example 6 Mother: 29 years old, G2P0, 35 weeks of gestation, boy, 2490 grams, *died in utero*	
Cause of death	Other; maternal disease, diabetes mellitus type I (5.2)
Mechanism	Cardiocirculatory insufficiency (1)
Origin of mechanism	Ketoacidosis
Contributing factor	Language/culture barrier
Co-morbidity	Hernia nuclei pulposi

CHAPTER 8

A placental cause of intra-uterine fetal death depends on the perinatal mortality classification system used

Fleurisca J. Korteweg,
Sanne J. Gordijn,
Albertus Timmer,
Jozien P. Holm,
Joke M. Ravisé,
Jan Jaap H.M. Erwich

Placenta 2008; 29: 71-80

Abstract

Different classification systems for the cause of intra-uterine fetal death (IUFD) are used internationally. About two thirds of these deaths are reported as unexplained and placental causes are often not addressed. Differences between systems could have consequences for the validity of vital statistics, for targeting preventive strategies and for counselling parents on recurrence risks. Our objective was to compare use of the Tulip classification with other currently used classification systems for causes of IUFD. We selected the extended Wigglesworth classification, modified Aberdeen and the classifications by Hey, Hovatta, de Galan-Roosen and Morrison. We also selected the ReCoDe system for relevant conditions, comparable to contributing factors in the Tulip classification. Panel classification for 485 IUFD cases in the different systems was performed by assessors after individual investigation of structured patient information. Distribution of cases into cause of death groups for the different systems varied, most of all for the placental and unknown groups. Systems with a high percentage of cases with an unknown cause of death and death groups consisting of clinical manifestations only are not discriminatory. Our largest cause of death group was placental pathology and classification systems without placental cause of death groups or minimal subdivision of this group are not useful in modern perinatal audit as loss of information occurs. The most frequent contributing factor was growth restriction. This illustrates the vital role of the placenta in determination of optimal fetal development. In the Tulip classification, mother, fetus and placenta are addressed together. The system has a clear defined subclassification of the placenta group, a low percentage of unknown causes and is easily applied by a multidisciplinary team. A useful classification aids future research into placental causes of IUFD.

Introduction

There are intensified demands on medical, political and epidemiological grounds for proper determination and classification of cause of perinatal death.[1-5] The largest subgroup of perinatal mortality worldwide is the stillbirth group consisting of intra-uterine fetal deaths (IUFD) and intrapartum deaths. Current use of classification systems for analyses of this subgroup consistently report of about two thirds of these deaths as being unexplained.[6] Classification of cause of death is needed for the individual patient in the process of mourning, for the purpose of counselling and prevention and for the comparison of health care nationally and internationally. Classification of IUFD is complex due to the complicated pathophysiological processes encountered in the mother, fetus and placenta, and as a result of their interaction.[7] The multiplicity of contributing factors and the different background of the clinicians involved, adds to the complexity.

Different classification systems have been designed for different reasons with different approaches, definitions, levels of complexity and availability of guidelines. No single system is universally accepted and each has strengths and weaknesses.[8,9] Problems occur during use and comparison of different systems. Our research group developed a new classification system for perinatal mortality: the Tulip classification, in anticipation of current needs.[8] This system was designed by a multidisciplinary panel. Placental causes of death formed our largest cause of death group. This is in accordance with others who also found placental causes of death in up to 60% of perinatal mortality cases.[2,10-13] However, availability of a placental death group varies in internationally used classification systems.

Our goal for this study was to investigate underlying cause of death for an IUFD group after evaluation of clinical and diagnostic information. Special interest was in placental causes. Our objective was to compare use of the Tulip classification with other currently used classification systems for IUFD. Question was whether information is gained or lost by classification in the different systems. This could have consequences for counselling parents on recurrence risks, for targeting placental research and preventive strategies, and for the validity of vital statistics.

Methods

In 2002 we initiated a national study on IUFD at the University Medical Center in Groningen (UMCG) with 50 participating hospitals throughout the Netherlands. Inclusion criteria for the study were singleton IUFD's diagnosed antepartum after 20 weeks of gestation. For each included IUFD a case record form was filled in and a standard diagnostic work-up protocol was performed.

Patient information sets included baseline characteristics such as date of delivery, gestational age, medical and obstetric history; maternal characteristics; fetal characteristics including fetal and placental weights at birth; pregnancy details and obstetric discharge letters. Apart from these characteristics, diagnostic test results were available including: pathological findings concerning autopsy and placental investigation; maternal blood tests; maternal viral serology; fetal blood tests; fetal viral serology; cultures from mother, fetus and placenta; and chromosomal investigation. Autopsy and placental examination were performed by local pathologists in participating hospitals after parental consent was obtained. No national pathological guidelines regarding autopsy and placental examination after IUFD exist, therefore we urged participating pathologists to follow our study guidelines for autopsy and placental examination based on the guidelines published by the Royal College of Obstetricians and Gynaecologists[14] and the Royal College of Pathologists and the College of American Pathologists.[15,16]

After patient sets were made as complete as possible panel classification sessions were initiated. Procedures were agreed upon in advance. For fetal and placental weights at birth gestational age at determination of IUFD was used. Small for gestational age (SGA) was defined as birth weight < 10^{th} percentile.[17] Placenta hypoplasia was defined as an absolute too low placenta weight < 10th percentile and/or a too low placenta/birth weight ratio.[18] We defined placental bed pathology for preterm cases as any infarctions found at placental histology and for term cases as extensive infarction that affected > 10% of the placental area.[19] Cause of death "placental bed pathology" was allocated if in our opinion the percentage of infarcted parenchyma in relation to the weight of the placenta was severe enough to cause death. The classification panel consisted of two obstetricians, an obstetric resident, and a paediatric pathologist. All panel members prepared each case individually using the patient information sets where after panel discussions were held and a panel consensus on cause of death was agreed upon. No other information sources were consulted. Only one underlying cause of death could be allocated. For each classification system we added "problematic classification" as cause of death group. This cause was classified if allocation of cause

of death caused confusion for a system and/or two causes of death groups could be allocated at the same time.

Used classification systems for cause of death

After panel discussion on the basis of use of existing classifications and current obstetric, pathologic and genetic literature on causes of IUFD we selected six classification systems besides the Tulip classification. These systems represent different approaches of classification with different definitions. The selected systems were as follows: the extended Wigglesworth,[20] the modified Aberdeen,[21] classification by Hey et al.,[22] by Hovatta et al.,[23] by de Galan-Roosen et al.,[24] and by Morrison and Olsen.[25] The reason for choice of the system as well as the system itself will be discussed in the following paragraphs.

The Tulip classification is a single cause classification system aiming to identify the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death. Cause of death is based on the combination of clinical findings and diagnostic test results, including pathological findings for the purpose of counselling and prevention.[8] As our goal was to particularly focus on placental causes of death we discuss this part of the guideline.

Placental cause of death

Cause of death is explained by a placental pathological abnormality supported by the clinical findings.

1 *Placental bed pathology*. Inadequate spiral artery remodelling and/or spiral artery pathology is leading to uteroplacental vascular insufficiency such as placental infarction and abruption.
2 *Placental pathology*. Placental pathology originated during development of the placenta itself, abnormalities in the parenchyma or localisation of the placenta.
   a *Development*. Morphologic abnormalities arise because of abnormal developmental processes. Examples: placenta circumvallata, vasa praevia, villous immaturity, and placenta hypoplasia.
   b *Parenchyma*. Acquired placenta parenchyma disorders of the villi or intervillous space. Examples: fetal thrombotic vasculopathy, maternal floor infarct, villitis of unknown origin, massive perivillous fibrin deposition and fetomaternal haemorrhage without obvious cause.
   c *Abnormal localisation*. Examples: placenta praevia.

3 *Umbilical cord complication*. Example: true knot with occlusion of the umbilical vessels.
4 *Not otherwise specified*. The cause of death can be allocated to the group placenta but, because of the combination of different placenta subclassifications, a choice cannot be made as to what was first in the chain of events leading to death.

The extended Wigglesworth classification, the modified Aberdeen and the classification by *Hey* et al.[20-22] are based on the earliest developed classification systems. These systems have different approaches and are the most commonly used systems for British statistics.[3] In addition, both the extended Wigglesworth and the modified Aberdeen[20,21] are most widely used throughout the world.[26-31] Wigglesworth's advocated a pathophysiological approach and the goal of the classification is to subdivide cases into groups with clear implications for priorities for prevention and alterations in clinical management. The modified Aberdeen is a clinicopathological classification, the first version was proposed by Baird et al.[21] and aim is to classify each death in accordance with the factor which probably initiated "the train of events ending in death". It is almost entirely based on clinical information as in the experience of the designers of the system post-mortem examinations fail to explain cause of death in many cases. The classification by Hey et al.[22] is based on the bound classification.[32,33] This classification has a pathologic approach based on fetal and neonatal entities and aim is to define the clinicopathological process within the baby and the way they contribute to, and help to explain the baby's death. Hovatta et al.[23] designed a system especially for the group of stillbirths. Aim is to classify underlying cause of death considering both clinical and autopsy findings. The classification groups are based on maternal, fetal, placental or a combination of these entities. Definitions for the placental causes, however, do not exist.

The classification by *de* Galan-Roosen et al. is one of the few systems based on maternal, fetal and placental entities.[24] Aim is to serve prevention and classify underlying cause of death with a clinicopathological approach based on the entities that initiated the chain of events leading to death. The group placenta pathology is defined as follows in the guideline.

1 *Acute/subacute placental pathology*: total or partial abruption of the placenta, placental haematomata with intervillous thrombosis, marginal haemorrhage, subchorial haematoma, placental infarction > 10%, velamentous insertion with vasolaceration or compression of the cord, and cord prolapse/compromise. Some-

times no placenta pathology can be found. Clinical manifestations in the fetus are signs of asphyxia with (in the subacute phase) time to aspirate meconium-stained amniotic fluid.

2. *Chronic/progressive placental pathology*: placental maldevelopment like in placenta praevia, uterine malformation or septum. Maternal circulation disorders and terminal villous deficiency like in pregnancy-induced hypertension (PIH), pre-eclampsia, and thrombophilia. Also when coagulation disorders are found in blood samples of the mother like in systemic lupus erythematosus (SLE). Examples: massive perivillous fibrin depositions, villitis of unknown origin, and diabetic changes in the placenta: pale, large and immature villi with oedema. Clinical manifestations of chronic placenta pathology in the fetus can be signs of small for gestational age.

The classification by Morrison and Olsen[25] is especially designed for stillbirths based on the clinicopathological classification of the British perinatal mortality survey.[34,45] The major contributing cause of death selected is based on maternal entities with an obstetric clinical approach and divided into specific weight categories. Aim is to serve prevention and study or define implications for that geographical area or clinic studied. Their group *hypoxia*; *placental insufficiency* is defined as: "autopsy evidence of hypoxia with appropriate weight for gestation, with meconium or meconium-stained membranes in vertex presentation; or birth weight/placental weight ratio > 7:1 or placental infarcts >25%". The group *hypoxia*; *cord accidents/compression* is defined as: "nuchal cord ≥ 2, or true knot, or prolapse, or perforation at amniocentesis".

Relevant conditions

The latest published classification is the system by Gardosi et al. in 2005.[3] Their ReCoDe classification seeks to establish relevant conditions at death taking into account mother, fetus and placenta. This system is not designed for allocation of cause of death. From the start of our panel sessions we classified contributing factors for the Tulip classification besides cause of death. Our contributing factors are defined as other known factors on the causal pathway to death, e.g. risk factors. These contributing factors are very similar to ReCoDe's relevant conditions. Combining information from our Tulip causes of death and contributing factors it was therefore possible to classify relevant conditions according to the ReCoDe classification.

Results

During the 4-year period of 2002–2006 we included 485 IUFD's. Median gestational age was 31 weeks and 4 days (range 20-42 weeks, 1 day). Median age of the mother was 30 years (range 18-46 years). Of the 485 IUFD's 263 were boys, 221 girls and for one case sex at birth could not be determined and no information on chromosomal or pathological examination was available. Autopsy was performed in 348 (71.7%) cases and external macroscopic fetal examination by a pathologist without autopsy in 18 cases (3.7%). Placental examination was performed in 481 cases (99.1%). The extent to which the placental examination guidelines were followed differed between cases. During the panel sessions all IUFD's were classified according to the eight selected classification systems. For the Tulip classification distribution of causes of death is shown in Table 1. Largest cause of death group for 312 cases was placenta (64.3%). Largest placenta subgroups were placental bed pathology in 166 cases (34.2%) and placental pathology/development in 76 cases (15.7%). No cases were allocated to the group prematurity as we studied on IUFD cohort. Eight cases were allocated to the infection group. In 113 cases (23.3%) cause of death remained unknown, and in 30 cases important information was missing.

Distribution of causes of death for the extended Wigglesworth the modified Aberdeen, the classification by Hey et al., by Hovatta et al., by de Galan-Roosen et al. and by Morrison et al. are shown in Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7, respectively. Relevant conditions for our 485 cases according to the ReCoDe classification by Gardosi et al. are shown in Table 8.

The extended Wigglesworth and the modified Aberdeen, which are amongst the internationally most used classification systems have an excessive number of unexplained cases and do not include placental causes of death in their system (Table 9). The Tulip system illustrates that a large group of these unexplained deaths have a placental cause of death. For the modified Aberdeen 293 cases were "unexplained" and four cases were "problematic". Contrary, eight "unknown" cases in the Tulip classification were allocated a known cause in the modified Aberdeen: congenital anomaly (n = 1); pre-eclampsia (n = 1); antepartum haemorrhage (n = 2) and maternal disorder (n = 4). For the extended Wigglesworth classification 429 cases were "unexplained" and one case was "problematic", and one case classified as "unknown" in the Tulip classification was classified as congenital defect/malformation in the Wigglesworth.

Table 1. Tulip classification of perinatal mortality: causes

Cause	n (%)	Subclassification		n
1 Congenital anomaly	142 (35)	1 Chromosomal defect	1 Numerical	12
			2 Structural	2
			3 Microdeletion/ uniparental disomy	-
		2 Syndrome	1 Monogenic	-
			2 Other	2
		3 Central nervous system		-
		4 Heart and circulatory system		3
		5 Respiratory system		-
		6 Digestive system		1
		7 Urogenital system		-
		8 Musculoskeletal system		-
		9 Endocrine/metabolic system		-
		10 Neoplasm		3
		11 Other	1 Single organ	-
			2 Multiple organ	5
2 Placenta	111 (27)	1 Placental bed pathology		166
		2 Placental pathology	1 Development	76
			2 Parenchyma	16
			3 Localisation	-
		3 Umbilical cord complication		25
		4 NOS		29
3 Prematurity immaturity	95 (23)	1 PPROM		-
		2 Preterm labour		-
		3 Cervical dysfunction		-
		4 Iatrogenous		-
		5 NOS		-
4 Infection	6 (1)	1 Transplacental		5
		2 Ascending		3
		3 Neonatal		-
		4 NOS		-

Table 1 (Continued)

Cause	n (%)	Subclassification		n
5 Other	13 (3)	1 Fetal hydrops of unknown origin		16
		2 Maternal disease		8
		3 Trauma	1 Maternal	-
			2 Fetal	-
		4 Out of the ordinary		-
6 Unknown	44 (11)	1 Despite thorough investigation		83
		2 Important information missing		30
Total				485

Table 2. Extended Wigglesworth: causes

Code	Classification	%	Subclassification	n
1.0	Congenital defect/malformation	6.0		29
2.0	Unexplained antepartum fetal death	88.5		429
3.0	Death from intrapartum asphyxia, anoxia or trauma	-		-
4.0	Immaturity	-		-
5.0	Infection	1.6		8
6.1	Due to other specific causes	3.7	Fetal conditions	18
6.2			Neonatal conditions	-
6.3			Paediatric conditions	-
7.0	Due to accident or non-intrapartum trauma	-		-
8.0	Sudden infant deaths, cause unknown	-		-
9.0	Unclassifiable	0.2		1
10.0	Problematic classification	-		-
Total		100		485

The largest group in the Tulip classification consisted of placental causes: 312 cases (64.3%). We plotted the Tulip placental causes against the causes of death in classification systems with at least one placental cause of death category 23-25. The classifications by Hovatta et al., de Galan-Roosen et al. and Morrison et al. have fewer unexplained cases than the other used systems. These systems contain placental

causes of death but as illustrated in Table 10 there is minimal subclassification of these categories. Besides, some causes of death groups represent clinical conditions which

Table 3. Modified Aberdeen: causes

Code	Classification	%	Subclassification	n
01	Congenital anomaly	6.6	Neural tube defects	2
02			Other anomalies	30
03	Isoimmunisation	-	Due to rhesus (D) antigen	-
04			Due to other antigens	-
05	Pre-eclampsia	6.4	Pre-eclampsia without APH	28
06			Pre-eclampsia complicated by APH	3
07	Antepartum haemorrhage (APH)	9.3	With placenta praevia	1
08			With placental abruption	38
09			Of uncertain origin	6
10	Mechanical	4.1	Cord prolapse or compression with vertex or face presentation	18
11			Other vertex or face presentation	-
12			Breech presentation	-
13			Oblique or compound presentation, uterine rupture etc.	2
14	Maternal disorder	8.7	Maternal hypertensive disease	10
15			Other maternal disease	24
16			Maternal infection	8
17	Miscellaneous	3.7	Neonatal infection	-
18			Other neonatal disease	-
19			Specific fetal conditions	18
20	Unexplained	60.4	Equal or greater than 2.5 kg	90
21			Less than 2.5 kg	203
22	Unclassified	-	Unclassifiable	-
23	Problematic classification	0.8		4
Total		100		485

Table 4. Classification by Hey et al.: causes

Code	Classification	%	Subclassification	n
01	Congenital anomaly	6.0	Chromosomal defect	13
02			Inborn error of metabolism	-
03			Neural tube defect	1
04			Congenital heart defect	3
05			Renal abnormality	-
06			Other malformation	12
07	Isoimmunisation			-
08	Asphyxia	88.4	Antepartum	429
09			Intrapartum	-
10	Birth trauma			-
11	Pulmonary immaturity			-
12	Hyaline membrane disease			-
13			With IVH	-
14			With infection	-
15	Intracranial haemorrhage		Intraventricular haemorrhage	-
16			Other intracranial bleeding	-
17	Infection	1.9	Necrotising enterocolitis	-
18			Antepartum	9
19			Intrapartum	-
20			Postpartum	-
21	Miscellaneous	3.7	Miscellaneous	18
22	Unclassifiable or unknown		Cot death	-
23			Unattended delivery	-
24			Other undocumented death	-
25	Problematic classification			-
Total		100		485

Table 5. Classification by Hovatta et al.: causes

Code	Classification	%	Subclassification	n
1.0	Abruption of the placenta	7.8		38
2.0	Large placental infarction	21.9		106
3.0	Cord complication	5.2		25
4.1	Other placental feature	27.2	Severe pre-eclampsia	5
4.2			Cholestasis of pregnancy	1
4.3			Twin pregnancy	-
4.4			Immature birth	-
4.5			Severe maternal trauma	-
4.6			Uterine anomaly	-
4.7			Other causes	126
5.0	Asphyxia for unexplained reasons	8.2		40
6.0	Maternal isoimmunisation	-		-
7.1	Fetal bleeding	1.2	Fetofetal transfusion	-
7.2			Fetomaternal transfusion	5
7.3			Other bleeding	1
8.0	Severe chorioamnionitis	1.0		5
9.0	Major malformations	5.8		28
10.0	Unexplained	19.4		94
11.0	Problematic classification	2.3		11
Total		100		485

Table 6. Classification by de Galan-Roosen et al.: causes

Code	Classification	%	Subclassification	Specification	n
1.1.0	Trauma	-	Antenatal		-
1.2.0			At birth		-
1.3.0			Postnatal		-
2.1.1	Infection	1.7	Antenatal	Haematogenous	5
2.1.2				Transamniotic	3
2.2.0			Postnatal		-
3.1.0	Placenta/cord pathology	44.5	Acute/subacute		98
3.2.0			Chronic/progressive		118
4.1.0	Maternal immune system pathology	-	Blood type incompatibility		-

Table 6 (Continued)

Code	Classification	%	Subclassification	Specification	n
4.2.0			Blood platelet antibody		-
5.1.0	Congenital malformations incompatible with life	4.9	Hereditary		-
5.2.0			Non-hereditary		24
6.1.0	Prematurity/immaturity complications	-	Cervix incompetence		-
6.2.0			Preterm labour iatrogenous		-
6.3.0			Preterm labour ECI		-
7.1.0	Unclassifiable	26.6	Despite thorough examination		99
7.2.0			Important information missing		30
8.0.0	Problematic classification	22.3			108
Total		100			485

Table 7. Classification by Morrison et al.: causes

Code	Classification	%	Subclassification	n
1.1	Hypoxia	55.6	Intra-uterine growth retardation	121
1.2			Cord accidents/compression	25
1.3			Maternal hypertension	11
1.4			Placental insufficiency	103
1.5			Postmaturity	-
1.6			Other	10
2.1	Antepartum haemorrhage	9.1	Major abruptio placentae	41
2.2			Placenta praevia	-
2.3			Significant unexplained antepartum haemorrhage	3
3.0	Congenital anomalies	6.0		29
4.1	Diabetes	2.9	Insulin dependent	7
4.2			Gestational	7
5.0	Miscellaneous	6.0		29
6.0	Trauma	-		-
7.0	Unclassified	19.2		93
8.0	Problematic classification	1.2		6
Total		100		485

Table 8. ReCoDe: relevant conditions

Code	Classification	%	Subclassification	*n*
A1	Fetus	53.0	Lethal congenital anomaly	28
A2			Infection	19
A3			Non-immune hydrops	19
A4			Isoimmunisation	-
A5			Fetomaternal haemorrhage	44
A6			Twin-twin transfusion	-
A7			Fetal growth restriction	147
B1	Umbilical cord	5.6	Prolapse	-
B2			Constricting loop or knot	6
B3			Velamentous insertion	6
B4			Other	15
C1	Placenta	26.4	Abruptio	30
C2			Praevia	-
C3			Vasa praevia	-
C4			Other "placental insufficiency"	98
C5			Other	-
D1	Amniotic fluid	-	Chorioamnionitis	-
D2			Oligohydramnios	-
D3			Polyhydramnios	-
D4			Other	-
E1	Uterus	-	Rupture	-
E2			Uterine anomalies	-
E3			Other	-
F1	Mother	0.8	Diabetes	2
F2			Thyroid diseases	-
F3			Essential hypertension	-
F4			Hypertensive disease in pregnancy	-
F5			Lupus or antiphospholipid syndrome	2
F6			Cholestasis	-
F7			Drug misuse	-
F8			Other	-
G1	Intrapartum	-	Asphyxia	-
G2			Birth trauma	-
H1	Trauma	-	External	-
H2			Iatrogenic	-
I1	Unclassified	14.2	No relevant condition identified	50
I2			No information available	19
Total		100		485

Table 9. Modified Aberdeen unexplained (n = 293) and problematic (n = 4) and extended Wigglesworth unexplained (n = 429) and problematic (n = 1) versus the Tulip classification

Tulip cause of death	Placental bed pathology	Placental pathology; development	Placental pathology; parenchyma	Umbilical cord complication	Placenta: not otherwise specified	Other: fetal hydrops of unknown origin	Other: maternal disease; diabetes mellitus	Other: maternal disease; other	Unknown: despite thorough investigation	Unknown: important information missing	**Total**
Modified Aberdeen											
Unexplained ≥2.5 kg	12	35	5		13				15	10	90
%	14	40	6		15				15	10	100
Unexplained <2.5 kg	75	26	7	5	12				60	18	203
%	37	13	3	2	6				30	9	100
Problematic classification	1		2							1	4
%	25		50							25	100
Extended Wigglesworth											
Unexplained antepartum fetal death	166	75	13	25	29	2	2	5	82	30	429
%	39	17	3	6	7	0.5	0.5	1	19	7	100
Unclassifiable			1								1
%			100								100

Table 10. De Galan-Roosen, Hovatta and Morrison and Olsen classifications versus the Tulip classification: placental causes (n = 312

	Tulip placental cause, n=312					
	Placental bed pathology	**Placental pathology; development**	**Placental pathology; parenchyma**	**Umbilical cord complication**	**Placenta: not otherwise specified**	**Total**
De Galan-Roosen etal.						
Placenta/cord pathology: acute/subacute	66	2	3	25	1	97
Placenta/cord pathology: chronic/ progressive	14	74	10		18	116
Problematic classification	86		3		10	99
Hovatta etal.						
Abruption of the placenta	38					38
Large placental infarction	102				1	103
Cord complication				25		25
Other placental feature; severe pre-eclampsia	4	1				5
Other placental feature; other causes	15	74	11		25	125
Fetal bleeding; fetomaternal transfusion			5			5
Fetal bleeding; other bleeding		1				1
Unexplained	6					6
Problematic classification	1				3	4
Morrison etal.						
Hypoxia; intra-uterine growth retardation	79	20	3		7	109
Hypoxia; cord accidents/compression				25		25
Hypoxia; maternal hypertension	9	1				10

Table 10 (Continued)

	Tulip placental cause, n=312					
	Placental bed pathology	**Placental pathology; development**	**Placental pathology; parenchyma**	**Umbilical cord complication**	**Placenta: not otherwise specified**	**Total**
Hypoxia; placental insufficiency	33	43	7		17	100
Hypoxia; other	1	2	4		1	8
Antepartum haemorrhage; major abruptio placentae	41					41
Antepartum haemorrhage; significant unexplained APH	1	1				2
Diabetes; insulin dependent		2			1	3
Diabetes; gestational		5			1	6
Miscellaneous			2			2
Problematic classification	2	2			2	6

Discussion

In anticipation of audit purposes and further international comparison of causes we investigated different classification systems for cause of IUFD. Our focus was on placental causes of death as these are becoming more and more recognized. We describe comparison of eight classification systems. The Tulip classification has an extensive subdivision of the placental group, a high percentage of cases with a "known" cause of death and cause of death groups do not consist of clinical manifestations of pathophysiological entities. In the other described systems, we encountered problems concerning at least one of these items resulting in loss of specific information.

The pathophysiology of IUFD is complex and involves maternal, fetal as well as placental entities. In order to assign a cause of death these entities should be addressed together. The main focus of this study was on placental causes of death. Four of the seven classification systems we used have a placental cause of death group.[8,23-25] In these systems except for the classification by Morrison et al. a placental cause of death was the largest death group varying from 44.5% for de Galan-Roosen et al. to 64.3% in the Tulip classification. This is in accordance with our previous study[8] and earlier published data.[2,10-13] A great number of cases classified as "unknown" in the extended Wigglesworth and the modified Aberdeen were allocated a placental cause of death in the Tulip classification (Table 9).

Minimal subclassification of placental causes results in loss of specific information, non-specific counselling of parents on recurrence risks and hampers targeting adequate preventive strategies. In this respect the classifications by Hovatta et al., de Galan-Roosen et al. and Morrison and Olsen[23-25] seem unsatisfactory (Table 10). Use of placental subgroups triggers the discussion on definitions of these groups. Largest placental subgroup for the Tulip classification was "placental bed pathology" (n = 166, 34.2%), in 42 cases this cause of death was allocated due to an abruptio placentae, in 122 cases due to placental infarctions and in two cases both were present. Others also worked with the same cut-off point for infarctions.[24,36] Morrison and Olsen have a higher (25%) cut-off point.[25] Second largest placenta subgroup was "placental pathology; development" in 76 cases (15.7%). In 50 cases this cause of death manifested as placental hypoplasia. We assume that part of this group comprehends cases with "placental bed pathology" as cause due to sampling error.[37] Moreover, dependent on the references used for placental weight and placenta/birth weight ratios, allocation of placental hypoplasia can vary.[18,38] To improve validity of statistics, uniformity of definitions of these large placental subgroups are needed.

The classification by de Galan-Roosen et al. has been validated with a low percentage (7%) of unclassifiable cases.[2] However, several placental pathological entities are crudely divided into two groups only. Ninety-eight cases (20.2%) were allocated to "placenta/cord pathology; acute/subacute" and 118 (24.3%) cases to "placenta/cord pathology; chronic/progressive". The second problem we faced was the large group allocated to "problematic classification" (108 cases). This was mainly due to the cases with > 10% placental infarctions (death group: "placenta/cord pathology; acute/subacute") together with a small for gestational age fetus ("placenta/cord pathology; chronic/progressive"). Although cause and mode of death are relevant aspects of the pathophysiology of IUFD, these items are two separate entities which should not be merged into one.

Any classification system that results in a low proportion of cases with a known cause of death does not seem to be fulfilling its purpose. Due to differences in definition, it is difficult to compare the percentages of unexplained cases in the different systems. For the total percentage of unknown cause of death groups we studied the groups "unknown", "unexplained", "unclassifiable" and "problematic classification" together. The cause of death group "unknown" varied from 0% in the classification by Hey et al. to 88.7% in the extended Wigglesworth. A short classification system such as the extended Wigglesworth may seem preferable but remains too general. This system only has cause of death groups for malformed stillbirths, stillbirths with clear microbiological evidence of infection or with hydrops fetalis. All other stillbirths are classified in the group "unexplained antepartum fetal death". Nevertheless, as is shown in Table 9 cause of death is evident for a large group of these stillbirths. For the classification by Hey et al. no deaths were classified as "unclassifiable" or "unknown", however, 88.4% of cases were allocated to the group "asphyxia antepartum". In our opinion asphyxia is not a cause of death but a clinical condition which is the result of an underlying cause of death and can be defined in many cases.[4] Similarly in the system of Hovatta et al. 8.3% of cases were classified as "asphyxia for unexplained reasons". In fact these cases should be added to the cause of death group "unknown" and, therefore, their percentage of "unknown" increases from 21.6% to 29.9%. This also accounts for the group "hypoxia; intra-uterine growth retardation" in the system by Morrison et al. (24.9%). As is shown in Table 10 most of the "asphyxia and hypoxia related" causes have placental pathology as underlying cause of death. A large group of unexplained IUFD's is often due to design of the system itself and lack of amendment of the system to present insight into pathophysiology of IUFD. In 23.3% of

cases the cause remained "unknown" for the Tulip classification (Table 1). In about two thirds of deaths the cause remained "unknown" because important information was missing. This suggests that many of these deaths may be under investigation rather than truly unexplained. Although some systems aim to classify underlying cause of death, mechanism of death and risk factors are often mixed.[39] Cause of death groups should consist of pathophysiological entities. Many systems consist of cause of death groups that encompass clinical conditions such as pre-eclampsia,[21] antepartum haemorrhage,[25] breech presentation[21] and intraventricular haemorrhage.[22] Similarly intra-uterine growth restriction is a clinical condition of several causes of death, see Table 10.

Recently Gardosi et al.[3] published their ReCoDe classification that seeks to establish relevant conditions at death considering mother, fetus and placenta. Their system has evoked a new discussion on classification as they do not classify cause of death. The system is easy to use, as panel sessions are not needed, with retainment of important information. However, guidelines for the ReCoDe classification are less clear and this resulted in confusion of allocation of relevant conditions. Hierarchy underestimates the importance of some of the items in the lower part of the system. Results of our cohort presented in Table 8 are comparable to the stillbirth cohort presented by Gardosi et al. Largest relevant condition for our group was fetal growth restriction (30.3%) compared to 43.0%.[3] In our IUFD cohort 14.2% of cases were unclassified versus 15.2%.[3] We agree with Gardosi et al. that these relevant conditions give insight into the death. However, if classification of the underlying cause of death is added more insight is warranted. For the Tulip classification 27.6% of cases in the placental group were small for gestational age at birth versus 8.7% in the other cause of death groups illustrating diversity in cause of death for these small fetuses. Recording of growth restriction as a contributing factor is nevertheless important for management and counselling of future pregnancies.

In conclusion, comparison of seven classification systems for cause of death and one system for relevant conditions applicable for the IUFD group illustrated different problems during use. Largest cause of death group for IUFD was placental pathology, and largest contributing factor was growth restriction. This illustrates the vital role of the placenta in determining optimal fetal development. Internationally used systems without placental cause of death groups or minimal subdivision of this group are in our opinion not useful in modern perinatal audit. Systems with a low proportion of known causes of death or cause or death groups consisting of clinical manifestations of

pathophysiological entities are not useful either as this results in loss of information. Of the systems we compared the Tulip classification met the requirements for a useful classification best. This classification is currently in use in the Netherlands for national audit studies.[40] International use of the same classification system for cause of death will facilitate comparison of statistics. Future classification efforts and research should be aimed at further definition of the placental cause of death groups, investigation into the differences in clinical manifestations of placental causes of death and the prevention of these deaths.

Reference list

1. S. Buitendijk, J. Zeitlin, M. Cuttini, J. Langhoff-Roos and J. Bottu, Indicators of fetal and infant health outcomes, Eur J Obstet Gynecol Reprod Biol 111 (Suppl. 1) (2003), pp. S66-S77.
2. A.E. de Galan-Roosen, J.C. Kuijpers, P.J. van der Straaten and J.M. Merkus, Evaluation of 239 cases of perinatal death using a fundamental classification system, Eur J Obstet Gynecol Reprod Biol 103 (2002), pp. 37-42.
3. J. Gardosi, S.M. Kady, P. McGeown, A. Francis and A. Tonks, Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study, BMJ 331 (2005), pp. 1113-1117.
4. R. Hanzlick, Principles for including or excluding 'mechanisms' of death when writing cause-of-death statements, Arch Pathol Lab Med 121 (1997), pp. 377-380.
5. M.S. Kramer, S. Liu, Z. Luo, H. Yuan, R.W. Platt and K.S. Joseph, Analysis of perinatal mortality and its components: time for a change , Am J Epidemiol 156 (2002), pp. 493-497.
6. Maternal and Child Health Consortium. CESDI 8th annual report: confidential enquiry of stillbirths and deaths during infancy. London; 2001.
7. J.S. Wigglesworth, Causes and classification of fetal and perinatal death, Fetal and perinatal pathology, Blackwell science, London (1998) p. 75-86.
8. F.J. Korteweg, S.J. Gordijn, A. Timmer, J.J. Erwich, K.A. Bergman and K. Bouman et al., The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement, BJOG 113 (2006), pp. 393-401
9. R.M. Silver, M.W. Varner, U. Reddy, R. Goldenberg, H. Pinar and D. Conway et al., Work-up of stillbirth: a review of the evidence, Am J Obstet Gynecol 196 (2007), pp. 433-444.
10. E. Agapitos, C. Papadopoulou, N. Kavantzas, J. Papoulias, V. Antonaki and P. Davaris, The contribution of pathological examination of the placenta in the investigation of the causes of foetal mortality, Arch Anat Cytol Pathol 44 (1996), pp. 5-11.
11. L.C. Horn, A. Langner, P. Stiehl, C. Wittekind and R. Faber, Identification of the causes of intrauterine death during 310 consecutive autopsies, Eur J Obstet Gynecol Reprod Biol 113 (2004), pp. 134-138.
12. M.H. Incerpi, D.A. Miller, R. Samadi, R.H. Settlage and T.M. Goodwin, Stillbirth evaluation: what tests are needed , Am J Obstet Gynecol 178 (1998), pp. 1121-1125.
13. W. Rayburn, C. Sander, M. Barr Jr. and R. Rygiel, The stillborn fetus: placental histologic examination in determining a cause, Obstet Gynecol 65 (1985), pp. 637-641.
14. RCOG. Fetal and perinatal pathology. Report of a working party. London; 2001.
15. K.E. Bove and Autopsy Committee of the College of American Pathologists, Practice guidelines for autopsy pathology: the perinatal and pediatric autopsy, Arch Pathol Lab Med 121 (1997), pp. 368-376.
16. C. Langston, C. Kaplan, T. Macpherson, E. Manci, K. Peevy and B. Clark et al., Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists, Arch Pathol Lab Med 121 (1997), pp. 449-476.
17. G.J. Kloosterman, On intrauterine growth. The significance of prenatal care, Int J Gynaecol Obstet 8 (1970), pp. 895-912.
18. H. Pinar, C.J. Sung, C.E. Oyer and D.B. Singer, Reference values for singleton and twin placental weights, Pediatr Pathol Lab Med 16 (1996), pp. 901-907.

19. H. Fox, Pathology of the placenta (2nd ed.), Saunders Company, London (1997).
20. CESDI. The confidential enquiry into stillbirths and deaths in infancy; 1993. p. 1-163.
21. D. Baird, J. Walker and A.M. Thomson, The causes and prevention of stillbirths and first week deaths. III. A classification of deaths by clinical cause; the effect of age, parity and length of gestation on death rates by cause, J Obstet Gynaecol Br Emp 61 (1954), pp. 433-448.
22. E.N. Hey, D.J. Lloyd and J.S. Wigglesworth, Classifying perinatal death: fetal and neonatal factors, Br J Obstet Gynaecol 93 (1986), pp. 1213-1223.
23. O. Hovatta, A. Lipasti, J. Rapola and O. Karjalainen, Causes of stillbirth: a clinicopathological study of 243 patients, Br J Obstet Gynaecol 90 (1983), pp. 691-696.
24. A.E. de Galan-Roosen, J.C. Kuijpers, P.J. van der Straaten and J.M. Merkus, Fundamental classification of perinatal death. Validation of a new classification system of perinatal death, Eur J Obstet Gynecol Reprod Biol 103 (2002), pp. 30-36.
25. I. Morrison and J. Olsen, Weight-specific stillbirths and associated causes of death: an analysis of 765 stillbirths, Am J Obstet Gynecol 152 (1985), pp. 975-980.
26. O. Abudu and A. Akinkugbe, Clinical causes and classification of perinatal mortality in Lagos, Int J Gynaecol Obstet 20 (1982), pp. 443-447.
27. O.N. Bhakoo, Wigglesworth's simplified classification of perinatal deaths, Indian J Pediatr 53 (1986), p. 669.
28. M.Y. el Zibdeh, S.A. Al Suleiman and M.H. Al Sibai, Perinatal mortality at King Fahd Hospital of the University Al-Khobar, Saudi Arabia, Int J Gynaecol Obstet 26 (1988), pp. 399-407.
29. S. Elamin, J. Langhoff-Roos, B. Boedker, S.A. Ibrahim, A.L. Ashmeig and G. Lindmark, Classification of perinatal death in a developing country, Int J Gynaecol Obstet 80 (2003), pp. 327-333.
30. G. Erdem, Perinatal mortality in Turkey, Paediatr Perinat Epidemiol 17 (2003), pp. 17-21.
31. R.S. Settatree and M. Watkinson, Classifying perinatal death: experience from a regional survey, Br J Obstet Gynaecol 100 (1993), pp. 110-121.
32. J.P. Bound, N.R. Butler and W.G. Spector, Classification and causes of perinatal mortality, Br Med J 12 (1956), pp. 1191-1196.
33. J.P. Bound, N.R. Butler and W.G. Spector, Classification and causes of perinatal mortality. II, Br Med J 44 (1956), pp. 1260-1265.
34. N.R. Butler and E.D. Alberman, Perinatal problems: the second report of the 1958 British perinatal mortality survey, E & S Livingstone Ltd, Edinburgh (1969).
35. N.R. Butler and D.G. Bonham, Perinatal mortality: the first report of the 1958 British perinatal mortality survey, E & S Livingstone Ltd, Edinburgh (1963).
36. A. Alonso, I. Soto, M.F. Urgelles, J.R. Corte, M.J. Rodriguez and C.R. Pinto, Acquired and inherited thrombophilia in women with unexplained fetal losses, Am J Obstet Gynecol 187 (2002), pp. 1337-1342.
37. T.Y. Khong and H.M. Chambers, Alternative method of sampling placentas for the assessment of uteroplacental vasculature, J Clin Pathol 45 (1992), pp. 925-927.
38. S. Heinonen, P. Taipale and S. Saarikoski, Weights of placentae from small-for-gestational age infants revisited, Placenta 22 (2001), pp. 399-404.
39. J.J. Erwich, Classification of stillbirth: cause, condition, or mechanism , BMJ 331 (2005), pp. 1269-1270.
40. M. Eskes and M. Van Diem, National perinatal audit study, College voor Zorgverzekeringen, Diemen (2005) p. 231.

CHAPTER 9

A MULTILAYERED APPROACH FOR THE ANALYSIS OF PERINATAL MORTALITY USING DIFFERENT CLASSIFICATION SYSTEMS

Sanne J. Gordijn,
Fleurisca J. Korteweg,
Jan Jaap H.M. Erwich,
Jozien P. Holm,
Mariet Th. van Diem,
Klasien A. Bergman,
Albertus Timmer

European Journal of Obstetrics and Gynecology and Reproductive Biology
2009; 144: 99-104

Abstract

Many classification systems for perinatal mortality are available, all with their own strengths and weaknesses: none of them has been universally accepted. We present a systematic multilayered approach for the analysis of perinatal mortality based on information related to the moment of death, the conditions associated with death and the underlying cause of death, using a combination of representatives of existing classification systems. We compared the existing classification systems regarding their definition of the perinatal period, level of complexity, inclusion of maternal, foetal and/or placental factors and whether they focus at a clinical or pathological viewpoint. Furthermore, we allocated the classification systems to one of three categories: 'when', 'what' or 'why', dependent on whether the allocation of the individual cases of perinatal mortality is based on the moment of death ('when'), the clinical conditions associated with death ('what'), or the underlying cause of death ('why'). A multilayered approach for the analysis and classification of perinatal mortality is possible by using combinations of existing systems; for example the Wigglesworth or Nordic Baltic ('when'), ReCoDe ('what') and Tulip ('why') classification systems. 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 the developing countries, where resources to investigate death are often limited.

Introduction

Classification of perinatal mortality can reveal trends in numbers as well as causes of mortality, it can help in audit of perinatal health management by analysis of substandard factors in the care process and it can direct attention towards issues for prevention and research. Different classification systems have been designed for different reasons with different approaches, definitions, levels of complexity and availability of guidelines. Here we present a systematic multilayered approach for the analysis of perinatal mortality based on information related to the moment of death, the conditions associated with death and the underlying cause of death.

Analysis of perinatal mortality and the use of classification systems

Perinatal mortality can be evaluated by analysis of individual mortality cases or as groups of mortality in a certain hospital, region or country.

When considering individual cases of perinatal mortality the main goal is to reveal the cause of death. To assign a cause of death insight in the pathophysiology is needed. This pathophysiology is complex and involves maternal, foetal, and/or neonatal as well as placental factors. In order to assign a cause of death these factors should be addressed together. Analysis usually includes an extensive evaluation of the clinical conditions and the chain of events leading to death, including diagnostic investigations such as blood tests, autopsy and placental examination. As a result the bereaved parents can be specifically counselled about their loss and possible preventive options for future pregnancies.

Additional analysis comprises cohort analysis of the cases. The cases can be categorised in classification systems in order to reveal trends in mortality and to serve prevention and audit of perinatal care. Requirements for analysis of trends of perinatal mortality are: a universally used classification system for all participating care providers and inclusion of all perinatal mortality cases that meet the definition of the perinatal period in the analysis. This in turn requires a complete perinatal mortality registration. The inadequacies in the perinatal mortality registration have been described elsewhere.[1] Apart from the registration problem there is also the lasting discussion on perinatal period definitions; there are marked differences in these definitions in and between countries hampering an adequate comparison of perinatal mortality.[2,3]

Two perinatal mortality classification systems and their modifications are widely used throughout the world: the 'Aberdeen' and the 'Wigglesworth' classifications.[4-6] Although the two systems have been amended, the modifications and originals allow

partial or complete comparison considering the consistency in categories between the systems.[7,8] Including the 'Aberdeen' and 'Wigglesworth' classifications, 36 systems have been introduced (published in English since 1954, introduced as a new or modified classification system, or referred to it as such by others, not mainly focusing at suboptimal care). Of these systems 21 focus on either pathological information or clinical details (Table 1). Half of the systems aim at classifying the underlying cause of death. However, the underlying cause of death, mechanism of death, clinical conditions and risk factors are often intermingled.[9] Some systems are brief and easy to use with only few categories where others are more detailed and more complex to use (Table 1). Clear uniform definitions and guidelines for classification are incomplete or not described in more than half of the systems. Seven of the analysed systems have been developed for stillbirths only, four systems for neonatal deaths only and 25 systems for perinatal mortality as a group (Table 1).

As stated, the pathophysiology of perinatal death is complex and factors involving the mother, foetus/neonate and placenta should be addressed together. Only six systems address all these factors (Table 1). No single system is generally accepted for its use and each system has its own strengths and weaknesses.[10,11]

When, what, why

Recently Smith et al. have stated that the analysis of perinatal mortality requires a systematic approach.[12] This systematic approach should in our opinion include: analysis of the moment of death, of the clinical conditions associated with death and analysis of the underlying cause of death. The possibilities to complete this proposed approach is dependent on the resources available for the postmortem investigations.

The moment of death (antepartum, intrapartum and neonatal) and also the gestational age at death are important factors that reveal *when* death occurred. The Wigglesworth[13] and Nordic Baltic[14] (Table 2) classification systems for example focus at the moment of mortality (except for the category of lethal congenital malformations in both systems). These systems are easy to use as the postmortem analysis only requires clinical details considering the moment of death and macroscopic foetal examination to allocate cases to the categories.

If classification is supposed to serve in counselling, prevention or audit it is essential to classify associated clinical conditions and underlying cause of death as well. The ReCoDe classification[15] for example seeks to establish the most relevant conditions at death taking into account mother, foetus and placenta, which explains *what* hap-

pened (Table 3). The postmortem analysis for case allocation to such a system requires more details: analysis of the medical and obstetric history, the clinical course and macroscopic examination of the foetus and placenta. Autopsy and histopathological examination of the placenta are desirable, although not always necessary to explain what happened.

Clinical conditions however, do not necessarily explain *why* perinatal death occurred. The reason for death is the underlying cause of death, defined as the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death. The Tulip classification[11] for example classifies these underlying causes and also the mechanism of death and contributing factors (Table 4). The postmortem analysis for these systems requires as much information as possible for establishing the underlying causes, based on clinical findings and diagnostic test results, preferably including autopsy and histopathological placental examination.

We agree with Gardosi et al that clinical conditions give insight into the scenario resulting in death. However, if (classification of) the underlying cause of death is added more insight is given. For example, in the Tulip classification 27.6% of cases (n = 134) in the placenta cause of death group were small for gestational age at birth, versus 8.7% (n = 42) in the other cause of death groups, illustrating diversity in distribution of small for gestational age foetuses between the cause of death groups.[16]

Table 1

Author, year	Version	When, what, why	Aim	Strategy	Entity	Definition SB	Definition NND	Categories
Baird[23] 1954	* *'Aberdeen'*	what	1	2	1	ns	<7 days	main: 8 sub: 0
Bound I[24;25] 1956	*	what	1	1	2	>28 wk	<7 days	main: 11 sub: 0
BPMS: Butler [26] 1963	Bound	what	1	1	2	>28 wk	<7 days	main: 17 sub: 0
Fairweather[27] 1966	*	what	3	3	3	ns	ns	main: 16 sub: 12
BPMS: Baird[28] 1969	Baird	what	1	3	1	>28 wk	<7 days	main: 10 sub: 18
Low[29] 1970	*	what	3	3	2	>20 wk	ns	main: 8 sub: 0
Low[30] 1971	*	what	4	3	2	>20 wk	<28 days	main: 8 sub: 16
Knutzen[31] 1975	*	what	1	2	3	>500 g	<7 days	main: 9 sub: 5
Naeye[32] 1977	Cause of death	what	1	1	2,4	>20 wk	<28 days	main: 20 sub: 0
McIlwaine[33] 1979	Baird	what	2,4	2	3	ns	ns	main: 9 sub: 28
Chang[34] 1979	*	what	1,3	2	2	>20 wk/> 400g	<28 days	main: 2 sub: 26
Wigglesworth[13] 1980	* *'Wigglesworth'*	when	1	1	2	ns	ns	main: 5 sub: 0
Autio-Harmainen[35] 1983	Cause of death	what	4	1	2	-	<28 days	main: 6 sub: 0
Hovatta[36] 1983	Cause of death	what	4	3	3,4	>26 wk	-	main: 10 sub: 10
Morrison[37] 1985	Baird	what	1,2	3	1,4	>20 wk	-	main: 7 sub: 9
Cole[38] 1986	Baird	what	1	2	1	>22 wk/>500 g	<28 days	main: 10 sub: 19
Hey[8] 1986	Wigglesworth	what	3	1	2	ns	ns	main: 6 sub: 0
Hey[8] 1986	Bound	what	3	1	2	ns	ns	main: 11 sub: 18
Whitfield[7] 1986	Baird	what	1,3	2	3	>20 wk	<1 year	main: 12 sub: 24
Pattinson[39] 1989	Baird	what	1	2	3	>500g	<1 year[B]	main: 12 sub: 8
Lammer[40] 1989[a]	*	what	4	3	3	>20 wk/350g	-	main: 6 sub: 0
Keeling[41] 1989	Wigglesworth	what	3,4	1	2	ns	ns	main: 5 sub: 0

Table 1 (Continued)

Author, year	Version	When, what, why	Aim	Strategy	Entity	Definition SB	Definition NND	Categories
Cole[42] 1989[a]	Wigglesworth *'ICE'*	what	3	3	2	-	<1 year	main: 8 sub: 0
Alberman[43] 1994[a]	Wigglesworth	what	1,3	3	3	-	<28 days	main: 4 sub: 10
CESDI[44] 1993	Wigglesworth	what	1	1	2	>20wk	<1year	main: 10 sub: 0
Langhoff Roos[14] 1996	* *'Nordic Baltic'*	what	1,2	4	2	>28 wk/1 kg	<7 days	main: 13 sub: 0
Alberman[45] 1997[a]	Wigglesworth	what	1,3	1	2	>24 wk	-	main: 3 sub: 10
Winbo[46] 1998[a]	Wigglesworth *'NICE'*	what	3	2	2	>28 wk	<28 days	main: 13 sub: 0
Yeo[47] 1998	Baird *'KKH Stillbirth'*	what	1	2	2	>28wk	-	main: 14 sub: 0
Allessandri[48] 2001	*	what	4	3	2	>400 g	ns	main: 10 sub: 18
Galan[49] 2002	*	why	1	3	3,4	>500 g	<7 days	main: 7 sub: 17
Chan[50] 2004	Baird *'PSANZ-PDC'*	what	1,3,4	2	1	ns	ns	main: 11 sub: 19
Chan[50] 2004	Baird *'PSANZ-NDC'*	what	1,3	3	2	-	ns	main: 7 sub: 13
Gardosi[15] 2005	* *'ReCoDe'*	what	1	3	3,4	ns	-	main: 9 sub: 39
Korteweg[11] 2006	* *'Tulip'*	why	1	3	3,4	>16wk	< 6months	Main: 6 sub: 42

Under script Table 1: Background, strategy and perinatal inclusions.

Version: name of the system, *: original classification system. The original author has been mentioned in case a system has been modified: Baird, Wigglesworth or Bound. Cause of death: originally published as an overview of causes of death in a certain area or hospital. When, what, why: analysis of the moment of death (when?), the clinical conditions associated with death (what?), and the underlying cause of death (why?). Aim: 1. serve prevention; 2. study perinatal mortality in a hospital or certain area,; 3. develop a classification itself; 4. other (for example: financial reasons). Strategy: main type of diagnostics applied in order to allocate the cases to a category in the system. 1. pathology results 2. obstetrical or clinical results 3. combined clinico-pathology results; 4. epidemiological. Entity: classifications by individual factors. 1. mostly maternal; 2. mostly foetal; 3. maternal and foetal; 4. including adequate placental subcategories. Definitions: Definitions of inclusion period in the system: ns: not stated; wk. weeks; SB: stillbirth; NND: neonatal death. Categories: the numbers of main- and subcategories as published in the articles.

[a]Computer system[B] Population follow up in this study was until hospital discharge (<1 year), further follow up in the South African situation was difficult.

Table 2. 'When'

Code	Classification
Wigglesworth[13]	
1	Normally formed macerated stillbirth
2	Congenital malformations
3	Conditions associated with immaturity
4	Asphyxial conditions developing in labour
5	Specific conditions other than above

Code	Classification
Nordic Baltic[14]	
I	Fetal malformation
II	Antenatal death, single growth retarded fetus ≥ 28 weeks of gestation
III	Antenatal death, single fetus ≥ 28 weeks of gestation
IV	Antenatal death, before 28 weeks of gestation
V	Antenatal death, multiple pregnancy
VI	Intrapartum death after admission (≥ 28 weeks of gestation)
VII	Intrapartum death after admission (before 28 weeks of gestation)
VIII	Neonatal death 28-33 weeks of gestation and Apgar score >6 after 5 min
IX	Neonatal death 28-33 weeks of gestation and Apgar score <7 after 5 min
X	Neonatal death ≥ 34weeks of gestation and Apgar score >6 after 5 min
XI	Neonatal death ≥ 34weeks of gestation and Apgar score <7 after 5 min
XII	Neonatal death before 28 weeks of gestation
XIII	Unclassified

Table 3. 'What'

Classification	Code	Sub classification
ReCoDe[15]		
A : Fetus	1	Lethal congenital anomaly
	2	Infection 2.1 chronic 2.2 Acute
	3	Non-immune hydrops
	4	Isoimmunisation
	5	Fetomaternal haemorrhage
	6	Twin-twin transfusion
	7	Fetal growth restriction (customised weight centiles)

Table 3 (Continued)

Classification	Code	Sub classification
B: Umbilical cord	1	Prolapse
	2	Constricting loop or knot[a]
	3	Velamentous insertion
	4	Other
C: Placenta	1	Abruptio
	2	Praevia
	3	Vasa praevia
	4	Other "placental insufficiency"[b]
	5	Other
D: Amniotic Fluid	1	Chorioamnionitis
	2	Oligohydramnios[a]
	3	Polyhydramnios[a]
	4	Other
E: Uterus	1	Rupture
	2	Uterine anomalies
	3	Other
F: Mother	1	Diabetes
	2	Thyroid diseases
	3	Essential hypertension
	4	Hypertensive diseases in pregnancy
	5	Lupus or antiphospholipid syndrome
	6	Cholestasis
	7	Drug misuse
	8	Other
G: Intrapartum	1	Asphyxia
	2	Birth trauma
H: Trauma	1	External
	2	Iatrogenic
I: Unclassified		No relevant condition identified
		No information available

[a]If severe enough to be considered relevant

[b]Histological diagnosis

Table 3 (Continued)

Code	Classification
PSANZ NDC[50]	
1	Congenital abnormality
2	Extreme prematurity
3	Cardio-respiratory disorders
4	Infection
5	Neurological
6	Gastrointestinal (Necrotising enterocolitis)
7	Other (SIDS, accidents)

Table 4: 'Why'

Code	Classification	subclassification	
Tulip[11]			
1.1.1	Congenital	Chromosomal defect	Numerical
1.1.2			Structural
1.1.3			Microdeletion/uniparental disomy
1.2.1		Syndrome	Monogenic
1.2.2			Other
1.3		Central nervous system	
1.4		Heart and circulatory system	
1.5		Respiratory system	
1.6		Digestive system	
1.7		Urogenital system	
1.8		Musculoskeletal system	
1.9		Endocrine/metabolic system	
1.10		Neoplasm	
1.11.1		Other	Single organ
1.11.2			Multiple organ
2.1	Placenta	Placental bed pathology	
2.2.1		Placental pathology	Development
2.2.2			Parenchyma
2.2.3			Localisation
2.3		Umbilical cord complication	
2.4		NOS	
3.1	Prematurity	PPROM	

Table 4 (Continued)

Code	Classification	Subclassification	
3.2		Preterm labour	
3.3		Cervical dysfunction	
3.4		Iatrogenous	
3.5		NOS	
4.1	Infection	Transplacental	
4.2		Ascending	
4.3		Neonatal	
4.4		NOS	
5.1	Other	Fetal hydrops of unknown origin	
5.2		Maternal disease	
5.3.1		Trauma	Maternal
5.3.2			Fetal
5.4		Out of the ordinary	
6.1	Unknown	Despite thorough investigation	
6.2		Important information missing	

We allocated the published perinatal mortality classification systems to one of three categories, dependent on whether the allocation of the individual cases of perinatal mortality is based on the moment of death ('when'), the clinical conditions associated with death ('what'), or the underlying cause of death ('why') (Table 1). As approximately 60% of stillbirth cases can be explained by placental causes it is not possible to classify the underlying cause of death in systems that do not have adequate subcategories for placental causes.[16,17] When terms as hypoxia, immaturity or (antepartum) haemorrhage were used, we considered the system to allocate a case primarily on the clinical condition associated with death ('what') and not on the underlying cause (Table 1).

Multilayered approach

We propose a systematic multilayered approach for the analysis of perinatal mortality based on answers related to the moment of death, the conditions associated with death and the underlying cause of death. In our proposal we use existing classification systems considering the fact that all systems have strengths and weaknesses and that between persons, hospitals and regions different preferences for classification systems apply. We do not think that a single perfect system will be developed, but a

well considered combination of representatives of existing systems can approach perfection. For purpose of international comparison a (standard) combination of existing systems would be preferable.

In our opinion systems preferably combine stillbirths and neonatal deaths for the proposed multilayered approach as the same underlying causes apply.[11] The main difference between stillbirths and neonatal deaths is the different organ system that gives expression to the underlying cause of death. For example: the organ system responsible for oxygen supply in the foetus is the placenta, in neonates the lungs are responsible. The underlying cause is independent of these differences as it is the *initial step* in the chain of events resulting in death. Abruption of the placenta for example can cause intrauterine death and it can also cause neonatal death. The mechanisms and clinical conditions between stillbirth and neonatal death however differ; in stillbirth cases the mechanism is placental insufficiency, the clinical condition is antepartum haemorrhage, in case of neonatal death the mechanisms is respiratory insufficiency, the clinical condition is respiratory distress syndrome.

Dependent on the working area and availability of resources (developing versus developed countries and secondary versus tertiary hospital), complete analysis is often not possible. For example in the developing countries with limited resources for investigation of death, the best possible analysis may be the analysis of the moment of death and the subsequent use of one of the applicable classification systems only.[18] The preventive strategies can then be focused at timing of care, for example improved intrapartum foetal monitoring or better facilities for neonatal resuscitation. However in the developed world this analysis is insufficient and one would like to analyse the other layers of our proposed approach as well. With such a complete analysis of perinatal mortality many details will be available for the development of preventive strategies, audit and research.

Ideally, a computerised multilayered system can be developed in order to combine in which period death occurred, what went wrong and under what circumstances using an algorithm that analyses every case in a standardised manner and gives insight into non-obvious associations.

Table 5: Appendix. Case examples

Example 1: 28 years old, G1P0, delivery at 27 weeks of gestation, girl, 560 grams, died *in utero*.		
When?	Antepartum, before 28 weeks.	Nordic Baltic category IV: Antenatal death, before 28 weeks of gestation.
		Wigglesworth category 1: normal formed macerated stillbirth.
What?	Intra uterine growth restriction, preeclampsia and placental infarctions.	ReCoDe category A7: Fetus, fetal growth restriction, category C4: other placental insufficiency and category F4: Hypertensive disease in pregnancy.
Why?	Placenta bed pathology (infarction).	Tulip category 2.1: Placental bed pathology.
In this example all systems classify details of this case that are useful for evaluation and prevention. No system allocates a (common) case like this in a category as "other" or "unknown".		
Example 2: 36 years old, G2P1, delivery at 37 weeks of gestation, boy 2950 grams died in utero.		
When?	Antepartum, 37-40 weeks of gestation.	Nordic Baltic category III: Antenatal death, single fetus > 28 weeks of gestation.
		Wigglesworth category 1: normal formed macerated stillbirth.
What?	Maternal diabetes, velamentous insertion .	ReCoDe category B3: Umbilical cord, velamentous insertion and category F1: Maternal, diabetes.
Why?	No cause could be determined after autopsy and histopathological placental examination.	Tulip category 6.1: Unknown, despite thorough investigation.
In this example the cause of death remains unknown but the circumstances provide clues for prevention. The perinatal period can be evaluated including the (combination of) conditions.		
Example 3: 32 years old, G1P0, delivery at 40 weeks, boy 3220 g died three hours after birth.		
When?	In the neonatal period within 24 hours.	Nordic Baltic category XI: Neonatal death > 34 weeks of gestation and Apgar score < 7 after 5 min.
		Wigglesworth category 4: asphyxial conditions developing in labour.
What?	Placental abruption, mild pregnancy induced hypertension.	ReCoDe/PSANZ NDC: category C1 Placenta abruption, category F4 hypertensive disease in pregnancy and category 7: Other.
Why?	Placental bed pathology (abruption)	Tulip category 2.1: Placental bed pathology.
In this example a neonate dies of a placental cause. The ReCoDe has originally been developed for stillbirths only, but in our opinion it provides a complete view on perinatal deaths when combined with neonatal PSANZ.		

Unknown and unexplained causes of perinatal mortality

Current use of classifications consistently report of about two-thirds of perinatal mortality as being unexplained or unknown.[11,15,19-21] A large group of unexplained or unknown cases is often due to design of the system itself and lack of amendment of the system to present insight into pathophysiology of perinatal mortality. Due to differences in definition, it is difficult to compare the percentages of unexplained or unknown cases in the different systems. Moreover the problem is that these categories have little consequence and, when aiming at preventive strategies for conditions or causes they will not result in change of management.

Systems that classify the underlying cause of death require an extensive analysis of cases for optimal use, especially the autopsy and histopathologic placental examinations, as mentioned earlier in this manuscript. Perinatal autopsy rates in many developed countries however have shown a diminishing trend mainly because lack of consent, although placental examination is usually allowed.[22] In developing countries the perinatal autopsy rates are also low because the facilities for the autopsy are only available in larger hospitals and in general the autopsy does not have medical priority. Placental examination is usually not performed either, among other reasons for the risk of spread of contagious, potential lethal, infections to the examiners, such as HIV. With incomplete analysis the underlying cause may remain unknown. For systems that classify the underlying cause of death it can be useful to define 'unknown despite thorough investigations' and 'unknown with missing important information' in order to give insight in the numbers of unknown causes due to the low autopsy rates.

The concept of our multilayered approach is particularly helpful when the underlying cause of death (with or without thorough investigations) remains unknown. The analysis of the clinical scenario with the maternal, foetal and placental conditions in that period does provide clues for preventive possibilities in the future. We used the ReCoDe (Table 3) as an example for systems that classify the clinical conditions, these systems reduce the predominance of cases formerly categorised as unknown when only classified in a system for the underlying cause of death. When in addition to these conditions the moment of death of the unknown causes is included, information can be provided considering time related conditions and the subsequent possibilities for interventions.

Approach for perinatal audit studies

At present for a regional audit study of perinatal mortality we use such a systematic multilayered approach. For when death occurred we register the gestational age at

delivery and whether death occurred antepartum (subcategories for gestational ages are used), intrapartum or in the neonatal period (subcategories are used for death within 24 hours, death from 24 hours until one week and death from one week until four weeks of life). To classify what happened the clinical conditions associated with perinatal mortality an amended non-hierarchical ReCoDe system is used in which we register as many items as applicable. For the clinical conditions in neonatal cases we added the PSANZ neonatal death categories as the ReCoDe has been developed for stillbirths only (Table 3). For the classification of the underlying cause of death the Tulip classification is used (Table 4). To demonstrate the benefit of such a multilayered approach for audit three case examples are provided (Table 5). The examples illustrate that with the subsequent use of representative classification systems maximum information is retained per case. Annual reports of mortality per hospital or region can summarise the figures of the selected classification systems to observe yearly trends. Subsequently additional analysis with cross-tabulation of the used systems, providing details regarding the moment of death and clinical scenario in relation to the underlying causes, is then possible, if desired in relation to substandard factors in the care process that may have contributed to death.

Summary and conclusions

In summary we present a systematic approach of the analysis of perinatal mortality using a combination of representatives of existing classification systems. From our point of view analysis of perinatal mortality should be multilayered and include answers related to the moment of death, the conditions associated with death, and the underlying cause of death. This multilayered approach is not only useful for in depth analysis of perinatal mortality in the developed world but also for analysis of perinatal mortality in the developing countries, where resources to investigate death are often limited, as it is possible to only apply one layer. Moreover, combinations of representatives of the applicable systems can provide a complete "three-dimensional" analysis that may reveal new associations between clinical conditions and causes of death in a certain perinatal period.

Reference list

1. Macfarlane A, Gissler M, Bolumar F, Rasmussen S. The availability of perinatal health indicators in Europe. Eur J Obstet Gynecol Reprod Biol 2003; 111 Suppl 1:S15-S32.
2. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961-1988. Obstet Gynecol 1992; 79(1):35-39.
3. Cartlidge PH, Stewart JH. Effect of changing the stillbirth definition on evaluation of perinatal mortality rates. Lancet 1995; 346(8973):486-488.
4. Abudu O, Akinkugbe A. Clinical causes and classification of perinatal mortality in Lagos. Int J Gynaecol Obstet 1982; 20(6):443-447.
5. Elamin S, Langhoff-Roos J, Boedker B, Ibrahim SA, Ashmeig AL, Lindmark G. Classification of perinatal death in a developing country. Int J Gynaecol Obstet 2003; 80(3):327-333.
6. Settatree RS, Watkinson M. Classifying perinatal death: experience from a regional survey. Br J Obstet Gynaecol 1993; 100(2):110-121.
7. Whitfield CR, Smith NC, Cockburn F, Gibson AA. Perinatally related wastage--a proposed classification of primary obstetric factors. Br J Obstet Gynaecol 1986; 93(7):694-703.
8. Hey EN, Lloyd DJ, Wigglesworth JS. Classifying perinatal death: fetal and neonatal factors. Br J Obstet Gynaecol 1986; 93(12):1213-1223.
9. Erwich JJ. Classification of stillbirth: cause, condition, or mechanism? BMJ 2005; 331(7527):1269-1270.
10. Silver RM, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D et al. Work-up of stillbirth: a review of the evidence. Am J Obstet Gynecol 2007; 196(5):433-444.
11. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. Br J Obstet Gynaecol 2006; 113(4):393-401.
12. Smith GC, Fretts RC. Stillbirth. Lancet 2007; 370(9600):1715-1725.
13. Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. Lancet 1980; 2(8196):684-686.
14. 14. Langhoff-Roos J, Borch-Christensen H, Larsen S, Lindberg B, Wennergren M. Potentially avoidable perinatal deaths in Denmark and Sweden 1991. Acta Obstet Gynecol Scand 1996; 75(9):820-825.
15. 15 Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ 2005; 331(7525):1113-1117.
16. 16 Korteweg FJ, Gordijn SJ, Timmer A, Holm JP, Ravise JM, Erwich JJ. A Placental cause of Intra-uterine fetal death depends on the perinatal mortality classification system used. Placenta 2008;29(1):71-80
17. Horn LC, Langner A, Stiehl P, Wittekind C, Faber R. Identification of the causes of intrauterine death during 310 consecutive autopsies. Eur J Obstet Gynecol Reprod Biol 2004; 113(2):134-138.
18. Raghuveer G. Perinatal deaths: relevance of Wigglesworth's classification. Paediatr Perinat Epidemiol 1992; 6(1):45-50.
19. Measey MA, Charles A, d'Espaignet ET, Harrison C, Deklerk N, Douglass C. Aetiology of stillbirth: unexplored is not unexplained. Aust N Z J Public Health 2007; 31(5):444-449.
20. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. Am J Obstet Gynecol 2001; 184(4):694-702.

21. 21 Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol 2005; 193(6):1923-1935.
22. Khong TY, Turnbull D, Staples A. Provider attitudes about gaining consent for perinatal autopsy. Obstet Gynecol 2001; 97(6):994-998.
23. Baird D, Walker J, Thomson AM. The causes and prevention of stillbirths and first week deaths. III. A classification of deaths by clinical cause; the effect of age, parity and length of gestation on death rates by cause. J Obstet Gynaecol Br Emp 1954; 61(4):433-448.
24. Bound JP, Butler NR, Spector WG. Classification and causes of perinatal mortality. II. Br Med J 1956; 44(5004):1260-1265.
25. 25. Bound JP, Butler NR, Spector WG. Classification and causes of perinatal mortality. Br Med J 1956; 12(5003):1191-1196.
26. 26. Butler NR, Bonham DG. Perinatal mortality: the first report of the 1958 British Perinatal Mortality Survey. 1963. Edingburgh, E & S Livingstone Ltd.
27. Fairweather DV, Russell JK, Anderson GS, Bird T, Millar DG, Pearcy PA. Perinatal mortality in Newcastle upon Tyne 1960-62. Lancet 1966; 1(7429):140-142.
28. Butler NR, Alberman ED. Perinatal problems: the second report of the 1958 British Perinatal Mortality Survey. 1969. Edinburgh, E&S Livingstone Ltd.
29. Low JA, Boston RW, Cervenko FW. A clinical classification of the mechanisms of perinatal wastage. Can Med Assoc J 1970; 102(4):365-368.
30. 30 Low JA, Boston RW, Crussi FG. Classification of perinatal mortality. Can Med Assoc J 1971; 105(10):1044-1046.
31. 31 Knutzen VK, Baillie P, Malan AF. Clinical classification of perinatal deaths. S Afr Med J 1975; 49(35):1434-1436.
32. Naeye RL. Causes of perinatal mortality in the US Collaborative Perinatal Project. JAMA 1977; 238(3):228-229.
33. McIlwaine GM, Howat RC, Dunn F, Macnaughton MC. The Scottish perinatal mortality survey. Br Med J 1979; 2(6198):1103-1106.
34. Chang A, Keeping JD, Morrison J, Esler EJ. Perinatal death: audit and classification. Aust N Z J Obstet Gynaecol 1979; 19(4):207-211.
35. Autio-Harmainen H, Rapola J, Hoppu K, Osterlund K. Causes of neonatal deaths in a pediatric hospital neonatal unit. An autopsy study of a ten-year period. Acta Paediatr Scand 1983; 72(3):333-337.
36. Hovatta O, Lipasti A, Rapola J, Karjalainen O. Causes of stillbirth: a clinicopathological study of 243 patients. Br J Obstet Gynaecol 1983; 90(8):691-696.
37. Morrison I, Olsen J. Weight-specific stillbirths and associated causes of death: an analysis of 765 stillbirths. Am J Obstet Gynecol 1985; 152(8):975-980.
38. Cole SK, Hey EN, Thomson AM. Classifying perinatal death: an obstetric approach. Br J Obstet Gynaecol 1986; 93(12):1204-1212.
39. Pattinson RC, De Jong G, Theron GB. Primary causes of total perinatally related wastage at Tygerberg Hospital. S Afr Med J 1989; 75(2):50-53.
40. Lammer EJ, Brown LE, Anderka MT, Guyer B. Classification and analysis of fetal deaths in Massachusetts. JAMA 1989; 261(12):1757-1762.
41. Keeling JW, MacGillivray I, Golding J, Wigglesworth J, Berry J, Dunn PM. Classification of perinatal death. Arch Dis Child 1989; 64(10 Spec No):1345-1351.
42. Cole S, Hartford RB, Bergsjo P, McCarthy B. International collaborative effort (ICE) on birth weight, plurality, perinatal, and infant mortality. III: A method of grouping underlying causes of infant death to aid international comparisons. Acta Obstet Gynecol Scand 1989; 68(2):113-117.

43. Alberman E, Botting B, Blatchley N, Twidell A. A new hierarchical classification of causes of infant deaths in England and Wales. Arch Dis Child 1994; 70(5):403-409.
44. CESDI. The confidential enquiry into stillbirths and deaths in infancy. Report March 1992-July 1993 :1-163.
45. Alberman E, Blatchley N, Botting B, Schuman J, Dunn A. Medical causes on stillbirth certificates in England and Wales: distribution and results of hierarchical classifications tested by the Office for National Statistics. Br J Obstet Gynaecol 1997; 104(9):1043-1049.
46. Winbo IG, Serenius FH, Dahlquist GG, Kallen BA. NICE, a new cause of death classification for stillbirths and neonatal deaths. Neonatal and Intrauterine Death Classification according to Etiology. Int J Epidemiol 1998; 27(3):499-504.
47. Yeo S.H., Tee C.S., Tan K.H. Stillbirths in KK Women's and Children's Hospital 1997. Report of the KKH Stillbirth Working Group.
48. Alessandri LM, Chambers HM, Blair EM, Read AW. Perinatal and postneonatal mortality among Indigenous and non-Indigenous infants born in Western Australia, 1980-1998. Med J Aust 2001; 175(4):185-189.
49. Galan-Roosen AE, Kuijpers JC, van der Straaten PJ, Merkus JM. Fundamental classification of perinatal death. Validation of a new classification system of perinatal death. Eur J Obstet Gynecol Reprod Biol 2002; 103(1):30-36.
50. Chan A, King JF, Flenady V, Haslam RH, Tudehope DI. Classification of perinatal deaths: development of the Australian and New Zealand classifications. J Paediatr Child Health 2004; 40(7):340-347.

CHAPTER 10

GENERAL DISCUSSION

Analysis of perinatal mortality

Ideally, we should know the underlying cause of death in all cases of perinatal mortality. The underlying cause is supplemented with the clinical conditions and contributing factors. Subsequently classification systems for perinatal mortality are used and the cases are discussed in a multidisciplinary audit. As a result we are able to take preventive measures and avert death. Unfortunately this is not possible in all cases, even in the developed countries with ample possibilities for investigations and high motivation for improvement of care. In the developing countries where by far most perinatal mortality cases occur only little possibilities for the analysis of perinatal mortality exist. Our efforts should not only be directed to our practice but to these low resource countries as well, much more improvement can be accomplished there.

From our data it can be concluded that in approximately 11% of perinatal mortality cases the cause of death remains unknown. Only 4% of causes remained unknown when (in our opinion) sufficient investigations had been performed.[1] No consensus has been reached so far regarding the investigations that should be performed in cases of perinatal death. A research project with the goal to determine useful investigations for stillbirths started in the Netherlands in 2001. (Zinnig Onderzoek bij Antepartum Sterfte; ZOBAS). A protocol for the investigations in case of stillbirth will be proposed. The investigations for intrapartum- and neonatal deaths can be extracted from that protocol since the underlying causes for perinatal mortality cases from every subgroup are the same. We hope that with the implementation of a standard protocol more insight will be gained in the pathofysiology of perinatal mortality. The karyotype, autopsy and placental examination already proved to be useful.[2-4] Multidisciplinary meetings with obstetricians, neonatologists, pathologists and geneticists provide the best insight in the pathofysiology of perinatal deaths. The obstetricians and neonatologists can explain the clinical details, the pathologist can explain the cause and mechanism of death as found during the autopsy and placental examination and the geneticist can explain observed congenital anomalies and the consequences.

Autopsy

The perinatal autopsy often confirms clinical diagnoses or reveals additional findings, as described in *Chapter 2.* Unfortunately the perinatal autopsy rate has declined over the past decades, although it is more or less stable now. We described in *Chapter 3* that one of the main reasons for the decline is the reluctance of doctors to ask for permission. Physicians should do better in their counselling to raise the perinatal autopsy

rates again. The first step towards better counselling would be to be familiar with the value of the autopsy, its procedure and the possible parental religious and cultural objections. One has to feel confident to discuss the topic and obtain consent from the parents. Counselling is a time consuming, difficult and emotional conversation that should take place without disturbances. The physician most involved with the patient should explain the value of the autopsy and the procedure. It is not important whether this is the youngest physician, midwife or head of the department. The pathologist (preferably specialised in perinatal pathology) can counsel the parents regarding the procedure as well. Parents are to be given the opportunity to discuss their fears and possible restrictions and can explain their possible wishes (such as photographs). Combined conversation with the doctor and the pathologist is also an option.

Placental pathology

Investigations of cases of perinatal mortality are incomplete if the placenta is not submitted for histopathological evaluation. In *Chapter 4* we describe the quality of placental reports and suggestions for improvement. The conclusions of placental investigations have well been reported. Clinicians may expect a clear explanation of the role of placental pathology present from the pathologist and pathologists need sufficient clinical detail from the clinician, as described in *Chapter 5*. Pathology reports should facilitate comprehension of the histological findings. Pathology reports could contain a short summary of the scenario that resulted in death (as provided by the clinician), it should at least provide a cause of death (or the statement: 'unexplained' cause of death) and preferably a recurrence risk as well. The clinician and pathologist are both responsible for the communication regarding the implications of their findings, between themselves and with the patient.

Not only should the placentas of stillbirths be submitted to the pathologist, but also the placentas of neonatal deaths and terminations of pregnancy for medical reasons. In general, placentas of stillbirths and terminations of pregnancies are easily available for evaluation, placentas of neonatal deaths after an apparently uncomplicated pregnancy are often problematic to obtain. These placentas are usually thrown away after birth when perinatal mortality seemed non apparent. In many hospitals placentas are anonymously collected in a freezer, to be cremated later, without the possibility of retaining the individual placentas when necessary. A system with labelled biological demolition plastic bags or a system with more freezers could solve the problem with the possibility of retaining placentas of neonatal mortality cases.

In developed countries placentas are usually available for histopathological analysis, in contrast to the developing countries. One of the reasons for the poor availability is the high contamination risk with blood transmittable infections for the involved examiner. Other reasons are that in rural areas most women deliver at home and not in a hospital with possibilities for placental analysis, that birth attendants are poorly educated with regard to the investigation of the placenta and moreover that the financial resources are directed towards care of women in labour and not to post-mortem investigations. When gloves are available for the examiner the placenta can be investigated macroscopically in developing countries as well, we suggest the use of a very basic placenta investigation protocol. In collaboration with the International Stillbirth Alliance (ISA) we plan to develop a format for placental investigations in the developing countries with the use of pictures on a poster.

In *Chapter 6* we focused at a specific placental cause of death: villous immaturity (VI). VI is an important cause of term stillbirth cases. No internationally accepted definition of VI exists. The etiology of VI is unclear. We classified it as an underlying cause of death as this entity is as far back in the chain of events we can go. It is possible however that with future research another entity is found to be associated with VI or is found to cause VI. The fact that we found 41 cases with VI as the only pathological entity resulting in foetal death strengthens our current opinion that VI is a cause of death.

Classification of perinatal mortality

We developed the Tulip classification system (*Chapter 7*) for classification of the underlying cause of death. Ideally all health workers use the same classification systems to allow comparison of figures. The Tulip classification system however is not suitable for all situations. In the developing countries, only little information is obtained, especially regarding the underlying cause of death. The category: "unknown with important information missing" would be over represented and the placental category would probably remain empty, which obscures comparison of figures. We have proposed a multilayered approach that uses a combination of existing systems to be used in sequence of increasing difficulty in *Chapter 9*. Using such a combination of systems compensates for the shortcomings of the individual systems (*Chapter 8*) and allows use in developing countries as well. In this approach it is not obligatory to complete all levels, it is possible to just complete the first level and then stop. Later on with more available investigations the second level and maybe the third can be completed as well. The ISA accommodates this approach in the development of a new classification for assistance

of the World Health Organisation in the adjustments of the O and P codes for the ICD 11 (International Classification of Diseases). We currently work on this new classification system (Maternal Antepartum Intrapartum Neonatal classification, MAIN).

Audit and multilayered approach for classification

The Peristat studies revealed that the Netherlands is amongst the countries with the highest perinatal mortality rates in Europe.[5] Several reasons have been provided for these numbers. The influence of substandard care was not investigated.[6] For that reason, a national feasibility study for audit of perinatal mortality was performed (Landelijke Perinatal Audit Study, LPAS). The conclusions from the LPAS were that need for national audit existed and that it was feasible. In about 20% of cases substandard care factors contributed to the death. All involved healthworkers considered audit as useful and they were willing to participate in a national audit of perinatal mortality. The RIVM (Rijksinstituut voor Volksgezondheid en Milieu) has initiated a national audit study and in Groningen a regional audit is implemented (IMPACT). Both audits use our proposed multilayered approach for classification of mortality cases. A classification for quality of care and substandard factors could be added as an additional layer of the approach to be used in audits. With this approach, the quality-improvement cycle can start to improve perinatal care and prevent adverse outcomes.

Reference list

1. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. BJOG 2006;113:393-401.
2. Incerpi MH, Miller DA, Samadi R, Settlage RH, Goodwin TM. Stillbirth evaluation: what tests are needed? Am J Obstet Gynecol 1998;178:1121-1125.
3. Bohra U, Regan C, O'Connell MP, Geary MP, Kelehan P, Keane DP. The role of investigations for term stillbirths. J Obstet Gynaecol 2004;24:133-134.
4. Gordijn SJ, Erwich JJ, Khong TY. Value of the perinatal autopsy: critique. Pediatr Dev Pathol 2002;5:480-488.
5. Buitendijk S, Zeitlin J, Cuttini M, Langhoff-Roos J, Bottu J. Indicators of fetal and infant health outcomes. Eur J Obstet Gynecol Reprod Biol 2003; 111 Suppl 1:S66-S77.
6. Hijlkema S. Niet verrassend, wel problematisch. Professionals uit de zorg, wetenschap en politiek reageren op Peristat-II. NTOG 2009; 122:3-5.

CHAPTER 11

SUMMARY

With this thesis we provide clues that can help to understand the value of the perinatal autopsy and placental examination, the importance of good communication between pathologists and clinicians and the use of classification systems in perinatal mortality. The first chapters focus at the perinatal autopsy, the next chapters focus at placental investigation and the communication between the pathologist and clinician and the last at classification of perinatal mortality.

Chapter 2: Value of the perinatal autopsy: critique

This chapter illustrates the value of the perinatal autopsy. In this literature review the autopsy reveals new diagnoses or important additional information in 22% to 76% of cases. If confirmation of clinical findings is included, then the value of perinatal autopsy is as high as 100%. Several confounding factors that may influence the value of the autopsy have been evaluated including the level of hospital, the autopsy protocols used, the expertise of the pathologist (perinatal/pediatric pathologist, fellow or general pathologist) and also selection of cases admitted for autopsy. The autopsy protocols and expertise of the performing pathologists differed between the institutions. In several articles the autopsy protocol was unknown and the expertise of the pathologist remained indistinct. The autopsy rates varied between 16% and 100%, the mean autopsy rate was 38%. The highest rates were seen among terminations of pregnancy (79-100%).

The reported value of the autopsy can be positively influenced by selecting cases for admission to pathology in scenarios where the autopsy adds more information, for example by requesting more autopsies in the group of deaths with an unknown clinical diagnosis. Another possibility to improve the reported value of the autopsy is to exclude cases in which the autopsy cannot provide much information, for example in macerated stillbirth. In the published literature however the description of such selections of cases for autopsy is often not included, obscuring the possibilities for comparison of the value of perinatal autopsies.

Chapter 3: The perinatal autopsy: pertinent issues in multicultural Western Europe

This chapter deals with the difficulties that exist regarding counseling of the perinatal autopsy. The average autopsy rate is only 38%, which is less than the proposed minimum of 75% by the Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists. The major reason for the low perinatal autopsy rates is the difficulty of obtaining permission for the autopsy from the parents. Furthermore, the

assumption that the autopsy can be replaced by current imaging techniques, adverse publicity regarding organ retention (e.g. Alder Hey scandal) and reports on the failing quality of perinatal autopsies all contribute to the low autopsy rates. Parents should be informed about the routine of the autopsy. In general this involves macroscopic examination of the body and internal organs. Organs will be taken out for weighing and tissue will be sampled for histologic examination. The organs will be replaced, but the tissue samples not. These samples will be stored for additional analysis or second opinion.

Alternatives such as limited autopsy or needle biopsy of selected organs and imaging techniques such as MRI and radiography are available. These alternatives however are less conclusive than the "Gold Standard" i.e. the autopsy.

The major religions and their end-of-life rituals in general allow the performance of an autopsy. Some require special treatment or timing. In Buddhism for example the body has to be left undisturbed for three days to allow the soul to make its transition. In the Islam faith the autopsy should be performed as soon as possible as burial should take place before sunset of the next day. When doctors are convinced of the value of the autopsy and the parents are counseled adequately in respect of their cultural and religious background, the autopsy rates can be raised again.

Chapter 4: Quality of placental reports

In this chapter we investigate the quality of placental reports. Of 218 placental reports from four hospitals, two percent failed to reach half the maximum granted points (points were rewarded for description of, and commentary on, gross and histologic examination, comments on the associated clinical lesions and the availability of recurrence risks) and 31% scored between 50 and 75% of maximum granted points.

Several details of the placental reports attracted attention. In our analysis only 10% of reports stated the trimmed placental weight although the standard placental weight charts are based on trimmed weights. Some components of a placental report were well documented, such as the number of umbilical vessels, cord diameter and length and the dimensions of the placental discs. Other components were poorly documented such as completeness of membranes and location of membrane rupture. In almost all reports a block code for the placental samples was assigned, which is important for retrieval of samples for additional analysis or for a second opinion. Commentary on the findings of the placenta and the possible relation to clinical details differed between the hospitals and ranged between 43% and 94%.

The description of normal findings is of equal importance as the description of abnormal findings, otherwise it remains unknown whether details have been studied if not mentioned at all. Communication between pathologist and clinician is lost by inconsistent reporting of commentaries on (ab)normal findings in the placental reports.

Chapter 5: Histopathological examination of the placenta: key issues for pathologists and obstetricians

In this chapter we illustrate the importance of placental examination and the importance of good communication about the results between the clinician and the pathologist. The placenta is often not submitted for histopathological examination, as clinicians are often sceptical as to the value of placental examination.

When a placenta is submitted to the pathologist, adequate details considering conditions in pregnancy and medical history for the interpretation of placental findings should be provided. The request form for placental investigation should therefore contain a list with important information for the pathologist (preferably a standardized form). In return, the obstetrician should be provided with adequate information for interpretation of the histological findings and the subsequent counseling of the parents.

Chronic villitis (lymphohistiocytic inflammation of the terminal villi) is an example of a histological diagnosis. It has an unknown aetiology and is associated with intrauterine growth restriction, preterm labour and fetal death, with a recurrence risk of up to 17%. In future pregnancies the foetus can be monitored by ultrasound and cardiotocography. Acute chorioamnionitis (associated with pathogenic vaginal micro organisms) is another example with a recurrence risk and possibilities for intervention.

For explanation and interpretation of histological abnormalities the involvement of pathologists in multidisciplinary meetings with obstetricians and neonatologists can be very useful, particularly in the case of apparent unexplained stillbirth or serious adverse outcome.

Chapter 6: Villous immaturity as an important cause of term foetal death

Villous immaturity of the placenta is an important cause of death in term intrauterine foetal deaths (over 252 days or 36 weeks of gestation). We evaluated 1025 foetal deaths and selected the cases beyond 36 weeks of gestation (n = 352). Based on the causes of death the intrauterine foetal deaths were divided in three groups: villous immaturity, other placental pathology and non-placental pathology.

A placental cause of death was identified in almost 80% (280/352). Of the placental causes 29% (81/280) were caused by villous immaturity. Of these cases 48% were caused by villous immaturity alone and 52% by villous immaturity in combination with other placental pathology. The prevalence of gestational diabetes was 2.5 fold-higher in the villous immaturity group than in the group caused by other placental pathology (13.9% vs. 5.5%) (p = 0.029) and 10 fold- higher than in the group caused by non-placental pathology (13.9% vs. 1.4%) (p = 0.005). Villous immaturity was also associated with placental hypoplasia in comparison to the group with a non-placental cause of death. Although oligohydramnios occurred almost twice as often in the group with villous immaturity (23.1%) than in the group with non-placental causes (12.5%), was this difference not statistically significant (p = 0.139). No associations were found for pre existent diabetes mellitus, hypertensive disorders, intoxications or foetal characteristics such as foetal weight. Previously described association with hyper coiling of the umbilical cord could not be confirmed.

Chapter 7: The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement

We developed a perinatal mortality classification system for cause and mechanism of death. The Tulip classification system classifies the underlying cause of death, defined as the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death, in 6 categories; 1: congenital anomalies, 2: placenta, 3: prematurity/immaturity, 4: infection, 5: other and 6: unknown. These main categories contain several subcategories. The system consequently classifies the mechanism of death (defined as the organ failure incompatible with life) and the origin of the mechanism. Finally, contributing factors (conditions like hypertension preeclampsia or risk factors such as smoking) are classified. We provide clear definitions and guidelines for case allocation.

After development of the system it has been tested for the inter-rater agreement between five panel members in 411 cases of perinatal mortality. The largest cause of death group was: congenital anomalies (35%), the second and third largest groups were placental and prematurity (27% and 23% respectively). Only 11% of deaths were allocated to the "unknown" group. The infection and "other" categories consisted of only 1% and 3% of deaths respectively. The kappa score was 0.81 for main cause of death (0.89 after excluding guideline misinterpretations) and 0.67 for sub classification of cause of death (0.76 after excluding guideline misinterpretations). The agreement

was highest in the congenital anomalies category and lowest in the category "other". To clarify some classification difficulties examples of cases have been provided.

Chapter 8: A Placental cause of intra-uterine foetal death depends on the perinatal mortality classification system used

Differences between perinatal mortality classification systems have consequences for vital statistics. We illustrated this by classification of 485 cases of foetal death in eight perinatal mortality classification systems (extended Wigglesworth, modified Aberdeen, ReCoDe, Tulip, and the classifications by Hey et al., Hovatta et al., de Galan-Roosen et al. and Morisson et al.). The cases were classified in a panel with two obstetricians, a pathologist and a registrar in Obstetrics and Gynaecology. Distribution of the 485 stillbirth cases into the different causal categories varied among the systems, predominantly in the "placental" and the "unknown" groups. The proportion of cases (for the same 485 cases) in the placental groups varied from 0% (no placental category provided in those systems) to 64.3% in the Tulip classification. In some systems cases with an unexplained cause of death comprised the largest group such as in the extended Wigglesworth (88.5%), while in other systems such as the system by Hey et al. no deaths were classified as unexplained. However in this system 88.4% of cases were allocated to the group "asphyxia antepartum".

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. Allocation of cases according to the underlying cause of death resulted in the largest group of deaths in the placental category and the most frequent contributing factor was intrauterine growth restriction.

Chapter 9: A multidimensional approach for the analysis of perinatal mortality using different classification systems

We identified 35 classification systems for perinatal mortality published since 1954. All systems have their own strengths and weaknesses, but none of them has been universally accepted for its use. In this chapter we propose a multilayered approach that uses the existing systems based on information related to the moment of death, the conditions associated with death and the underlying cause of death. Three questions in sequence of complexity can be asked: *When did it happen?* What was the gestational age and when did it occur? Antepartum, intrapartum or in the neonatal period? Two systems mainly focus at when death occurred. They both include a category for lethal

foetal malformations as well. For reliable allocation of cases foetal macroscopy is required. The next question that can be asked is: *What happened?* What were the fetal, maternal and/or placental conditions that have contributed to death? To answer this question more investigations are necessary: analysis of clinical conditions, foetal and placental macroscopy and preferably the autopsy as well. Most of the developed systems classify what happened. The final and most complex question that can be asked is: *Why did it happen?* What is the underlying cause of death, the event that initiated the chain of events that eventually resulted in death? Extensive analysis including placental histopathology is required to reliably allocate the cases to these categories.

Classification systems that do not have adequate placental categories or have categories such as hypoxia or antepartum haemorrhage are not considered to classify the underlying cause of death. When 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 add to each other, which is why we propose the multilayered approach.

For audit purposes cross tables of the different systems can be made to see the relation between timing of death, conditions, underlying cause and additionally possible substandard factors in the care.

CHAPTER 12

SAMENVATTING

Het sterven van een baby is voor ouders een uitermate verdrietige en traumatische ervaring. Niet alleen de ouders, maar ook vrienden, familie en zorgverleners zijn betrokken bij het verlies. Om vragen te kunnen beantwoorden als "waarom is dit gebeurd?" zullen In de periode net na het overlijden verschillende lastige onderwerpen besproken moeten worden. In dit proefschrift richten we ons op een aantal van deze onderwerpen. Dat leidt tot suggesties om in meer gevallen vragen beantwoord te krijgen zoals: het optimaal counselen betreffende toestemming voor obductie, verbetering van rapportage over placentaonderzoek onder andere door een betere communicatie tussen clinicus en patholoog en het gebruik van classificatiesystemen voor perinatale sterfte. In grote lijnen handelen de hoofdstukken twee en drie over de perinatale obductie, de volgende drie hoofdstukken over placentaonderzoek en de laatste drie over het gebruik van classificatiesystemen voor perinatale sterfte.

Hoofdstuk 2: De waarde van de perinatale obductie: een kritische beschouwing

De toegevoegde waarde van perinatale obductie wordt in dit hoofdstuk besproken. Uit een literatuurreview blijkt dat obductie in 22 tot 76% van de gevallen nieuwe diagnoses of belangrijke aanvullende informatie levert. Als ook de bevestiging van een klinische diagnose als waardevol wordt gezien, blijkt dat percentage tot 100% te zijn.

We hebben verschillende factoren die de waarde van de obductie kunnen beïnvloeden geëvalueerd, zoals het ziekenhuisniveau, het gebruikte obductieprotocol, de expertise van de uitvoerend patholoog en de eventuele selectie van casus die ter obductie werden aangeboden. De expertise van de patholoog en de obductieprotocollen verschilden per ziekenhuis. Helaas bleef in verschillende artikelen het obductieprotocol en de mate van specialisatie van de patholoog onduidelijk. De obductiepercentages varieerden van 16 tot 100% met een gemiddelde van 38%. Het hoogste percentage werd gezien na zwangerschapsafbrekingen (79-100%). Neonatale en doodgeboorte-obductiepercentages varieerden van respectievelijk 33 tot 100% en 5 tot 100%.

De gerapporteerde waarde van de obductie kan positief beïnvloed worden door dié casus voor obductie aan te bieden waar deze gemakkelijk nieuwe diagnoses levert, zoals in geval van onbekende klinische diagnoses. Ook wordt de gerapporteerde waarde van de obductie verbeterd als obductie niet wordt aangevraagd bij casus waarbij bij de obductie weinig informatie wordt verwacht, zoals bij gemacereerde doodgeboorten. In de gepubliceerde literatuur is de casusselectie vaak niet beschreven, wat betrouwbare vergelijking moeilijk maakt.

Hoofdstuk 3: De perinatale obductie: belemmeringen in multicultureel West-Europa

In dit hoofdstuk beschrijven we verschillende factoren die het proces van de perinatale obductie en de counseling daarvan compliceren. Deze complicaties hebben geleid tot een gemiddeld obductiepercentage van slechts 38%. Dit is ruim onder de norm van 75%, die als minimum wordt voorgesteld door de Royal College of Obstetricians and Gynecologists en de Royal College of Pathologists.

De voornaamste oorzaak van de lage obductiepercentages is, dat het moeilijk is toestemming voor obductie te verkrijgen van de ouders. Daarnaast spelen een rol: negatieve media-aandacht over het achterhouden van organen na obductie (zoals het Alder-Hey schandaal), rapporten over verminderde kwaliteit van de obductie, en de aanname dat de huidige afbeeldende technieken de obductie kunnen vervangen.

De ouders moeten geïnformeerd worden over de procedure van de obductie. Over het algemeen houdt die een schouwing van het lichaam en van de organen in. Vervolgens wordt uit de organen enig weefsel genomen voor histologisch onderzoek. De organen worden teruggeplaatst, echter zonder het materiaal dat voor histologische onderzoek is uitgenomen. De coupes worden uiteindelijk opgeslagen voor eventuele aanvullende analyses of herbeoordeling.

Er zijn alternatieven voor obductie, zoals beperkte obductie of naaldbiopsie van mogelijk afwijkende organen, afbeeldende technieken als MRI en röntgenfoto's. Aan deze alternatieven zijn echter veel minder conclusies te verbinden dan de "gouden standaard", de obductie.

De grote religieuze stromingen en hun levenseinderituelen staan over het algemeen obductie toe. Sommige vereisen echter speciale behandeling of timing. In het Boeddhisme bijvoorbeeld moet het lichaam drie dagen ongestoord gelaten worden, zodat de ziel de "overgang" kan maken. In de Islam moet de obductie zo snel mogelijk gebeuren, aangezien de begrafenis de volgende dag voor zonsopgang moet plaatsvinden.De obductiepercentages zullen stijgen als artsen overtuigd zijn van de waarde van obductie en de ouders hierover informeren in het licht van hun culturele en religieuze achtergrond.

Hoofdstuk 4: Kwaliteit van placentarapporten

In dit hoofdstuk onderzoeken we de kwaliteit van de placentarapporten. Van 218 rapporten van vier ziekenhuizen haalde 2% de helft van het maximaal te halen punten niet en 31% scoorde tussen de 50 en 75% van het maximaal te halen punten.

Verschillende details van de rapporten vielen op. Slechts in 10% van de rapporten werd een placentagewicht zonder vliezen beschreven, hoewel dat de standaard is. Sommige onderdelen van de rapporten werden goed beschreven, zoals het aantal navelstrengvaten, de lengte en diameter van de navelstreng en de afmetingen van de placenta. Andere onderdelen werden matig beschreven, zoals het compleet zijn van de vliezen en de locatie van de vliesscheur. In bijna alle rapporten werd een blokcode gegeven per placentacoupe, wat belangrijk is voor het opvragen van coupes voor herbeoordeling of second opinion. Het bespreken van de bevindingen van de patholoog in relatie tot de klinische details verschilde per ziekenhuis en varieerde van 43 tot 94%. De beschrijving van normale bevindingen is even belangrijk als die van afwijkende bevindingen, omdat anders onduidelijk blijft of details bestudeerd zijn of niet. Een mogelijkheid voor goede communicatie tussen patholoog en clinicus gaat verloren als er inconsistent wordt gerapporteerd over (ab)normale bevindingen in de placenta.

Hoofdstuk 5: Histopathologisch onderzoek van de placenta: sleutelonderwerpen voor patholoog en obstetricus

In dit hoofdstuk illustreren we het belang van placentaonderzoek en goede communicatie tussen clinicus en patholoog. De placenta wordt vaak niet ingestuurd voor onderzoek wanneer de clinicus sceptisch is over de waarde van dat onderzoek. Als de placenta wel wordt ingestuurd moet de patholoog voldoende details krijgen over de omstandigheden van de zwangerschap en de medische voorgeschiedenis om de placentagegevens te kunnen interpreteren. Het aanvraagformulier voor het onderzoek zou het liefst gestandaardiseerd moeten zijn met een checklist voor belangrijke informatie voor de patholoog. De obstetricus zou vervolgens adequate informatie moeten krijgen van de patholoog om de gegevens van het microscopisch onderzoek te kunnen interpreteren. Dit zal de kans op het achterhalen van de doodsoorzaak vergroten en een optimale counseling voor de ouders betekenen.

Chronische villitis (lymfohistiocytaire ontsteking van de terminale villous) is een voorbeeld van een diagnose die door de patholoog wordt gesteld met consequenties voor een toekomstige zwangerschap. Het wordt geassocieerd met intra-uteriene groeibeperking, vroeggeboorte en doodgeboorte. Het heeft een herhalingsrisico tot 17%. In toekomstige zwangerschappen kan de groei van de foetus echoscopisch gevolgd worden. Acute chorioamnionitis (geassocieerd met pathogene vaginale micro-organismen) is een ander voorbeeld van een placentaire diagnose met een verhoogd herhalingsrisico en een mogelijke interventie.

De betrokkenheid van een patholoog in multidisciplinaire bijeenkomsten is nuttig voor uitleg en interpretatie van de histologische afwijkingen, ook in die gevallen, waarin op het oog de doodgeboorte onverklaard is.

Hoofdstuk 6: Villusimmaturiteit als belangrijke oorzaak voor a tèrme doodgeboorten

In dit hoofdstuk tonen we aan, dat villusimmaturiteit een belangrijke doodsoorzaak is in de à terme periode (zwangerschapsduur vanaf 252 dagen of 36 weken). Van de 1025 intra-uteriene sterftes die we geëvalueerd hebben, traden er 352 à terme op. Op basis van de doodsoorzaak werden de casus opgedeeld in drie groepen: villus immaturiteit, andere placentaire doodsoorzaken en niet placentaire doodsoorzaken. In 80% van deze casus werd de dood veroorzaakt door placentapathologie. In 29% daarvan was villusimmaturiteit de oorzaak. Van de casus met villusimmaturiteit als doodsoorzaak was in 48% villusimmaturiteit de enige afwijking, in 52% was er een combinatie met andere placentaire afwijkingen. Villusimmaturiteit als doodsoorzaak was geassocieerd met diabetes gravidarum. Er bleek eveneens een associatie te bestaan met placentahypoplasie in vergelijking met niet-placentaire doodsoorzaken.

Hoewel oligohydramnion twee keer vaker optrad bij villusimmaturiteit dan bij de niet placentaire oorzaken (23.1% vs 12.5%), was dat verschil statistisch niet significant. ($p = 0.139$). Er werd geen associatie gevonden met maternale diabetes mellitus, hypertensieve aandoeningen, intoxicaties of foetale karakteristieken als foetale groei of sexe.

Hoofdstuk 7: De Tulip-classificatie van perinatale sterfte, introductie en multidisciplinaire interbeoordelaarovereenstemming

We hebben een classificatiesysteem voor perinatale sterfte ontwikkeld, dat de doodsoorzaak (gedefinieerd als de initiële aantoonbare pathofysiologische entiteit welke de trein van gebeurtenissen start die uiteindelijk resulteren in sterfte) en het mechanisme van sterfte classificeert. Deze Tulip-classificatie kent 6 categorieën van doodsoorzaken: 1: Aangeboren afwijkingen, 2: Placenta, 3: Prematuriteit/immaturiteit, 4: Infectie, 5: Overige en 6: Onbekend. Deze hoofdcategorieën kennen weer subcategorieën. Zo bevat categorie 2 subcategorieën voor placentabedpathologie, placentapathologie en navelstrengcomplicaties. Het mechanisme van overlijden, gedefinieerd als het orgaanfalen dat incompatibel is met leven, en de oorsprong van het mechanisme, zoals luchtwegobstructie bij respiratoire insufficiëntie worden geclassificeerd. Tevens wordt dat

gedaan voor de bijdragende factoren (aandoeningen als hypertensie of pre-eclampsie of risicofactoren als roken). We geven duidelijke definities en richtlijnen voor toewijzing van casus in dit systeem.

Na de ontwikkeling van het systeem is het getest op de (interbeoordelaar)overeenstemming tussen vijf panelleden in 411 casus van perinatale sterfte. De grootste groep van doodsoorzaken bleek de groep van aangeboren afwijkingen te zijn (35%), de tweede en derde grootste groep waren placentaire oorzaken en prematuriteit/immaturiteit (respectievelijk 27% en 23%). Slechts 11% van de casus werd geclassificeerd als onbekend. De infectie en "overige" groep bevatten slechts respectievelijk 1% en 3%. De kappascore was 0.81 voor de hoofdcategorieën (0.89 na exclusie van misclassificatie door misinterpretaties van de richtlijn) en 0.67 voor de subcategorieën van sterfte (0.76 na exclusie van misclassificatie door richtlijn misinterpretaties). De overeenstemming was het hoogste in de categorie van aangeboren afwijkingen en het laagste in de categorie "overige". Voorbeeldcasus werden gegeven om een aantal ingewikkelde details in het classificatiesysteem te verduidelijken.

Hoofdstuk 8: Een placentaire oorzaak van doodgeboorte hangt af van het gebruikte classificatiesysteem voor perinatale sterfte

Verschillen tussen classificatiesystemen voor perinatale sterfte hebben consequenties voor getallen in de statistieken. We hebben dit geïllustreerd door in een panel 485 intra-uteriene sterftes te classificeren in acht classificatiesystemen voor perinatale sterfte (extended Wigglesworth, modified Aberdeen, ReCoDe, Tulip, en de classificatiesystemen door Hey et al., Hovatta et al., de Galan-Roosen et al. en Morisson et al.). De verdeling van de casus in de verschillende categorieën varieerde tussen de systemen, vooral in de placentacategorieën en de groep "onbekend". Het percentage van de casus geclassificeerd in de placentagroepen varieerde van 0% (geen placentacategorie in het systeem) tot 64.3% in de Tulip-classificatie. In sommige systemen was de categorie met onbekende doodsoorzaak de grootste, zoals in de extended Wigglesworth (88.5%), terwijl in andere systemen, zoals in dat van Hey et al., geen enkele casus werd geclassificeerd als onbekend of niet classificeerbaar. In dit systeem werden echter wel 88.4% van de casus geclassificeerd in de groep: "antepartum asfyxie" wat in feite een onbekende doodsoorzaak is.

De systemen die geen placentacategorieën hebben en die de meeste casus in de onbekende categorieën classificeren en de systemen die alleen klinische manifestaties classificeren, discrimineren niet voor de onderliggende doodsoorzaak.

Bij het classificeren van de 485 casus in de verschillende systemen bleek de grootste groep van sterfte veroorzaakt door placentapathologie wanneer de onderliggende doodsoorzaak wordt geclassificeerd. De meest voorkomende bijdragende factor (aandoening) was daarbij intra-uteriene groeibeperking.

Hoofdstuk 9: Een gelaagde benadering voor de analyse van perinatale sterfte met gebruik van bestaande classificatiesystemen

We hebben 35 classificatiesystemen voor perinatale sterfte, gepubliceerd na 1954, gevonden. Alle systemen hebben hun eigen sterke en zwakke punten, maar er is geen enkel systeem dat universeel gebruikt wordt. In dit hoofdstuk stellen we een gelaagde benadering van perinatale sterfte voor met gebruik van verschillende bestaande classificatiesystemen. Deze benadering is gebaseerd op informatie over het moment van overlijden, aandoeningen geassocieerd met de sterfte en de onderliggende doodsoorzaak. Drie vragen in volgorde van complexiteit kunnen worden gesteld: *Wanneer gebeurde het?* Wat was de zwangerschapsduur? Gebeurde het antepartum, intrapartum of in de neonatale periode? Twee van de gevonden systemen concentreren zich vooral op wanneer sterfte optrad. Beide bevatten ook een groep voor letale aangeboren afwijkingen. Voor betrouwbare classificatie in deze systemen is schouwing van de foetus noodzakelijk. De volgende vraag die beantwoord kan worden is: *Wat gebeurde er?* Wat waren de foetale, maternale en of placentaire aandoeningen die bijdroegen aan de sterfte? Om deze vraag goed te beantwoorden is meer onderzoek nodig: analyse van de klinische situatie, schouwing van de foetus en placenta en het liefst ook obductie. De meeste van de systemen classificeren "wat er gebeurde". De laatste en meest ingewikkelde vraag is: *Waarom gebeurde het?* Wat is de onderliggende doodsoorzaak? (initiële aantoonbare pathofysiologische entiteit welke de trein van gebeurtenissen start die uiteindelijk resulteren in sterfte) Uitgebreide analyse inclusief microscopisch onderzoek van de placenta en obductie zijn nodig voor betrouwbare classificatie. Slechts twee systemen classificeren de onderliggende doodsoorzaak.

Indien doodsoorzaken en aandoeningen door elkaar worden gebruikt kan dat resulteren in overlap tussen de categorieën en dus niet-uniforme classificatie. Informatie gaat dan verloren en vergelijking van getallen is onbetrouwbaar. Als doodsoorzaken en aandoeningen apart van elkaar worden gebruikt vullen ze elkaar juist aan, wat ons de gelaagde benadering doet voorstellen.

Voor audit van sterfte kunnen kruistabellen van de verschillende systemen worden gebruikt om de relatie tussen periode van sterfte, aandoeningen en onderliggende doodsoorzaak te vinden met mogelijk het gebruik van substandaardfactoren.

Dankwoord

Zonder mijn co-promotoren Jan Jaap Erwich en Bert Timmer was dit proefschrift er niet geweest. Jan Jaap, bedankt, je stelde me eerst in de gelegenheid om van het onderzoek naar perinatale sterfte mijn hobby te maken, later wees je me op de mogelijkheid om er op te promoveren. Bedankt voor de inspiratie tot dit proefschrift en je betrokkenheid bij het tot standkomen ervan. Bert, bedankt voor al je goede adviezen en kritische blik. Als patholoog was je bij dit onderzoek absoluut onmisbaar. Je leerde me naar placenta coupes kijken met de ogen van een patholoog. We waren het –zij het via een omweg- eigenlijk altijd met elkaar eens.

Yee Khong has been of great value for the basis of my thesis. Yee, thank you so much for your advice and patience during my first steps in the world of scientific investigation. I have learned a lot in the period in Adelaide and enjoyed it that much that I even have given serious consideration to become a perinatal pathologist.

Mijn grote steun en toeverlaat waren Jozien Holm en Fleurisca Korteweg. Jozien, ik had geen betere promotor kunnen wensen! Bedankt voor je voortvarendheid, je betrokkenheid bij het onderzoek en je hulp in lastige periodes. Ik kijk met groot genoegen terug op de contacten die we de afgelopen jaren hadden, zowel op het gebied van onderzoek als daarbuiten. Fleur, van jou leerde ik dat doorzettingsvermogen en optimisme binnen het onderzoek belangrijke kwaliteiten zijn. Jij beschikt er in ruime mate over. Bedankt voor de samenwerking, die van mij nog tijden mag duren!

Voor datamanagement en statistiek wil ik Joke Ravisé en Nic Veeger bedanken. Joke, ondanks de drukte wist je steeds tijd voor me vrij te maken, sterker: je liet me geloven dat je er op zat te wachten Onoverzichtelijke getallenreeksen zette je om in bruikbare tabellen, ik ben je daar heel dankbaar voor.

Nic, bedankt voor je statistische ondersteuning bij mijn laatste artikel. Ik was onder de indruk van je oneindige geduld bij al mijn vragen. Je passie voor getallen is inspirerend.

De laatste plaats is voor degenen die voor mij op de eerste plaats staan. Bas en Guus, ik ben er weer!

GRADUATE SCHOOL FOR HEALTH RESEARCH SHARE

This thesis is published within the Graduate School for Health Research SHARE (embedded in the University Medical Center Groningen / University of Groningen).
More information regarding the institute and its research can be obtained from our internetsite: www.rug.nl/share.

Recent dissertations:

Boersma C (2009) *Health economics of cardiovascular & renal disease prevention*
Supervisors: prof dr MJ Postma, prof dr LTW de Jong-van den Berg,
prof dr PE de Jong
Co-supervisor: dr T Gansevoort

El-Sayed Hussein El-Baz N (2009) *Effect of clinical pathway implementation and patients' characteristics on outcomes of coronary artery bypass graft surgery*
Supervisor: prof dr SA Reijneveld
Co-supervisors: dr LJ Middel, dr JP van Dijk, dr PW Boonstra

Buitenhuis J (2009) *The course of whiplash; its psychological determinants and consequences for work disability*
Supervisors: prof dr JW Groothoff, prof dr PJ de Jong
Co-supervisor: dr JPC Jaspers

Soer R (2009) *Functional capacity evaluation; measurement qualities and normative values*
Supervisors: prof dr JHB Geertzen, prof dr JW Groothoff
Co-supervisors: dr MF Reneman, dr CP van der Schans

Knibbe M (2009) *'Not a matter of choice'. Ethical perspectives on decision making about living parental liver donation*
Supervisors: prof dr MA Verkerk, prof dr MJH Slooff
Co-supervisor: dr ELM Maeckelberghe

Santvoort, MM van (2009) *Disability in Europe; policy, social participation and subjective well-being*
Supervisor: prof dr WJA van den Heuvel
Co-supervisors: dr JP van Dijk, dr LJ Middel

Stewart RE (2009) *A multilevel perspective of patients and general practitioners*
Supervisors: prof dr B Meyboom-de Jong, prof dr TAB Snijders,
prof dr FM Haaijer-Ruskamp

Vroom F (2009) *Drug use in pregnancy; exploring the field of DMARDs in pregnancy*
Supervisors: prof dr LTW de Jong-van den Berg, prof dr JRBJ Brouwers,
prof dr MAFJ van de Laar
Co-supervisor: dr HEK de Walle

Jong J de (2009) *The GALM effect study; changes in physical activity, health and fitness of sedentary and underactive older adults aged 55-65*
Supervisor: prof dr EJA Scherder
Co-supervisors: dr KAPM Lemmink, dr M Stevens

Berendsen, A. (2009) *Samenwerking tussen huisarts en specialist*
Supervisor: prof dr B Meyboom-de Jong
Co-supervisor: dr J Schuling