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Classification of stillbirths is an ongoing dilemma

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Abstract

Aim: To compare different classification systems in a cohort of stillbirths undergoing a comprehensive workup; to establish whether a particular classification system is most suitable and useful in determining cause of death, purporting the lowest percentage of unexplained death.
Methods: Cases of stillbirth at gestational age 22–41 weeks occurring at the Department of Gynecology and Obstetrics of Foggia University during a 4 year period were collected. The World Health Organization (WHO) diagnosis of stillbirth was used. All the data collection was based on the recommendations of an Italian diagnostic workup for stillbirth. Two expert obstetricians reviewed all cases and classified causes according to five classification systems.
Results: Relevant Condition at Death (ReCoDe) and Causes Of Death and Associated Conditions (CODAC) classification systems performed best in retaining information. The ReCoDe system provided the lowest rate of unexplained stillbirth (14%) compared to de Galan-Roosen (16%), CODAC (16%), Tulip (18%), Wigglesworth (62%).
Conclusion: Classification of stillbirth is influenced by the multiplicity of possible causes and factors related to fetal death. Fetal autopsy, placental histology and cytogenetic analysis are strongly recommended to have a complete diagnostic evaluation. Commonly employed classification systems performed differently in our experience, the most satisfactory being the ReCoDe. Given the rate of "unexplained" cases, none can be considered optimal and further efforts are necessary to work out a clinically useful system.

Keywords: Cause of death; classification systems; pregnancy complications; stillbirth; unexplained fetal death.

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Introduction

Stillbirth is defined as death before expulsion or extraction of the fetus from the mother. It is determined by no signs of life after delivery. World Health Organization (WHO) recommendations define stillbirth as fetal death at 22 weeks of gestation or greater or birthweight higher than 500 g if the gestational age is unknown. If neither weight nor gestational age is available, crown-heel length ≥25 cm is used as a criterion for reporting fetal death and distinguishing a fetal death from a miscarriage [1].

Despite intensive obstetric surveillance, stillbirths rate at gestational age >22 weeks has remained constant for the past three decades, still a major problem in developed countries, ranging from 3 to 5.3 per 1000 births [2, 3].

Classifying perinatal deaths improves the understanding of the etiology of perinatal mortality and enables the causes to be ranked in order of frequency of occurrence. However, because of the complicated pathophysiologic processes involving mother, fetus and placenta, and the fact that stillbirths often result from interaction of different processes, univocal classifications are often difficult to assess [4]. Up to 35 classification systems have been developed to define stillbirth and there is no international consensus on which one to be used. Furthermore, the definition of stillbirth varies among investigators and many systems are developed including both stillbirth and perinatal neonatal mortality, including all cases of perinatal death, thus increasing the variability in literature results.

The goal of a classification system for registration of stillbirth should be to give as much insight as possible in the underlying causes of death by retaining important information. The purpose of a classification is to identify the deficiencies in the provision of care, to focus attention where improvements are already possible and to

indicate where new developments may be expected to lead to further advance, in order to recognize preventive measures that can be used for lowering mortality rates in the future. A good classification system should be easy to understand and apply, easy to expand in terms of sub-classification, result in a high percentage of classifiable cases and low percentage of unexplained cases and have high inter-observer agreement. The main sources of important information about stillbirth come from the placenta, the fetal karyotype, the maternal and fetal health and history and the autopsy [5].

Five important classification systems have to be mentioned: Wigglesworth [6], de Galan Roosen [7], ReCoDe [8], Tulip [9], CODAC [10].

Aim of the study

The aim of this study is to compare different classification systems in a cohort of stillbirths undergoing a comprehensive workup. We also aim to establish whether a particular classification is most suitable and useful in determining the cause of death and has lower percentage of unexplained deaths.

Methods

This study collected a cohort of cases of stillbirth occurred at the Department of Gynecology and Obstetrics of Foggia University between 2010 and 2013. The WHO diagnosis of stillbirth has been used [1]. Gestational age ranged between 22 and 41 weeks of gestation. For each case the data collection included date of delivery, gestational age (g.a.), parents' familial and personal history, histological examination of the placenta, fetal sex and birth weight, fetal autopsy, maternal blood group, results of lab tests, pregnancy details, delivery details. All the data collection was based on the recommendations of an Italian diagnostic workup for stillbirth [11, 12]. All autopsies of the fetus and placental examinations were performed according to established international guidelines [13]. All patients gave their consent for the publication of the reported data.

Two expert obstetricians reviewed all cases and classified each of them according to the chosen classification system for characterization of causes of stillbirth: Wigglesworth [6], de Galan-Roosen [7], ReCoDe [8], Tulip [9], CODAC [10]. The principles of the Helsinki Declaration were followed.

Statistical analysis

This was a cohort retrospective observational study. All data were analyzed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

Results

Fifty cases of stillbirth were registered during the study period. Clinical records, laboratory tests, histological examination of placenta and autopsy were available for all patients. Mean gestational age at delivery was 31.6 weeks, median 31.8 (range 22–41 weeks). Forty-six were singleton pregnancies (92%), two were bichorionic biamniotic twin pregnancies (4%) and two monochorionic biamniotic twin pregnancies (4%). Death of both twins occurred in one bichorionic biamniotic pregnancy, death of only one twin in the others.

Chorionamnionitis was recorded in 11 cases (22%), placental pathology in 33 (66%), umbilical cord anomalies in 19 (38%), fetal malformations in four (8%), IUGR in seven (14%). Four mothers were affected by gestational diabetes (8%) and three from gestational hypertension (6%). None of the cases of congenital malformation has been considered as cause of death. The anomalies were congenital foot deformity, congenital spina bifida, syndactyly of the hand, common mesentery. No fetuses presented abnormal karyotype. More than one condition can be related to a single case. Associated conditions do not necessarily explain fetal death.

The Wigglesworth classification, as presented in Table 1, defined seven cases (14%) belonging to group 4 (asphyxial conditions developing in labor). Five of them were associated with abruption, so they were included in subgroup 4-b. The remaining 43 cases belong to group 5 (specific conditions other than above), including: 11 specific infections (22%), one twin to twin transfusion syndrome (2%), 31 unexplained fetal deaths (62%). Twenty-seven out of 50 (54%) did not have any sign of maceration. The remaining 23/50 (46%) presented any grade of maceration. Maceration was defined by authors as a fetal characteristic, not as a cause of death. All fetuses presenting maceration were classified in the group "specific conditions other than above", according to Wigglesworth classification.

According to de Galan-Roosen classification (Table 2), the causes underlying fetal death were classified as

Table 1: Application of Wigglesworth classification.

Group	Primary classification	n	%
1	Normally formed macerated stillbirth – death before the start of labor	0	0
2	Congenital malformations	0	0
3	Conditions associated with immaturity	0	0
4	Asphyxial conditions developing in labor	7	14
5	Specific conditions other than above	43	86

Table 2: Application of de Galan-Roosen classification.

Classification	Subclassification	n	%
1. Trauma	[…]	0	0
2. Infection	1. Antenatal		
	a) Hematogenous	0	0
	b) Transamniotic	10	20
	2. Postnatal	0	0
3. Placental/cord pathology	1. Acute/subacute	8	16
	2. Chronic/progressive	24	48
4. Maternal immune system pathology	[…]	0	0
5. Congenital malformations incompatible with life	[…]	0	0
6. Prematurity/immaturity complications	[…]	0	0
7. Unclassifiable	1. Despite thorough investigation	8	16
	2. Important information missing	0	0

follows: 10 antenatal transamniotic infection (group 2.1.b), of whom one specifically due to aspiration pneumonia. Thirty-two cases for placental/cord pathology, in particular eight due to acute placental event – fetal asphyxia (group 3.1), and 24 due to chronic placental pathology (group 3.2). Eight cases were unclassifiable despite thorough investigation (group 7.1).

The ReCoDe classification (Table 3), revealed three cases (6%) to belong to group A (fetus). All of them were related to subgroup 7: fetal growth restriction. Two cases (4%) were classified in group B (umbilical cord): one sub-classified as B2 (constricting loop or knot) and one B3 (velamentous insertion). Twenty-six cases (52%) were in group C (placenta): five in subgroup C1 (abruptio), five in subgroup C4 (other placental insufficiency), 16 in subgroup C5 (other placental pathology). Eleven cases (22%) were in group D (amniotic fluid), all of them classified in subgroup D1 (chorioamnionitis). One case (2%) was attributed to group G (intrapartum event), subgroup G1 (intrapartum asphyxia). Seven cases (14%) were classified in group I, all of them because of "no relevant condition identified" (group I1). In 13 cases a secondary code was attributed, in order to increase descriptiveness while maintaining the hierarchy of primary conditions, to reflect clinical relevance.

The Tulip classification (Table 4) identified 30 cases due to placental cause (60%): five of them subclassified in group "placental bed" (16.7%), 24 because of "placental pathology" (80%), of whom three due to development disorders, 21 because of parenchymal causes. One belonged to the "umbilical and cord complications" subclassification (3.3%). Eleven cases were due to infection, all of them belonging to the non otherwise specified (NOS) group (22%). Nine cases were classified as "unknown cause" (18%).

Table 3: Application of ReCoDe classification.

Group	Classification	Subclassification	n	%
A	Fetus	1. Lethal congenital anomaly	0	0
		2. Infection […]	0	0
		3. Non-immune hydrops	0	0
		4. Iso-immunization	0	0
		5. Fetomaternal hemorrhage	0	0
		6. Twin-twin transfusion	0	0
		7. Fetal growth restriction	3	6
		8. Other	0	0
B	Umbilical cord	1. Prolapse	0	0
		2. Constricting loop or knot	1	2
		3. Velamentous insertion	1	2
		4. Other	0	0
C	Placenta	1. Abruptio	5	10
		2. Praevia	0	0
		3. Vasa Praevia	0	0
		4. Placental insufficiency / infarction	5	10
		5. Other	16	32
D	Amniotic fluid	1. Chorioamnionitis	11	22
		2. Oligohydramnios	0	0
		3. Polyhydramnios	0	0
		4. Other	0	0
E	Uterus	[…]	0	0
F	Mother	[…]	0	0
G	Intrapartum	1. Asphyxia	1	2
		2. Birth trauma		
H	Trauma	[…]	0	0
I	Unclassified	1. No relevant condition identified	7	14
		2. No information available	0	0

Table 4: Application of Tulip classification.

Code	Cause of death	Subclassification	n	%
1	Congenital anomaly	[…]	0	0
2	Placenta	1. Placental bed pathology	5	10
		2. Placental pathology (1. Development, 2. Parenchyma, 3 localization)	24	48
		3. Umbilical cord complication	1	2
		4. NOS	0	0
3	Prematurity/ immaturity	[…]	0	0
4	Infection	1. Transplacental	0	0
		2. Ascending	0	0
		3. Neonatal	0	0
		4. NOS	11	22
5	Other	[…]		
6	Unknown	1. Despite thorough investigation	9	18
		2. Important information missing		

Table 5: Application of simplified CODAC classification.

COD		n	%
0) Infection	0.00 Unknown	11	22
	[…]	0	0
1) Neonatal	[…]	0	0
2) Intrapartum	[…]	0	0
	0.29 Unknown (fetal respiratory failure/asphyxia)	2	4
3) Congenital anomaly	[…]	0	0
4) Fetal	[…]	0	0
5) Cord	0.51 Knots	0	0
	0.52 Loops	1	2
	0.53 Abnormal insertion	0	0
6) Placenta	0.63 Abruption	5	10
	0.64 Infarction and thrombi	22	44
7) Maternal	0.71 Hypertensive disorders	0	0
	0.73 Diabetes	1	2
	0.79 Infection	0	0
8) Unknown	0.81 Unknown	8	16
	0.85 Unexplained	0	0
	0.86 Unclassifiable	0	0
9) Termination	[…]	0	0

Finally, we classified our cases according to CODAC classification (Table 5) by identifying one main cause of death (COD) and an associated condition (AC or secondary COD). Eleven cases had infection of unknown origin as a COD (0.00), of whom five had extreme prematurity (1.11) as AC and one had neonatal infection (1.19). Two cases had intrapartum event of unknown origin, related to fetal respiratory failure or asphyxia (COD 2.29). One was due to cord loops (COD 5.52). Twenty-seven cases were related to placental cause: five due to placental abruption (COD 6.63) and 22 due to placental infarction and thrombi (COD 6.64). Most of them were related to associated conditions, including cord complications, maternal hypertension, maternal infection, neonatal cardio-respiratory causes. One case had maternal diabetes as main COD (7.73), and small for gestational age as AC (8.81). In eight cases (16%) the COD was unknown (COD 8.81).

Discussion

The cause of stillbirth is often difficult to identify because a great number of factors may contribute to this event and many causes can be considered as responsible or risk factors for stillbirth itself. Moreover, tests and investigations have been developed in order to recognize factors related to fetal death, even if the detection of a positive test does not necessarily explain the stillbirth [14]. Autopsy, karyotype, placental histopathological examination and evaluation of a potential maternal-fetal hemorrhage should be considered at the basis of the workup aimed at identifying causes of stillbirth [15, 16]. A detailed overview of events related to fetal deaths is needed to give correct explanation to parents about the reason why their baby died, whether they are exposed to an increased risk for similar events in future pregnancies and to clarify the pathogenetic mechanisms in order to develop prevention strategies [17]. The most useful information about the specific causes of stillbirth comes from hospitals or regions that systematically review and classify these deaths over time. In our experience, complete workup recommendations, drawn up after a workshop discussion by an expert study-group, guided a complete collection of data and specific issues [11].

Many classification systems have been published in an attempt to recognize the most important issues and establish a hierarchy of relevance. They differ in terms of clinical approach, level of complexity, definitions. All of them have their own strong and weak points and none have been universally accepted. Older systems included only a small number of categories [6], while subsequent systems attempted to capture more information, including aberrations of fetal growth, placental pathology and maternal conditions [7–10]. In order to overcome the limitations, some authors presented a systematic multilayered approach of the analysis of perinatal mortality using a combination of existing classification systems, in order to provide a complete analysis that may reveal new associations between clinical conditions and causes of death [18].

In our study we considered five of the most frequently used classification systems. Wigglesworth is an old pathophysiological classification system, developed in 1980 and extended later on. It has the purpose to subdivide cases into five groups with clear implication for clinical management. It focuses on the moment of mortality and only requires macroscopic fetal examination to allocate the cases to the categories [6, 19]. The de Galan-Roosen classification system, developed in 2002, uses simple principles of obstetrical and neonatal pathology based on the factor that initiated the train of events leading to death, according to the principle that causes of pregnancy loss and perinatal death are limited to a small number of classic categories underlying pathological conditions [7]. The Relevant Condition at Death (ReCoDe) classification system, published in 2005, seeks to identify a relevant condition at the time of death in utero. It is a hierarchical system aiming to establish what went wrong, not necessarily why. The hierarchy starts from conditions affecting the fetus and moves outwards in groups which are subdivided into pathophysiological conditions. The primary

condition should be the first one applicable to each case and a secondary coding can be used to increase the descriptiveness while maintaining a hierarchy to reflect clinical relevance. This system is developed exclusively for stillbirth [8]. The 2009 Tulip classification aims to identify a single demonstrable pathophysiological cause for the death. It consists of six groups of main causes and six perinatal mortality mechanisms and "origin of the mechanism" of death, drawn up by a panel through the causal analysis of events related to death [9]. The CODAC system is developed to describe the cause of death (COD) and two associated conditions (AC), which are considered as secondary COD. To classify in CODAC only a minimum of information are needed, but more detailed information usually allow a more detailed classification [10].

In our study the main causes of stillbirth have been reviewed according to these classification systems. Placental pathology involved more than 50% of cases according to each classification system, apart from Wigglesworth classification, that does not include details about placental examination. This is a higher percentage compared to the rate of placental cause described in literature. A large number of studies analyzed the placental findings both in stillbirth and in live births [20–22]. A recent one stated how the prevalence of any specific placental finding rarely exceeded 30% and the most common placental findings were inflammatory and thrombotic lesions and retroplacental hematoma, reflecting the heterogeneity of placental conditions associated with stillbirth. Single umbilical artery, diffuse terminal villous immaturity, avascular villi and placental edema also represent less frequent pathological findings related to stillbirth. All these lesions are not exclusively found in stillbirths, this suggesting the uncertainty about the cause and effect. However, knowledge of lesions prevalence within gestational age groups in both stillbirth and life birth controls contributes to an understanding of the association between placental pathology and stillbirth itself [23, 24]. Considering that the placental pathology is the largest cause of death group, any classification system not encompassing placental causes of death, such as Wigglesworth, is not useful in modern workup of fetal deaths [14].

Infection was described as the second cause of death, found in more than 20% of cases in our study, according to de Galan-Roosen, ReCoDe, Tulip and CODAC classification. These data are comparable to literature results, reporting that in developed countries 10–25% of stillbirth appear to be caused by maternal or fetal infection [25–27].

Other causes related to fetal death in our study were less frequently identified by the different classification systems. Asphyxia was detected 14% of stillbirth according to the Wigglesworth system and in 4% according to CODAC, 2% according to ReCoDe.

Fetal growth restriction was identified as a relevant condition in ReCoDe classification in 6% of cases. Stillbirth is strongly related to impaired fetal growth. The vital role of the placenta in determination of optimal fetal development has to be considered. Given these results, a correct assessment of fetal growth is an important matter of debate and stillbirth prevention strategies should focus on pregnancies with impaired growth [28–30]. In our study the introduction of fetal growth restriction in ReCoDe classification system allowed a further reduction of unexplained stillbirth, both ReCoDe and CODAC performing best in retaining important information [14].

Large studies identified further probable or possible causes of death in the past. As an example, fetal genetic or structural abnormalities have been mentioned as causes in 13.7–21.5% of cases [31, 32]. Our sample did not reveal any important genetic or morphological abnormalities related to fetal death. Minor or non-lethal anomalies were registered but not considered as causal. This result can be related to the relatively small sample or probably because of the differences in the examined population. It is noticeable that the gestational age in the mentioned studies is lower, since stillbirth is defined as fetal death at 20 weeks of gestation or later and younger fetuses tend to have more genetic or lethal structural abnormalities.

The rate of unexplained stillbirth ranges from 9 to 71% in literature, depending on the quality of information available and on the chosen classification system. Usually systems capable of detailing as much information as possible are related to lower percentage of unexplained death [33]. In our study the rate of unknown cause was 14% in ReCoDe, 16% in de Galan-Roosen and CODAC, 18% in Tulip, 62% in Wigglesworth classification. According to literature, Wigglesworth result in a large proportion of unexplained stillbirths (up to 50.2%), while ReCoDe performed best in our cohort, as in other reports (13.8%) [5].

Finally, as a high inter-rater agreement rate is an important requirement for any classification system, reported inter-rater agreement rates have to be mentioned: Tulip classification has the best kappa coefficient (0.86 for main cause of death), followed by de Galan-Rosen (0.70), CODAC and ReCoDe (0.65 and 0.51, respectively) and Wigglesworth (0.25) [5].

Conclusion

Classification of stillbirth is an ongoing dilemma, influenced by the multiplicity of possible causes and factors

related to fetal death. It has to provide the clinician a guide in the identification of possible causal pathways for stillbirth, in the presence of more than one risk factor. Fetal autopsy, placental histology and cytogenetic analysis are strongly recommended. The obstetrician has to know that the positivity of one test does not necessarily explain the fetal death and different conditions may be considered as causes or risk factors. Optimizing the rate of retained information and minimizing the unexplained stillbirths is a fundamental goal of any classification system, in order to provide explanation to parents and to better understand the pathophysiological mechanisms underlying death and the possible preventing actions. Commonly employed classification systems performed differently in our experience, the most satisfactory being the ReCoDe. Given the rate of "unexplained" cases, none can be considered optimal and further efforts are necessary to work out a clinically useful system.

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