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A Placental Cause of Intra-uterine Fetal Death Depends on the Perinatal Mortality Classification System Used

F.J. Korteweg [a], S.J. Gordijn [a], A. Timmer [b], J.P. Holm [a], J.M. Ravisé [a], J.J.H.M. Erwich [a,*]

[a] Department of Obstetrics and Gynaecology, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands
[b] Department of Pathology, University Medical Centre Groningen, The Netherlands

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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.

Keywords: Placental cause of death; Classification system; Intra-uterine fetal death; Antepartum stillbirth

1. 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

* Corresponding author. Tel.: +31 50 3613020.
E-mail address: j.j.h.m.erwich@og.umcg.nl (J.J.H.M. Erwich).

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[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.

2. Materials and methods

In 2002 we initiated a national study on IUFD at the University Medical Centre 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 $<$10th 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.

3. 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.

3.1. 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, villus 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