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Stillbirth - where are we and what can we do?

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Abstract:
Background*: Stillbirth is the most prevalent adverse outcome in pregnancy and remains a challenge in our clinical practice. The aim of this study is to determine the causes of stillbirth in the last 11 years, in a tertiary hospital.*
Materials and Methods*: Descriptive, retrospective study on fetal deaths that occurred between 2008 and 2018, in a tertiary hospital.*
Results*: In the last 11 years, 84 stillbirths have occurred. The fetal mortality rate was 2.8 ‰. There was an absence of pregnancy surveillance in only 2% of cases and late surveillance in 11% of pregnant women monitored. 88% of the analyzed pregnancies were unifetal and 12% multiple. 93% of stillbirths occurred antepartum and 7% intrapartum. Most were late stillbirths (79%), occurring after 28 weeks of gestation. The average gestational age at diagnosis was 32 weeks and the birth weight was 1630g. Anatomopathological study was performed in 92% of the fetuses and 95% of the placentas. In 11 cases, the cause remained unknown, despite the clinical, analytical and anatomopathological studies carried out. The most frequent causes of fetal death were: Umbilical cord abnormalities (14.3%), placental abruption (13.1%) and genetic or structural fetal anomalies (9.5%).*
Conclusion:*Despite the correct gestational surveillance, the number of fetal deaths remains constant. The use of a study protocol in cases of fetal death is essential to determine the causes and possible establishment of new strategies. For now, most of the causes reported in this study do not appear to be preventable.*
Key Word*: Stillbirth; Fetal Death; Pregnancy Outcome; Pregnancy Complications.*

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I. Introduction

Stillbirth is defined as that which occurs after 22 weeks of gestation or with a weight ≥500 g, according to the World Health Organization (WHO). [1] Worldwide, the fetal mortality rate is about 15 deaths/1000 live births. The rate in developed countries is significantly lower, approximately 3 deaths/1000 live births. This is mainly due to different health care systems between countries. [2] In Portugal the rate of late fetal mortality in 2019 was 2.3 ‰. [3] There are no data that include early fetal mortality. Although the Portuguese National Institute of Statistics reports stillbirths, there is no systematic investigation protocol that is used by all health institutions. In addition, in most international studies, the anatomopathological study of the fetus and/or placenta was not performed. [4] Risk factors associated with fetal death include maternal medical disorders, namely diabetes mellitus and hypertension, nulliparity, smoking or toxicophilic habits, advanced maternal age and previous fetal death. [5] The causes of stillbirths in developed countries seem to be mainly associated with congenital anomalies, placental abnormalities and maternal medical disorders. [6] Information on causes of fetal death in Portugal is limited. The aim of this study is to determine the causes of fetal death in a tertiary hospital in Portugal.

II. Material And Methods

Descriptive, retrospective study on stillbirths that occurred in 11 years, between 2008 and 2018, in a tertiary hospital in Portugal. This report contains data from the Perinatal Mortality Data File from the National Statistics System of DireçãoGeral de Saúde (DGS). These statistics contains information from all reports of fetal death filed in our institution. Only fetuses with gestational age over 22 weeks and weight over 500g were included. Medical terminations of pregnancy were not included in this study. All fetal deaths were assessed according to the service's protocol, with the necessary clinical data collected, including demographic characterization and parameters related to birth. An anatomopathological study of the placenta and fetus was also carried out and a maternal analytical study was carried out whenever justified (research of infections, cultures, HbA1c, TSH and free T4, indirect Coombs, measurement of toxins in the urine and study of thrombophilia). Causes of death were classified according to the Modified Stillbirth Collaborative Research Network classification system. [7]

Study Design: Descriptive, retrospective study
Study Location: This was a tertiary care teaching in Portugal.

Study Duration:2008 to 2018.
Sample size: 84.

Statistical analysis

The constitution and manipulation of the database, as well as the statistical analysis were performed using the SPSS program version 23. A descriptive analysis of the distribution of patients was carried out, considering various sociodemographic variables. Categorical variables are presented as frequencies and percentages and continuous variables as means and standard deviations or medians and interquartile ranges. The test for normal data distribution was performed using the Shapiro-Wilk test or by analyzing the values of skewness and kurtosis. Categorical variables were compared with the use of Fisher's exact test or the chi-square test, as appropriate.

III. Result

In the past 11 years, there have been 84 stillbirths. The fetal mortality rate was 2.8 ‰. The number of stillbirths over the years and the respective fetal mortality rate can be seen in graphic 1. There was a slight decrease in 2011, remaining, afterwards, practically constant. The demographic characterization is described in table 1. The average maternal age was 32 years (SD 4.936), with 30% having advanced maternal age (≥ 35 years old). The average parity was 0.7 (SD 0.827). 37 (44%) had comorbidities, with emphasis on hypertensive disorders, diabetes and thrombophilia. One of the women suffered from chronic alcoholism and another had syphilis during pregnancy. None of the women were HIV positive or had toxicophilic habits. None had a history of previous fetal death. 10 stillbirths occurred in multiple pregnancies. There was an absence of pregnancy surveillance in only 2% of cases and late surveillance in 11% of pregnant women monitored. Most fetal deaths occurred antepartum, as described in table 1. Early stillbirths (from 22 to 27 weeks of gestation) occurred in 21% of the sample (N = 18) and late stillbirths (gestational age 28 weeks) in 79% (N = 66). 64 (76%) were preterm (<37 weeks) and 2 (2%) post-term pregnancies (41 weeks). Of the 6 cases of intrapartum fetal death, 2 were preterm and one post-term. The average gestational age at diagnosis was 32 weeks (SD 4,098) and birth weight 1630 g (SD 882,995). Most had vaginal deliveries. An autopsy was performed on 77 fetuses (92%) and an anatomopathological study of 80 placentas (95%). The placental findings are shown in table 2. Umbilical cord thrombosis and placental infarction were the most frequently observed abnormalities in the pathological anatomy of the placenta.

The conditions that contributed to fetal death were classified according to the Modified Stillbirth Collaborative Research Network classification system, and are listed in table 3. In 11 cases (13%), the cause remained unknown, despite the clinical, analytical and anatomopathological studies carried out, according to the institution's protocol. The most frequent causes of fetal death were: pathological conditions of the placenta (32%) and clinical obstetric complications (29%). Of the pathological conditions of the placenta, the most frequent corresponded to anomalies of the umbilical cord (14.3%), and of the obstetric clinical complications, the most frequent was placental abruption (13.1%). Fetal genetic or structural abnormalities were found in 9.5% of cases. 9.5% of fetal deaths were secondary to maternal conditions. The 4 cases associated with diabetes had poor metabolic control. There was also a case of uterine rupture not in labour, with consequent hypovolemic shock. Infection was found in 6 cases (7%), and it was possible to isolate the etiologic agent in 4 of these: Ureaplasma spp., Gardenerella vaginalis, Mycoplasma hominis and E.coli. Two cases had negative cultures despite histological findings compatible with chorioamnionitis.

Table no 1: Demographic characterization and stillbirths.

Maternal age (years), N (%)			
	< 18		0
	18-35		59 (70,2)
	>= 35		25 (29,8)
Parity, N (%)	0		40 (47,6)
	1-4		44 (52,4)
	>= 5		0
Medical history, N (%)	Hypertensive disorder		7 (8,3)
		Gestational hypertension	2 (2,4)
		Chronic hypertension	5 (6,0)
	Diabetes		11 (13,1)
		Gestational diabetes	8 (9,5)
		Previous diabetes	3 (3,6)
	Thrombophilia		6 (7,1)
	Thyroid disorder		5 (6,0)
	Other disorders		8 (9,5)
Timing ofstillbirth, N (%)	Antepartum		78 (92,9)
	Intrapartum		6 (7,1)
Gestational age (weeks), N (%)			
	22-27		18 (21,7)
	28-32		29 (34,9)
	33-36		17 (20,5)
	37-40		17 (20,5)
	>= 41s		2 (2,4)
Delivery, N (%)	Caesarean		15 (17,9)
	Vaginal		69 (82,1)
		Eutocic	42 (50,0)
		Pelvic	17 (20,2)
		Vaccum	8 (9,5)
		Forceps	2 (2,4)
Sex, N (%)	Feminine		42 (50)
	Male		42 (50)
Birthweight (grams), N (%)			
	500-999		24 (28,6)
	1000-1499		23 (27,4)
	1500-2499		18 (21,4)
	2500-3999		18 (21,4)
	> 4000		1 (1,2)

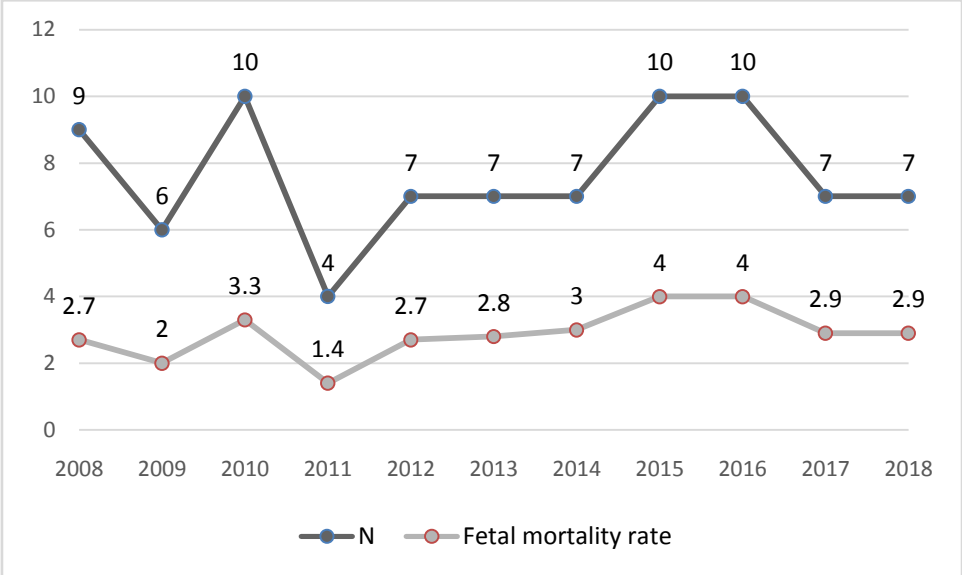
Table no2: Pathological anatomy of the placenta.

Umbilical cord, N (%)			
	Insertion of the umbilical cord	Central	74 (96,1)
		Marginal	1 (1,3)
		Velamentous	2 (2,6)
	Cordwith 3 vessels		74 (96,1)
	Cordthrombosis		8 (10,8)
	Cordknot		1 (1,3)
Placentalmembranes, N (%)			
	Chorioamnionitis		5 (6,3)
	Chronicvasculitis		4 (5,0)
Placentalparenchyma, N (%)			
	Infarct		25 (31,3)
	Retroplacental hematoma		7 (8,8)
	Intervillousfibrin		5 (6,3)
	Intervillousfibrin		2 (2,5)
	Villitis		5 (6,3)

Table no3: Conditions that contributed to stillbirth**.**

Maternal medical condition during pregnancy		8 (9,5)
	Hypertensivedisorder	3 (3,6)
	Diabetes	4 (4,8)
	Shock	1 (1,2)
Clinicalobstetriccomplications		24 (28,6)
	Intrapartum fetal distress with asphyxia or hypoxic intrapartum fetal distress	2 (2,4)
	Abruption	11 (13,1)
	Multiplepregnancycomplications	7 (8,3)

	Uterinerupture		1 (1,2)
	Uteroplacentalinsufficiency		3 (3,6)
Fetal genetic or structural abnormalities			8 (9,5)
Infection			6 (7,1)
	Fetal infection		3 (3,6)
	Placental infection and decreased function		3 (3,6)
Pathological conditions of the placenta			27 (32,1)
	Placentaldisc	Abnormal development of the villous parenchyma	4 (4,8)
	Umbilical cord		12 (14,3)
		Nuchal cord with evidence of occlusion and fetal hypoxia	6 (7,1)
		True knot, narrowing with obstruction	6 (7,1)
	Circulatoryanomalies		11 (13,1)
Unknown			11 (13,1)



Graphic 1 - Number of fetal deaths per year and respective fetal mortality rates.

IV. Discussion

Stillbirth is a rare event with an important impact on health. The incidence varies by country. The fetal mortality rate at our center is similar to the reported in the literature for developed countries [2], which reflects good obstetric care, with correct gestational surveillance and induction of labor whenever clinically indicated. This study made it possible to identify conditions associated with fetal death in 87% of cases. In the vast majority of situations, it would not be possible to prevent or treat the underlying causes, namely in the case of placental abruption or umbilical cord anomalies. The recognition of risk factors is essential. This study shows that only 2% of women had no prenatal surveillance; most women were included in the optimal number of examinations in accordance with national recommendations. This implies that other factors have influenced perinatal outcomes. In this study, advanced maternal age was the main risk factor identified (30%), immediately followed by maternal medical disorders (44%). The gestational approach and surveillance in these situations must be adapted in order to improve obstetric outcomes. In addition, maternal disorders were considered a probable cause of death in 9.5% of cases. Diabetes increases the risk of fetal death, particularly near term. [8] Hyperglycemia appears to be the main cause, leading to increased fetal oxygen consumption and consequent hypoxemia, and the associated vasculopathy can lead to decreased uteroplacental perfusion. [9] We had 4 cases of diabetes with poor metabolic control. Hypertension may be associated with placental insufficiency. The correct approach to situations of arterial hypertension, gestational hypertension and pre-eclampsia are fundamental in reducing this risk, and preterm delivery is often necessary. Placental abruption contributed to fetal death in 11 cases (13%). Although rare, affecting about 1% of pregnancies, is the objective cause in 10-20% of fetal deaths. [10] Anomalies in the umbilical cord were observed in 14% of cases, which is higher than

reported in the literature. [11] This can be explained by the use of a stillbirth study protocol and by conducting an anatomopathological examination. Fetal genetic or structural abnormalities occurred in 10% of the sample. This percentage is also lower than that reported in the literature (15 to 20%) and is mainly due to the existence of an organized prenatal diagnosis service and the possibility of terminating pregnancy in fetuses with major anomalies. [7] Infections are extremely common in developing countries, but in developed countries they account for about 10% of the causes of fetal death. [12,13] In this study the microorganisms involved were Ureaplasma, Gardnerella Vaginalis, Mycoplasma hominis and E. coli. The mechanism of infection is usually the rise of the microorganism from the lower genital tract. To consider infection as a cause of fetal death, there must be evidence of placental and/or fetal infection, hence the study protocol must include pathological anatomy, autopsy and cultures. [14] Although a woman was positive for syphilis, there was no evidence of placental or fetal infection. The pathological anatomy of the placenta played a key role in this study, and it is reported to aid in about 65% of diagnoses. [15] In this study, 32% of the causes of fetal death were attributed to pathological conditions of the placenta. Umbilical cord abnormalities is often cited as a cause of fetal death in the third trimester, corresponding to about 20% of the causes of stillbirth. [16] The cause of stillbirth remained unexplained in 13% of the sample, lower than that reported in the literature (25-60%), probably due to the detailed study carried out by our institution. [8, 17]

The strength of this study is that is based in the perinatal mortality audit of the national health statistics which enables all the stillbirths in our population. The results can be considered reliable and representative for our population, providing one opportunity to learn from adverse events, identifying and analyzing risks factors. This study has the limitation of being retrospective, obtaining only the information previously described in the clinical process, and the lack of other perinatal health care indicators, as perinatal morbidity and outcomes with physical, neurological and cognitive impairments.

Our findings are important, as they provide information about fetal deaths in our center and in Portugal. Being a tertiary hospital, it has a higher number of high-risk pregnancies, preterm births and, probably, fetal deaths, due to referral from other centers. Thus, it may not represent the population of the remaining Portuguese centers. The use of a study protocol is essential to identify possible causes and, consequently, allow the establishment of strategies to reduce them, to a better perinatal quality assessment.

V. Conclusion

The pregnancy still involve risk for pregnant women and their babies, remaining an important public health problem. Correct surveillance of pregnancy is essential in order to reduce the prevalence of associated complications. The use of a study protocol in cases of fetal death is essential to determine the causes and possible establishment of new strategies. For now, most of the causes reported in this study do not appear to be preventable

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