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Clinicopathological changes of perinatal mortality during the last 20 years in a tertiary hospital of Greece

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Summary

Introduction: Perinatal period is the period that includes fetuses weighing > 500 grams (22nd week of gestation) and newborns aged up to seven days. Perinatal mortality is one of the earliest quantitative measurements of quality in obstetric care and affects approximately 0.5% to 1% of all pregnancies. *Aim:* The purpose of this study was the identification, classification, and frequency of causes of perinatal mortality in premature infants during 20 years (1992-2012) in a tertiary Maternity Hospital in Athens. *Materials and Methods:* This was a retrospective study based on Pathology Department record and contains autopsy findings of fetuses, newborns, and membranes of the period 1992-2012 in conjunction with clinical information. The authors excluded pharmaceutical miscarriage and those containing vague variables. The total population birth to the mentioned years in this Hospital was 23,703 and there were 278 deaths. The authors used the classification system of ReCoDe (2005) which best suited the present data. Changes in perinatal death cause were estimated and compared every five years during this period (1993-1997, 1998-2002, 2003-2007, and 2008-2012) and also divided according to the following gestational ages: 22-27, 28-31, 32-36, and 37-43 weeks using the SPSS 19.0. *Results:* Perinatal mortality was reduced up to 72.3% during these years. The vast majority of stillbirths were in their 22-27 week of gestation. Almost half of the fetal deaths were caused by fetal abnormalities, while in 78% the placenta had a main or secondary role. A detailed description of embryo-membranes and clinical status of the mother was performed. Finally the authors identified 15 newborns who had reached the 28th day of their life, of which 12 (80%) were premature. The majority were females and the mean age of the mothers was 28 years. Seven out of 12 newborns died of fetal problems, while three out of 12 due to intrapartum pathology. *Conclusion:* Pathogenesis of perinatal mortality is often unclear and associated to multiple causes. Impressive reduction of neonatal mortality has been realized during recent years due to the developments in obstetric and neonatal intensive care, but still many improvements are needed to be done.

Key words: Perinatal mortality; Stillbirth; Gestational age; Fetal death in Greece; ReCoDe; Cause of fetal death.

Introduction

Perinatal mortality is one of the earliest quantitative measurements of quality in obstetric care. Perinatal deaths affect approximately 0.5% to 1% of all pregnancies [1]. Stillbirth or fetal death is death prior to the complete expulsion or extraction from the mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles [2].

Perinatal period commences at 22 completed weeks (154 days) of gestation (the time when birth weight is normally 500 grams and body length 25 cm crown-heel and ends seven completed days after birth. More than 3.3 million stillbirths and over three million early neonatal deaths are estimated to take place every year. In the 2000, over 6.3 million perinatal deaths occurred worldwide: almost all of them (98%) occurred in developing countries and 27% in the least developed countries. In developed countries, where interventions have largely eliminated excess early neonatal mortality, over six out of ten perinatal deaths are stillbirths [3].

Assignment of a probable cause of death is important to develop interventions for stillbirth prevention. There are currently at least 32 classification systems of stillbirth, many of which have been developed for different purposes. They have different categories for classifying causes, numerous definitions for relevant conditions, and varying levels of complexity. After reviewing the existing systems – Wigglesworth, Aberdeen, NICE, TULIP, Nordic-Baltic *etc* - the authors selected the ReCoDe 2005. The hierarchy started from conditions affecting the fetus and moved outward in simple anatomical groups, which were subdivided into pathophysiological conditions. The analysis of secondary codes provided further insight into the conditions leading to death [4].

The aim of this retrospective study was to assess any changes in cause-specific fetal death rates in the population of a specific tertiary care unit reflecting the level of perinatal care of this region. It was possible to conduct such a study at this institution because all fetal deaths occurring in the last two decades have been analyzed and the vast majority has had complete postmortem examination. It is important to

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note that no other study with this time duration, parameters, and large population has ever been realized in Greece [5].

Materials and Methods

The purpose was to study changes in gestational-age-specific risk of fetal death among all pregnancies after 22 weeks of gestation in a central-university hospital of Athens from 1993 to 2012. The study was a population-based registry study. The authors excluded stillbirths less than 22 weeks of gestation and therapeutic abortions-terminated pregnancies. Any additional births that lacked information on potentially confounding variables were also excluded. As a result, 23,520 births were included

Collected data included medical and obstetric history, maternal and fetal characteristics, and birth details. The authors utilized the ReCoDe classification system 2005, because after reviewing the literature, it was the system that provided the largest number of cases classified according to the information of the present data. Autopsy (gross and microscopic examination of all organs) was performed in all cases.

Perinatal mortality, early neonatal mortality, and stillbirth rate were calculated according to the World Health Organization definitions [2]. Gestational age was calculated from the last menstrual period; ultrasound dating measurements were given priority when they were available. In few cases of 1990s during which the gestational age was not provided, the authors used the crown-rump length. It is, however, unlikely that change in estimation of gestational length has significantly biased the present results because gestational age was grouped and term pregnancies were defined as 37 weeks of gestation or above. Any overestimation of term pregnancies by using last menstrual period for prediction of term would rather underestimate than overestimate the reduction in fetal death rate at term in the later time periods of this study. The authors used the age at the estimated date of fetal death rather than age at delivery because delivery sometimes occurred many days after death. To determine whether the fetus was small for gestational age (SGA), the authors compared fetal weight with the mean birth weight for the infants born at the same gestational age.

The study population consisted of 278 stillbirths of occurring 23,520 births in a tertiary care unit during 1993-2012. Data were collected from the file of Pathology Department of the hospital. The population served was mainly white and from all socioeconomic classes.

Quantitative variables were expressed as mean values (SD), while qualitative variables were expressed as absolute and relative frequencies. Rates of fetal death per 1,000 ongoing pregnancies were calculated in total sample and by year of delivery. Relative risks of fetal death and their 95% confidence intervals (CIs) were calculated for each time period, with 1993-1997 as the reference period. Statistical significance was set at $p < 0.05$ and analyses were conducted using SPSS statistical software (version 19.0).

Results

A total of 23,520 births in the present hospital from 1993 to 2012 were included in the study. In the study period, 278 fetal deaths (11.8‰) occurred. Characteristics of the fetal deaths are presented in Table 1. The majority of fetal deaths occurred between 22nd and 27th week of gestation (61.2%). Also, 33.2% of the miscarriages occurred in mothers aged from 25 to 30 years and 31.8% in mothers aged from 31 to 35 years. Among the perinatal deaths, 134 were males (52.1%). Most miscarriages occurred in premature labors (< 37th gestational week) with the percentage being 90.3%. Mean birth weight was 1029.3 (SD = 849.8) grams and mean weight percentile was 29.8 (SD = 26.4). In 78.4% of the miscarriages, there was a problem in the placenta and in 27.7% a problem in the umbilical cord. Also, 33.0% of the miscarriages occurred with multiple pregnancy and 94.6% were stillbirths.

Table 1. — *Fetal death characteristics.*

	Fetal deaths (n=278) n (%)
Gestational week	
22nd – 27th	170 (61.2)
28th – 31th	28 (10.1)
32nd – 36th	53 (19.1)
37th – 43rd	27 (9.7)
Maternal age (years)	
< 25	38 (17)
25-30	74 (33.2)
31-35	71 (31.8)
36-40	27 (12.1)
> 40	13 (5.8)
Gender	
Males	134 (52.1)
Females	123 (47.9)
Premature labor	
No	27 (9.7)
Yes	251 (90.3)
Birth weight (grams), mean (SD)	1029.3 (849.8)
Weight percentile, mean (SD)	29.8 (26.4)
Placenta	
Abnormal	185 (78.4)
Normal	51 (21.6)
Umbilical Cord	
Abnormal	77 (27.7)
Normal	201 (72.3)
Multiple pregnancy	
No	118 (67.0)
Yes	58 (33.0)
Way of miscarriage	
Stillbirth	263 (94.6)
Newborn	15 (5.4)

The perinatal mortality decreased by 72.3%, from 21.3 per 1,000 births in the years 1993-1997 to 6.3 per 1,000 births in the years 2008-2012 (Figures 1 and 2). The relative risk of fetal death in 1998-2002 was 0.72 (95% CI: 0.53–0.97) and significant lower comparing births during 1993-1997 (Table 2). Also, the relative risk of fetal death in 2003-2007 was 0.44 (95% CI: 0.31–0.61) and significant lower comparing births during 1993-1997, while for the period 2008-2012, it was 0.29 (95% CI: 0.20–0.41) and significant lower comparing births during 1993-1997.

In the total sample, most common cause for miscarriage was regarding problems of the fetus (reported in 44.6% of

Table 2. — *The number of fetal deaths and relative risks (RR) with 95% CI of fetal death according to year of delivery.*

Year	Fetal deaths N (%)	Births N (%)	Miscarriages (%)	RR (95% CI)*
1993-1997	86 (30.9)	3959 (17.0)	21.3	1.00‡
1998-2002	85 (30.6)	5453 (23.5)	15.3	0.72 (0.53–0.97)
2003-2007	59 (21.2)	6227 (26.8)	9.4	0.44 (0.31–0.61)
2008-2012	48 (17.3)	7603 (32.7)	6.3	0.29 (0.20–0.41)
Total	278 (100.0)	23242 (100.0)	11.8	-

*RR (95% confidence interval). ‡ indicates reference category.

the cases), followed by problems in the placenta (19.4%) (Table 3). Similar were the results when causes were reported according to year of delivery and by gestational age, except for cases occurring between 37th and 43rd week of gestation, where most common cause reported was asphyxia (37.0%).

Discussion

In the western world, the stillbirth rate has declined since the 1950s [6]. The decline was most pronounced early in this period [7]; indeed increasing stillbirth rates have been reported since 2001 [8]. While national and international attention, statistics, and interventions focus on live infants, stillborn infants have largely been overlooked. However, these deaths do matter to the mother, family, society, and to the healthcare system [3].

Although social factors exert the main influence on the outcome of a birth, as societies advance, good medical care tends to play a greater role. New technologies are not necessarily beneficial, as sex-selection procedures and inappro-

Table 3. — *Fetal deaths due to miscellaneous causes in total sample, and according to year of delivery and gestational week.*

	Total sample (n=278) n (%)	Year 1993-1997 n (%)	1998-2002 n (%)	2003-2007 n (%)	2008-2012 n (%)	Gestational week 22nd–27nd n (%)	28th–31st n (%)	32nd–36th n (%)	37th–43rd n (%)
Amniotic fluid	10 (3.6)	7 (8.1)	1 (1.2)	0 (0.0)	2 (4.2)	9 (5.3)	0 (0.0)	0 (0.0)	1 (3.7)
Chorioamnionitis	8 (2.9)	6 (7)	1 (1.2)	0 (0.0)	1 (2.1)	8 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Oligohydramnios	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Polyhydramnios	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Fetus	124 (44.6)	33 (38.4)	33 (38.8)	37 (62.7)	21 (43.8)	77 (45.3)	12 (42.9)	32 (60.4)	3 (11.1)
Lethal congenital anomaly	47 (16.9)	13 (15.1)	13 (15.3)	14 (23.7)	7 (14.6)	32 (18.8)	2 (7.1)	11 (20.8)	2 (7.4)
Infection	25 (9)	6 (7)	6 (7.1)	9 (15.3)	4 (8.3)	22 (12.9)	1 (3.6)	2 (3.8)	0 (0.0)
Non-immune hydrops	3 (1.1)	1 (1.2)	1 (1.2)	1 (1.7)	0 (0.0)	2 (1.2)	0 (0.0)	1 (1.9)	0 (0.0)
Iso-immunisation	2 (0.7)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.6)	1 (3.6)	0 (0.0)	0 (0.0)
Fetomaternal haemorrhage	1 (0.4)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Twin-twin transfusion	3 (1.1)	0 (0.0)	0 (0.0)	1 (1.7)	2 (4.2)	2 (1.2)	1 (3.6)	0 (0.0)	0 (0.0)
Fetal growth restriction	43 (15.5)	12 (14)	11 (12.9)	12 (20.3)	8 (16.7)	17 (10)	7 (25)	18 (34)	1 (3.7)
Intrapartum	22 (7.9)	13 (15.1)	7 (8.2)	1 (1.7)	1 (2.1)	0 (0.0)	3 (10.7)	9 (17)	10 (37)
Asphyxia	22 (7.9)	13 (15.1)	7 (8.2)	1 (1.7)	1 (2.1)	0 (0.0)	3 (10.7)	9 (17)	10 (37)
Mother	5 (1.8)	0 (0.0)	4 (4.7)	0 (0.0)	1 (2.1)	4 (2.4)	0 (0.0)	1 (1.9)	0 (0.0)
Hypertensive diseases in pregnancy	3 (1.1)	0 (0.0)	3 (3.5)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Lupus/ antiphospholipid syndrome	1 (0.4)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Placenta	54 (19.4)	9 (10.5)	19 (22.4)	11 (18.6)	15 (31.3)	35 (20.6)	9 (32.1)	7 (13.2)	3 (11.1)
Abruption	24 (8.6)	8 (9.3)	5 (5.9)	5 (8.5)	6 (12.5)	14 (8.2)	6 (21.4)	4 (7.5)	0 (0.0)
Praevia	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Placental insufficiency/infarction	27 (9.7)	1 (1.2)	14 (16.5)	5 (8.5)	7 (14.6)	18 (10.6)	3 (10.7)	3 (5.7)	3 (11.1)
Other	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.2)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Trauma	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Iatrogenic	1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
Umbilical Cord	20 (7.2)	8 (9.3)	8 (9.4)	2 (3.4)	2 (4.2)	11 (6.5)	1 (3.6)	3 (5.7)	5 (18.5)
Prolapse	2 (0.7)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (3.7)
Constricting loop or knot	9 (3.2)	6 (7)	1 (1.2)	2 (3.4)	0 (0.0)	4 (2.4)	0 (0.0)	1 (1.9)	4 (14.8)
Velamentous insertion	3 (1.1)	2 (2.3)	0 (0.0)	0 (0.0)	1 (2.1)	1 (0.6)	1 (3.6)	1 (1.9)	0 (0.0)
Other	6 (2.2)	0 (0.0)	5 (5.9)	0 (0.0)	1 (2.1)	5 (3.0)	0 (0.0)	1 (1.9)	0 (0.0)
Uterus	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Rupture	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unclassified	41 (14.7)	15 (17.4)	13 (15.3)	8 (13.6)	5 (10.4)	33 (19.4)	3 (10.7)	1 (1.9)	4 (14.8)
No information available	25 (9)	13 (15.1)	9 (10.6)	1 (1.7)	2 (4.2)	22 (12.9)	3 (10.7)	0 (0.0)	0 (0.0)
No relevant condition identified	16 (5.8)	2 (2.3)	4 (4.7)	7 (11.9)	3 (6.3)	11 (6.5)	0 (0.0)	1 (1.9)	4 (14.8)

Figure 1. — Perinatal mortality during the last 20 years.

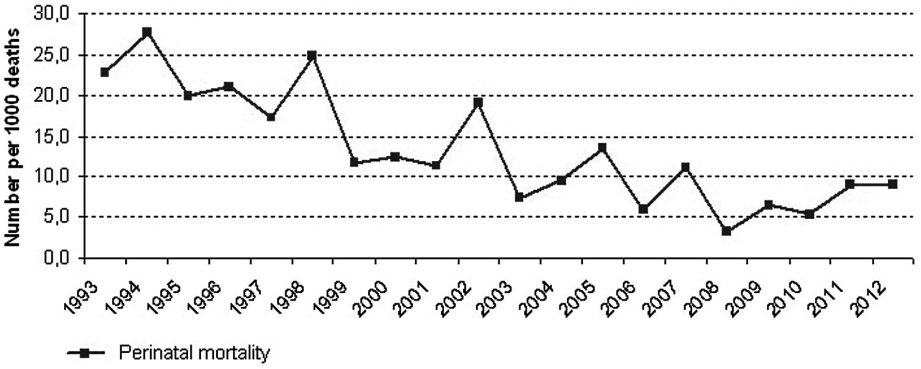

Figure 2. — Perinatal mortality during the last 20 years.

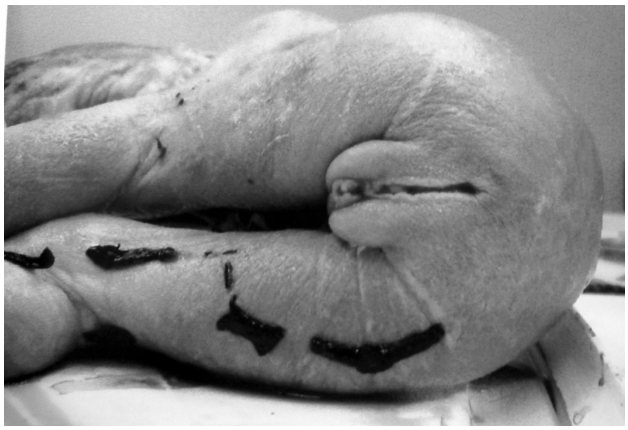

Figure 3. — Female stillbirth (30 wog) with cat-eye syndrome-chromosomal anomaly (inv.dup.22), congenital abnormalities, and intraventricular communication combined with placental hematoma.

priate assisted reproduction show. The way they contribute to adverse pregnancy outcomes is not captured in current methods of collecting, analyzing or presenting perinatal data [2].

In the western world, perinatal mortality has declined since the mid-19th century from 26-43 per 1,000 births to a level of five to ten per 1,000 births in the first decade of the 21st century. Also, the fetal death rate has been reported to decline. In Europe, the fetal death rate after 28 weeks of gestation has declined from 25-45 to three to five per 1,000 births form 1940 to 2000 [3]. During our study period the fetal death rate declined in pregnancies lasting longer than 22 weeks and the decline was more prominent in pregnancies at term.

The most common cause of death was due to a fetal problem (44.6%) and especially a lethal congenital anomaly, infection or fetal growth restriction (Figures 3 and 4). According to European Surveillance of Congenital Anomalies (EUROCAT), the prevalence of chromosomal anomalies is 3.6 per 1,000 births, contributing 28% of stillbirths and 48% of all terminations of pregnancy following prenatal diagnosis. Congenital heart defects are the most common non-chromosomal anomalies, followed by limb defects, anomalies of urinary system, and nervous system defects [9]. In the present study, infections have been reported to account for 9%, while 10-25% of fetal deaths are attributed to congenital infections in developed countries [10]. On the other hand, fetal growth restriction is a condition of fetal death related to many parameters and reaches 15.5% of perinatal mortality of the present data. While 70% of small fetuses are small for normal reasons and not at risk, 30% are pathologically small at risk for numerous complications. There are no randomized trials addressing the timing of delivery of IUGR fetus in the late preterm or early-term period, taking under consideration factors such as non-stress testing, fetal movement, interval

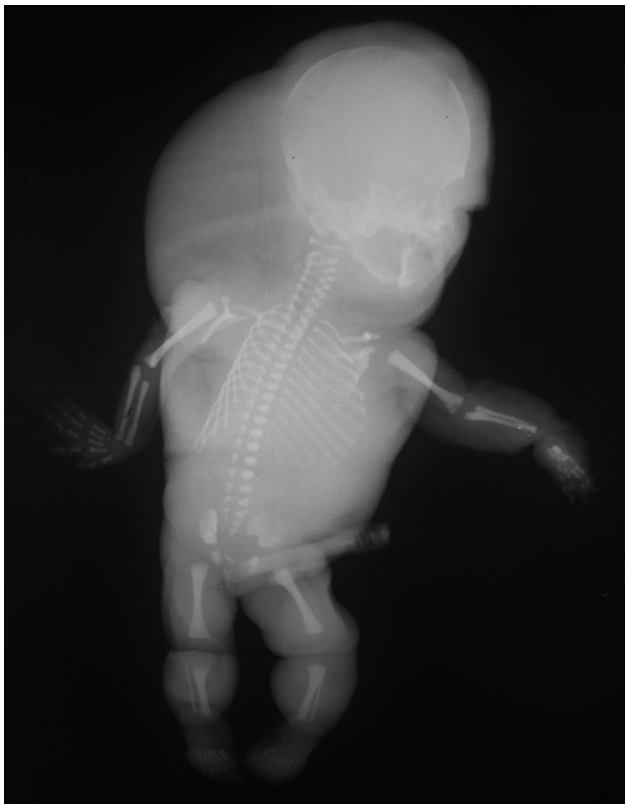

Figure 4. — Male stillbirth (27 wog). Non-immune hydrops with no other pathology.

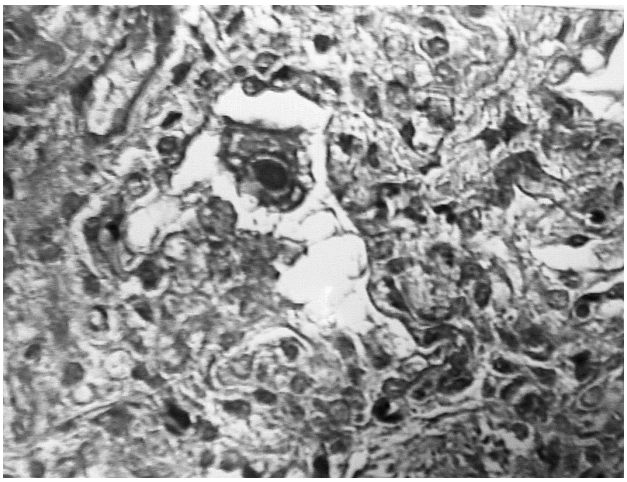

Figure 5. — Placenta of male stillbirth (29 wog) infected by CMV. Maturation abnormalities and micro-calcifications can be noted.

growth, amniotic fluid volume, *etc* [11, 12].

In the present study, 33% of the miscarriages occurred in multiple pregnancy, 94.6% were automatic (stillbirth), and the rest live births. The potential causes of fetal death in multiple gestations are numerous and include virtually every obstetric complication, including placental insufficiency, abruption, preeclampsia, and preterm labor. Other problems are unique to multiple gestations, especially in cases of monochorionic placentation, such as twin-twin transfusion syndrome, cord enlargement, and twin-reverse arterial perfusion [10].

Assisted reproductive technologies (ART) have a high rate of multiple gestations (31% in USA) and yet there are concerns about the risk for adverse pregnancy outcomes. In association with maternal age, ART is accused of spontaneous abortion, ectopic pregnancies, chromosomal abnormalities, imprinting disorders, prematurity, birth defects, IUGR, preeclampsia, and placental abruption. As a result of common use of in vitro fertility, -2.5% of French infants in 2006-future initiatives are needed to characterize ART as the main cause or the substrate of a fetal abnormality [13-15].

Many cases of fetal death, especially at term, are attributed to umbilical cord accidents. Thus the demonstration of cord occlusion, fetal hypoxia, and the exclusion of other causes is required to confirm the diagnosis. In the present population, umbilical abnormality was the main cause for 20% of perinatal deaths, the majority of which referred to constricting loop or knot.

In 78.4% of the miscarriages, there was pathology in the placenta and in 19.4%, it was the main cause of death. Among the placental anomalies, abruption and placental insufficiency or infractions were the most common. The placenta can be considered the diary of pregnancy; after death, it remains viable for several days. The value of examining the placenta for determining or excluding a cause of death in stillbirths is evident and varies from 28-85% (Figure 5). Thus, placental causes of death have been found in up to 60% of perinatal mortality cases and 64% of intrauterine fetal deaths depending on the classification system [16].

As a result of membranes' or fetus' malfunction, the present authors estimated amniotic fluid pathology which reached 3.6% of the perinatal mortality. A variety of other disorders such as uterine rupture (0.4%) and trauma (0.4%) were more rare conditions of death.

Several maternal medical disorders are associated with an increased risk for fetal death. It is debatable as to whether these conditions are causal or risk factors, because most affected women deliver live infants. It is estimated that maternal diseases play a role in 10% of perinatal mortality [17]. Hypertensive disease during pregnancy is the most common cause of maternal disease which led to fetal predicament and death (1.1%) in the present study.

Delivery-related perinatal death is defined as intrapartum stillbirth or neonatal death that is unrelated to congenital abnormality. The causes of intrapartum stillbirth indicate that most of these stillbirths are caused by events that will occur only during labor and delivery, such as asphyxia in the present population (7.9%). Similarly, having excluded deaths because of congenital abnormality, most neonatal deaths are due to intrapartum events or the effects

of prematurity [18, 19].

Finally, in each classification of stillbirth population, there is a percentage of unclassified/unexplained fetal deaths; in the present case this accounted for 14.7% (61% of which was due to no information provided). In the majority of studies, many cases remain unexplained even after extensive evaluation. Losses later in gestation (third trimester) are more likely to be unexplained than losses earlier in gestation. Such losses are strongly associated with IUGR as well as most of the previously described risk factors [20]. Hence, these deaths are largely linked to maternal health conditions before pregnancy, complications of pregnancy, such as preeclampsia, and placental dysfunction, without being able to establish a cause [21].

It is likely that the causes of fetal deaths differ according to the length of gestation [22]. However, infections are assumed to be linked to mid-pregnancy fetal deaths, [23] whereas fetal deaths at or near term may be caused by preeclampsia, placental abruption, fetal growth restriction or complications during delivery [24]. Developed-country historical data suggest that, as smaller and sicker babies survive, an increasing number of small babies are registered.

In the present population, the majority of the fetal deaths occurred between 22nd and 27th week of gestation (61.2%), while the intrapartum asphyxia was noticed from 32nd to 43rd weeks of gestation (86%). Also, 33.2% of the miscarriages occurred in mothers aged from 25 to 30 years and 31.8% in mothers aged from 31 to 35 years. Hence, knowledge of changes in gestational-age-specific mortality over time may reveal underlying causes of fetal death and also be an evaluation of obstetric care [25].

Consistent demographic factors for fetal death induce race, low socioeconomic status, inadequate prenatal care, less education, and advanced maternal age [6]. This fact is proven in many studies including in the present study; after the end of 2008 when the economic and humanitarian crisis began in Greece, it is interesting to note a small rise of fetal mortality in the present Hospital (Figure 2).

Conclusion

The perinatal mortality indicator plays an important role in providing the information needed to improve the health status of pregnant women, new mother, and newborns. That information allows decision-makers to identify problems, track temporal and geographical trends, disparities, and assess changes in public health policy and practice.

Common causes and risk factors for fetal death include chromosomal abnormalities, placental disorders, and intrapartum asphyxia. Clinicians should encourage families to allow a thorough investigation of potential causes of fetal deaths to facilitate emotional closure, to assess recurrence risk.

Prospective surveillance can result in the timely delivery of a fetus at risk from an unfavourable intrauterine environment. This is now assisted by technological methods, whereas problems as prematurity and fetal growth restriction still remain unrecognized antenatally.

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