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# FETAL DEATH IN UTERO. TEN YEARS RETROSPECTIVE ANALYSIS OF A TERTIARY MATERNITY

Anca M. Panaitescu[1,2], Luminița Ceaușelu[2], Nicolae Gică[1,2,*], Anca M. Ciobanu[2], George Gheoca[2], Andreea Dumitru[2], Alina Veduță[2], Corina Gică[2], Gheorghe Peltecu[1,2], Radu Botezatu[1,2]

[1]*"Carol Davila" University of Medicine and Pharmacy, Department of Obstetrics and Gynecology,*
[2]*"Filantropia" Clinical Hospital, Bucharest, Romania*

**Abstract:** Fetal death in utero is complex problem. It is a major public health problem and a tragedy for individual families. It has no common definitions in medicine and legislation. There are no public educational programs or preventive medical strategies. This is a retrospective analysis of fetal deaths in utero in the last ten years in a tertiary maternity.

Fetal death in utero was defined as delivery of a non-viable fetus at or beyond 24 weeks gestation. Intrapartum fetal deaths were excluded. All the dead fetuses in utero had an autopsy according to the standard protocols of the Romanian Society of Pathologists. Potential causes of the fetal deaths were classified into two categories, explained and unexplained and the explained causes were further classified into preventable and nonpreventable. The percentage of unexplained causes was similar to that reported in the literature. A strategy to reduce the preventable fetal deaths in utero should be defined including educational and medical aspects. Its implementation is a strong need.

**Keywords:** fetal death, stillbirth, in utero, etiology, preventable, unpreventable, strategy.

## INTRODUCTION

Fetal death in utero is a major public health problem [1, 2]. It has different and controversial definitions. Even in the United States definitions vary between states and the European Union has no common definitions and legislation for member states.

The definition of the fetal death in utero recommended by WHO for international comparison is "a baby born with no sign of life at or after 28 weeks' gestation [3].

The Perinatal Mortality Surveillance Report (CEMACH) defines stillbirth in the UK as a "baby delivered with no sign of life known to have died after 24 weeks of pregnancy". Intrauterine fetal death refers to babies with no signs of life in utero [4].

The United States National Center for Health Statistics defines stillbirth as a fetal death or loss that occurs after 20 weeks of pregnancy and before or during delivery, with further division into early stillbirth (20 to 27 completed weeks), late stillbirth (28 to 36 completed weeks), and term stillbirth (≥37 completed weeks) [5]. The divisions, although arbitrary, allow separate consideration of stillbirths, that are early and difficult to prevent with any intervention, from those that are late and potentially preventable by preterm delivery [6].

In the English medical literature a distinction is defined between stillbirth and fetal death in utero in the sense that stillbirth refers to a viable fetus born dead, while fetal death refers to the death of a fetus before delivery. This distinction is easier nowadays thanks to the use of imaging technology making possible the identification the lack of signs of viability anytime during pregnancy.

Timing of stillbirth is important for maternal follow-up in the next pregnancy. Data related to the fetal death have more etiologic and prognostic value, as compared to gestational age at stillbirth. Observational studies support the idea that the risk of fetal death in utero during of a second pregnancy is predicted by the gestational age at which fetal death occurred in the first pregnancy.

In Romania the fetal death in utero is not specifically defined, nor in guidelines of obstetrics and

*Correspondence to: Nicolae Gică, "Filantropia" Clinical Hospital, 11-13, Blvd. Ion Mihalache, 11171, Bucharest, Romania, E-mail: gica.nicolae@gmail.com

gynecology or textbook of forensic medicine, neither in legislation.

In 2015 there were 2,6 million stillbirths globally with more than 7178 deaths a day. Majority of deaths were registered in developing countries. By 28 weeks' gestation the rate of still births in high-income countries will be 1 in 250 pregnancies, while the rate in low- and middle-income countries will be 1 in 22 [7].

***Epidemiological associations and prognostic factors for antepartum stillbirth***

Multiple risk factors were analyzed to establish a possible relation with fetal death in utero (low socio-economic status, maternal age ≥ 40 years, pre-existing hypertension, HIV/AIDS diagnosed prior to pregnancy, bleeding after 15 weeks, preeclampsia/eclampsia, multiple pregnancies, fetal growth restriction) [8]. This list could be extended by other maternal conditions (poorly controlled diabetes mellitus, systemic lupus erythematous, antiphospholipid syndrome, thrombophilia), fetal congenital and genetic abnormalities and infections (parvovirus B19, CMV, Listeria) [9-11].

No significant association with antepartum stillbirth was demonstrated with smoking, illicit drug use, or body mass index. Women with a history of either a previous perinatal loss, preterm delivery, a baby born with low (<2500 g) or high (>4500 g) birthweight, or more miscarriages in the their past history, had a higher risk of antepartum stillbirth [8].

## MATERIAL AND METHOD

This was a retrospective study including all stillbirth cases with a postmortem examination between January 2010 and July 2020 recorded in a single tertiary maternity. Stillbirth was defined as delivery of a nonviable fetus at or beyond 24 weeks gestation. Gestational age was determined according to the last menstrual period or by ultrasound measurements in the first or second trimester. In our analysis we have excluded cases with a nonviable fetus prior to 24 weeks gestation, intrapartum fetal death and neonatal death. All data regarding maternal demographic characteristics, medical history, pregnancy complications, birth weight, anatomopathological results were retrieved from the hospital stillbirth registry. Causes of fetal death were subsequently classified as explained, when a possible cause was identified, and unexplained. Within the explained etiology of fetal death, two other categories were described, preventable causes, when a medical intervention, more intense prenatal monitoring or timely delivery, could have potentially changed the pregnancy outcome, and nonpreventable cause, when the stillbirth was a sudden adverse event which could not have been predicted or changed by any medical intervention. Preventable causes included mainly placental pathology clinically manifested as fetal growth restriction or maternal preeclampsia. Obstetric cholestasis, maternal diabetes mellitus, maternal infections, velamentous cord insertion and vasa previa, complicated monochorionic twin gestation or isoimmunization requiring fetal blood transfusion, were also amongst preventable causes. On the other hand, within the unpreventable group were included causes related to fetal malformations, genetic conditions or sudden placental abruption.

Most of the pregnant women described, retrospectively, a lack of perception of fetal movements but the diagnosis of fetal death in utero was confirmed in all cases by ultrasonography.

All the information was provided to the pathologist at the time of postmortem exam. All autopsies were performed according to the standard protocols of the Romanian Society of Pathologists (external examination, prosection and internal exam and ancillary investigations-histology, microbiology, virology).

The study was approved by the hospital research ethics committee.

## RESULTS

Between 1st of January 2010 and 1st of July 2020 a total of 41,103 babies were born at Filantropia Clinical Hospital. During the same period a number of 462 fetal death in utero were registered, representing an overall fetal death rate of 11,2/1000 live births.

Out of all stillbirths recorded, 182 cases, 22 twins and 160 singleton pregnancies, met the inclusion criteria and were included in the final analysis. Out of these, 75 (41%) had an unexplained cause, while 107 (59%) had a potential recognizable cause. In the latter group, there were 66 cases (62%) unpreventable and the remaining 41 cases (38%) were potentially preventable (Fig. 1).

The median gestational age at the time of diagnosis in the study population was 31.9 weeks. The proportion of stillbirths was analyzed between three different gestational age groups, extreme preterm (24-27+6 weeks), preterm (28-33+6 weeks) and late (34-42 weeks). Of all stillbirths, 45% were found in the preterm group. This group encounter also the highest proportion of the preventable cases. In the late stillbirths group there were 37% of all cases of fetal death, but no post-

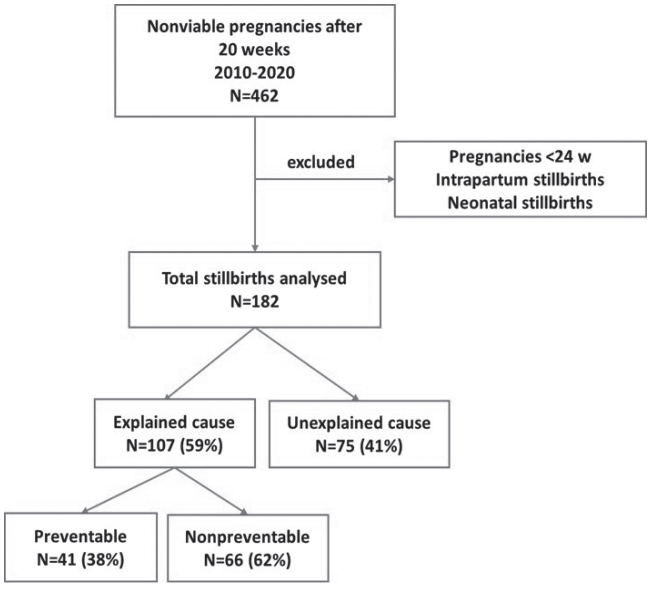


**Figure 1.** Analysis of fetal deaths in utero in "Filantropia" Clinical Hospital between 2010-2020.

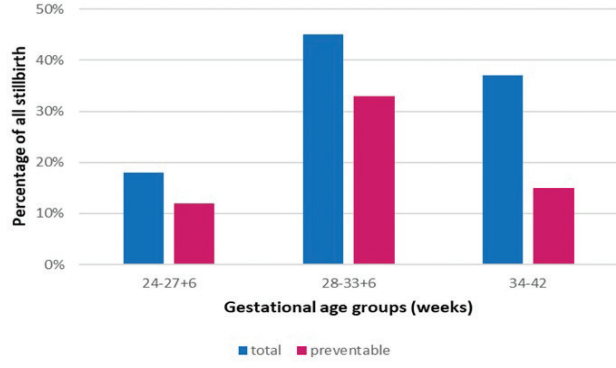


**Figure 2.** Analysis of fetal deaths in utero separated in three gestational age groups (extreme preterm, preterm and late).

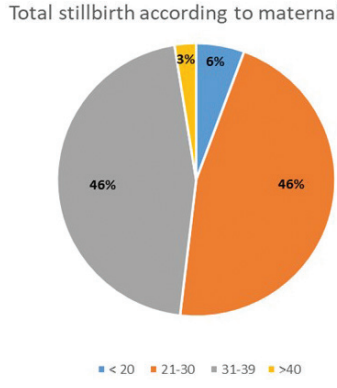


**Figure 3.** Fetal death in utero according to maternal age.

**Table 1.** Comparison preventable vs. unpreventable groups

| | Preventable n=41 | Unpreventable n=66 | P value |
|---|---|---|---|
| **Maternal age (y)** | 31 (26-34) | 30 (26-33) | 0.25 |
| **Nulliparity (%)** | 57% | 58% | 0.30 |
| **Gestational age (W)** | 32.0 (29.0-33.8) | 31.5 (29.0-34.5) | 0.69 |
| **Birth weight (g)** | 1350 (1025-1800) | 1762 (1200-2700) | **0.02** |

term stillbirth, after 41 weeks gestation, was recorded (Fig. 2).

The median maternal age in the study population was 29 years. The most cases occurred in the age group 21-39 years, while age above 40 years, as a risk factor accounted for 4% of all cases of fetal death (Fig. 3).

Comparing the two groups of preventable *versus* unpreventable causes, there were no statistically significant differences regarding maternal age, nulliparity or gestational age at diagnosis, but as expected, the birth weight was significantly lower in the preventable group than in the unpreventable group due to fetal growth restriction which complicated 63% (27 out of 41) of those pregnancies.

More than 80% of these cases were attributed to placental dysfunction under the aspect of preeclampsia and fetal growth restriction, defined as birth weight < 10$^{th}$ percentile according to the Fetal Medicine Foundation (FMF) fetal growth charts. Of these, 20% were accompanied by placental abruption. There were 3 cases of fetal death in relation to maternal conditions such as diabetes mellitus type 1 and obstetric cholestasis. Maternal HIV infection led to one fetal death and monochorionic twin pregnancy complicated by twin-to twin transfusion syndrome determined 3 cases of stillbirth.

Fetal death in utero of unknown etiology represents a particular problem. Because of a high number of etiologies, it is difficult to determine the risk of fetal deaths for any particular pregnancy.

## DISCUSSION

Globally less than 5% of stillbirths are recorded [12].

Fetal death in utero is the 5$^{th}$ leading cause of death worldwide and there are no preventive programs because there is a limited understanding of the pathophysiology responsible for this entity. Worldwide, unexplained fetal deaths in utero are estimated to be between 50 and 76% of cases [12-14].

In our study 41% of all cases of fetal death in utero had unexplained causes, being within the same wide range of variation estimated in the literature.

The Eunice Kennedy Shriver National Institute of Child Health Development (NICHD) created the Stillbirth Collaborative Research Network to evaluate the causes of fetal death and to define the optimal diagnostic evaluation [15].

The Lancet took the initiative to helped to promote global public health efforts publishing "The Ending Preventable Stillbirths Series Study Group". The initial goal was to reduce the stillbirth rate to less than 15/1000 [12]. This target is achievable in many industrialized countries but is a dream too far for countries in Africa and Asia, where the highest number of stillbirths are attributed to the lack of access to health care system. WHO estimates that 98% of global stillbirths occur in low and middle-income countries [12].

Although many efforts have been made over the last decade to enhance the prediction strategies of stillbirth and to develop effective preventive measures, the results are still far from being perfect. Various placental markers, maternal characteristics, ultrasound biometrical and fetal doppler studies have been incorporated in algorithms for prediction of stillbirth which have tested starting as early as the first trimester of pregnancy. The detection rate of these methods varies between 40 and 70% [16, 17].

Placental disfunction manifested by preeclampsia and fetal growth restriction is a well-recognized preventable cause of adverse perinatal outcome and stillbirth. Many attempts have been made to predict early in pregnancy those cases complicated by placental insufficiency and therefore at high risk of fetal death in utero. Using screening by maternal characteristics, mean arterial pressure, uterine artery blood flow and placental markers, applied during the first trimester of pregnancy we are able now to predict almost 90% of the cases that will develop early onset preeclampsia and treatment with Aspirin 150 mg/day may prevent 60% of those cases [18]. Also screening in the first trimester may predict 50% of early onset fetal growth restriction which would require intense monitoring during pregnancy and possible early delivery [19]. Screening for gestational diabetes has also a detection rate of 80% when performed at 12 weeks of gestation [20]. Detailed ultrasound at 12 weeks of gestation, apart from identifying severe structural or chromosomal abnormalities leading to fetal death, it can also provide valuable information regarding placental structure, umbilical cord insertion and subsequent risks related to vasa previa or abnormal placenta.

Regarding late onset complications which can lead to late stillbirth, screening at 35-36 weeks gestation for fetal growth restriction can predict 70% of those cases which will be more carefully monitored and will benefit from timely delivery [21]. Late preeclampsia with onset after 37 weeks, although not as severe as early onset preeclampsia, can potentially determine late fetal death, may be predicted by screening at 35 weeks based on maternal characteristics and placental markers and planned delivery at 39 weeks for high risk group may prevent subsequent maternal and fetal complications [22]. A recent randomized study showed that routine planned induction at 39 weeks even in low risk nulliparous women could reduce the risk of maternal hypertension and perinatal morbidity and mortality without increasing the rate of cesarean section comparing to expectant management until 41 weeks. The analysis concluded that induction of labor resulted in 795 fewer cases of stillbirth [23]. At least 50% of all cases of stillbirth do not have an evident cause and these cases are impossible to predict or prevent through antenatal interventions. The triple risk model for unexplained late stillbirth hypothesizes that stillbirth may result from an inter-relationship of three groups of factors: a vulnerable baby (e.g. small-for-gestational-age), an adverse maternal factor (e.g. obesity) and an additional stressor (e.g. reduced uterine blood flow associated with supine going-to-sleep position) [24].

The risk of recurrence is about nine-fold higher in women with previous stillbirth when compared to women with a live birth [25]. However, the recurrence risk of unexplained stillbirth remains unclear. Recent studies have shown that previous stillbirth increases the risk of other pregnancy complications: preterm birth, low birth weight, and placental vascular complications including preeclampsia and placental abruption. Stillbirth is a serious complication with a long-term impact on parents' emotional health. Most patients find increased fetal surveillance with the next pregnancy reassuring, even though such testing is not clearly beneficial. The American College of Obstetricians and Gynecologists (ACOG) recommends antepartum testing starting at 32-34 weeks' gestation in an otherwise healthy mother with history of stillbirth [16]. Weekly biophysical profile or fetal heart rate testing can be combined with maternal kick counts in the third trimester. For patients who have experienced earlier loss, frequent ultrasound is reassuring. As the risk of stillbirth increases after 39 weeks of gestation the current recommendation after an unexplained stillbirth is delivery at 39 weeks [26].

Although our hospital has a fetal medicine unit and an integrated screening strategy following international protocols applied mainly in the first trimester but also later in pregnancy, our unit is a referral hospital and many of those cases complicated by stillbirth due to fetal growth restriction or maternal preeclampsia had a poor access to appropriate management and monitoring or delayed referral to specialized centers. Recently we have reported that the incidence of hypertensive disorders of pregnancy in our hospital, in a population which might be considered representative for our region, was around 3.7% and the rate of stillbirth in relation to the hypertensive complications was estimated at 6.2% [27]. Therefore, it is important to highlight the need of improving antenatal care by effective screening for pregnancy complications, appropriate preventive measures and standardized management protocols. Fetal death is considered an indicator of progress toward the Sustainable Development Goals [28].

Evidence-based models such as Active Management of Risk in Pregnancy at Term (AMOR-IPAT) has been created as an effort to better estimate this risk [29].

***Limitations***

The study analyzes the fetal death in utero of a tertiary referral maternity with a number of annual deliveries, during the analyzed period, between 3000 and 5000. Despite the size of the study, its characteristics of unselected cohort, the fact that all intrauterine fetal death had an autopsy, the study has limitations. Our cases may have been preselected by the referral physicians from external institutions. Full antenatal data notes were not available from the referral specialist, such as body mass index or even maternal blood pressure. Due to incomplete data we were not able to establish an association of fetal death in utero with smocking, BMI, a history of prior fetal death or premature delivery, miscarriages in preceding pregnancies.

**In conclusion,** the prevention of stillbirth remains a major global challenge and in order to develop efficient strategies, health providers should agree to a universal definition of stillbirth for a comprehensive system of classification, accurate database and increasing data reporting. All these measures will help to accurately identify the causes of stillbirth and to identify the high-risk groups. Appropriate intervention measures to reduce the risk of stillbirth require firstly patients and public education regarding modifiable factors associate with stillbirth consisting of demographic, environmental, nutritional, lifestyle factors and maternal infections. Access to adequate prenatal care and screening methods in specialized clinics will lead to early risk stratification and appropriate preventive measures which could potentially prevent at least 50% of all cases of still birth.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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