Late Stillbirth: a ten year Cohort Study

Fetomortalidade Tardia: Estudo Coorte de dez anos

Raquel ROBALO[1], Célia PEDROSO[1], Njila AMARAL[1], Clara SOARES[1]

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ABSTRACT

Introduction: Late fetal death is a desolating event that inspite the effort to implement new surveillance protocols in perinatal continues to defy our clinical pratice.

Objective: To examine etiological factors contributing to main causes and conditions associated with fetal death in late pregnancies over a 10-year period.

Methods: Retrospective cohort analysis of 208 late singleton stillbirth delived in a tertiary-perinatal referral maternity over a 10-year period. Clinical charts, laboratory data and feto-placental pathology findings were systematically reviewed.

Results: The incidence of late fetal demise was 3.5 per 1000 pregnancies. No significant trend in the incidence of stillbirth was demonstrated during the study period. Stillbirth was intrapartum in 12 (5.8%) cases and 72 (35%) were term pregnancies. Fourteen percent of cases were undersurveilled pregnancies. Mean gestacional age at diagnosis was 34 weeks. The primary cause of death was fetal, it was present in 59 cases, 25% were considered small for gestational age. Stillbirths were unexplained in 24.5% of cases. Maternal medical disorders were identified in 21%. Hypertensive disorders were frequent and associated with early gestacional age (p = 0.028).

Conclusion: There was no change in the incidence of late stillbirth during the 10 years under evaluation. The incidence was 3.5 ‰ which was identical to that described in developed countries. About one quarter of the stillbirths was unexplained. The most frequent maternal pathology was chronic hypertension.

Keywords: Pregnancy Complications; Pregnancy Trimester, Third; Stillbirth; Cohort Studies.

RESUMO

Introdução: A morte fetal tardia é um acontecimento que se mantém na prática diária, apesar de protocolos de vigilância pré-natal e intraparto.

Objectivo: Análise dos factores que contribuíram para a causa principal ou condições associadas a morte fetal tardia num período de 10 anos

Métodos: *Coorte* retrospectiva de 208 gestações tardias simples, cujo parto em unidade terciária de cuidados perinatais resultou no nascimento de um nado morto, num período de dez anos. Através de consulta de processo clínico foram analisados dados clínicos, laboratoriais e resultados de estudo anatomo-patológico feto-placentário.

Resultados: A incidência de morte fetal tardia foi de 3,5 por cada 1000 nascimentos. Não foram encontradas quaisquer tendências na incidência de MF tardia ao longo do tempo de estudo. Em 12 (5,8%) casos a morte fetal foi um acontecimento intraparto e 72 (35%) eram gestações de termo. Em 14% a gravidez não foi vigiada. A IG média de diagnóstico foi 34 semanas. A principal causa de morte associou-se a patologia fetal, tendo sido identificados factores fetais em 59 casos, destes 25% foram considerados leves para a idade gestacional. Em 24.5% dos casos a causa de morte foi inexplicada. Identificaram-se factores de risco materno em 21% dos casos, a patologia hipertensiva foi frequente e foi associada a idade gestacional precoce (p = 0,028).

Conclusões: Não houve oscilações na incidência de morte fetal tardia ao longo dos dez anos avaliados. A incidência foi de 3,5‰, idêntica à descrita em países desenvolvidos. Cerca de um quarto das mortes fetais foram inexplicadas. A patologia materna mais frequente foi a hipertensão crónica.

Palavras-chave: Complicações na Gravidez; Morte Fetal Tardia; Terceiro Trimestre da Gravidez; Estudo de Coorte.

INTRODUCTION

The World Health Organization (WHO) defines stillbirth as a "fetal death late in pregnancy",[1] allowing each country to define the gestational age at which fetal death is considered stillbirth. Early stillbirths are typically defined as those occurring between 20 and 27 weeks of gestation, while late stillbirths occur at or after 28 weeks of gestation.

Stillbirth is one of the most common adverse pregnancy outcomes worldwide; over 3 million deliveries annually are stillborn[2]. In the United States, 1 of every 160 deliveries ends in stillbirth with an overall rate of 6.2 / 1 000 in 2005.[3]

It is essential to determinate the probable cause of death in order to establish interventions for stillbirth prevention. The overall recurrence risk for stillbirth is increased 2 to 10 folds in the next pregnancy, depending on the circumstances.[4] The importance of counselling affected parents, prevention of recurrence and treatment of previously undiagnosed medical conditions is undeniable. Unfortunately, in a significant number of cases, either the evaluation is incomplete or the prior stillbirth remains unexplained despite a complete work-up.

The authors studied all late stillbirths (at or after 28 weeks of gestation) delivered in our institution over a 10-year period.

1. Department of Obstetrics and Gynecology. Alfredo da Costa Maternity. Lisbon. Portugal.

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METHODS

This was a retrospective cohort analysis of 208 singleton stillbirth delivered in a tertiary-perinatal referral maternity from January 2000 to December 2009.

Late stillbirth was defined as the birth of an infant with no signs of life (Apgar *score* 0/0 at 1st and 5th minute, respectively) at or beyond 28 weeks gestation.

Satisfactory antenatal care surveillance was defined as having 3 appointments in a medical center and one ultrasound.

The cause of death was classified following the ReCoDe system (Gardosi et al [6]).

Small for gestational age (SGA) was defined as a newborn birth weight below the 10th centile for GA and gender.[6] All cases of unsatisfactory antenatal care were excluded for the analysis considering birth weight.

Analysed data included:

- Prenatal care data: maternal age, race, tobacco use, parity, obstetrical past history (including previous fetal demise, previous fetal growth restriction, or preterm delivery), maternal medical disease (chronic hypertension and preeclampsia, thrombophilia, gestational diabetes, maternal infectious disease), fetal related pathology (growth restriction, oligohydramnios, isoimmunisation, congenital malformations) and placental abnormalities (insertion or implantation site abnormalities).
- Delivery data: gestational age (GA) at birth (determined from ultrasound or last menstrual period if the former was not available) and birth weight.
- Post-partum study: results of fetal autopsy and pathological examination of the placenta and umbilical cord.

Statistical analysis was performed using SPSS for windows 13th version. For comparison of proportions the χ^2 test or, when appropriate, the Fisher's exact test was applied. Observed differences between data were considered statistically significant when $P < 0.05$ or confidence limits did not embrace unity.

RESULTS

Over the study period there were 208 cases of singleton stillbirths. Considering the 59873 institutional births that occurred during the 10-year period, the stillbirth overall incidence was 3.5 per 1000 pregnancies. Of these, 197 (95%) were antepartum and 12 (5.8%) occurred intrapartum.

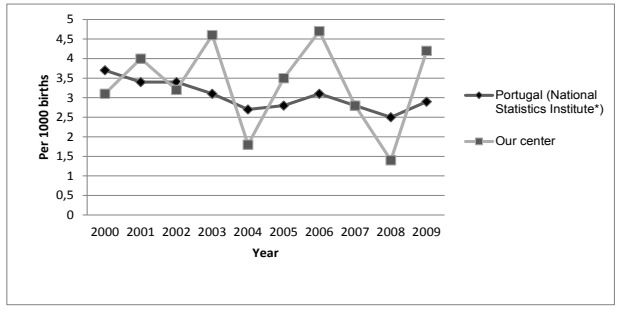

Figure 1: Trends in late stillbirths, 2000-2009. p = ns. (*www.ine.pt;).

During this time no significant trend in the incidence of stillbirth was demonstrated (Fig. 1).

The median maternal age was 30y (P 25-75; 25-34), 23% were over 35 years. Fifty per cent were nulliparous.

In 14% of cases there was no antenatal care.

The most relevant feto-maternal characteristics are reported in Table 1.

The mean (±SD) gestational age (GA) at diagnosis was 34 weeks (±4) and 72 (35%) were term pregnancies (incidence 1.2 ‰). Mean (SD) birth weight was 2168g (±919).

The primary cause of death was fetal, corresponding to the isolated factors most likely contributing to fetal demise (Table 2). In 51 cases (24.5%) no relevant condition was found.

No trend in the incidence of stillbirth secondary to different aetiologies was demonstrated over the years.

Of the 208 total stillbirths, 51 (24.5%) were unexplained. To ascertain a definite diagnosis, the quality of diagnostic information available, including autopsy and placental histopathological findings are crucial. Unfortunately, in the study period, we were only able to obtain complete data in 21 (41%) of unexplained cases. Only 61% (31 / 51) had autopsy examination and data from placental examination were available in only 47% (24 / 51).

Unexplained stillbirth was associated with nulliparity ($p < 0.001$). Poor antenatal care, advanced maternal age and GA had no statistically significant association with unexplained stillbirth.

Fetal conditions were present in 59 cases: 25% (45 / 180) were considered SGA; in this group, in 24 cases (53%), this was the only relevant condition found (without any other fetal-maternal disease associated). Mean (±SD) GA at diagnosis in SGA was 33 weeks (± 4) and there was an association between SGA and early GA ($p = 0.016$).

There were 4 cases of severe fetal anomaly and 1 stillbirth secondary to congenital cardiac disease. Infection (confirmed by placental and fetal evidence) was well documented in 6 cases (3 cases of *Candida albicans* spp pneumonia, 1 case of Herpes simplex viral infection, 1 case of malaria infection and 1 *Escherichia coli*). Two stillbirths had non-immune hydropsia and in 1 case there was a fetomaternal haemorrhage.

There were 56 cases where placental factors were identified, which included 36 deaths from placental abruption, 18 deaths from placental insufficiency and 2 cases of acute bleeding in placenta *praevia*. In 24 cases (67%) no risk factors for placental abruption were identified. In eight cases hypertensive disorders were present and five were smokers (> 10 cigarretes).

Placental factors were associated with early GA ($P = 0.027$, Fig. 2).

Maternal medical disorders were identified in 44 stillbirths over the study period. Hypertensive disorders were an important risk factor in twenty three deaths and there was a correlation with early gestacional age ($p = 0.028$). Five women had diabetes mellitus; three had subsequentely diagnosis of trombophilia (antiphospholipid antibody

Table 1: Feto-maternal characteristics*

Age (median; P 25 - 50)	30 (25 - 34)
Parity	
Nulliparous	104 (50 %)
Multiparous	96 (46 %)
Parity of four or more	8 (4 %)
Maternal race (N = 185)	
Caucasian	130 (63 %)
African	40 (19 %)
Other	12 (5 %)
Smokers : >10 cigarretes (N = 188)	47 (23 %)
Birth weight g (Mean; ± SD)	2168 (± 919)

* N=208 except were stated

Table 2: Etiology of late stillbirths

Fetal death primary cause	N (%)
Unexplained	51 (24.5)
Associated with:	
Fetal pathology	59 (28.4)
Placental factors	56 (26.9)
Maternal conditions	44 (21.2)
Amniotic fluid disorders	22 (10.6)
Umbilical cord events	20 (9.6)

syndrome, protein C deficiency and factor V Leiden heterozigoty) and the remaining had other conditions known to be associated with an increased risk of stillbirth (obstetric cholestasis, renal infection disease, multiple medication, toxic abuse and one case of maternal injury with uterine rupture). Amniotic fluid disorders were identified in 22 deaths, in all cases infection (chorioamnionitis) was well documentated in pathological examination.

Twenty stillbirths were secondary to umbilical cord accidents: 10 cases occurred at term pregnancies and in 3 cases stillbirth was a intrapartum phenomenon. The diagnosis of umbilical cord accident was made only with pathological evidence of obstruction or circulatory compromise on umbilical cord examination and other causes of stillbirth were excluded. There were fourteen cases of constricting loop or knot, 1 prolapse and 1 velamentous insertion. There were also three cases of infection (funisitis) and one cord rupture. The overall cord factors were associated with late GA (*P* = 0.002, Fig. 3).

DISCUSSION

Stillbirth is a major obstetric complication. Stanton and is co-workers estimated as 3.2 million the number of global stillbirths; stillbirth rates ranged from 5 per 1 000 in rich countries to 32 per 1 000 in developing countries for the year 2 000 using data from 190 countries.[2] The overall ten year old prevalence of 3.5 per 1 000 rate observed in our study was comparable with the nationwide and to those reported by developed countries. The improvement in antenatal assistance observed in recent years has not affected late fetal mortality and during the study period no significant trend in the incidence of stillbirth was demonstrated.

Despite the efforts made to identify the main culprits, a significant percentage still lacks an explanation; however, this is a concept that can only be applied to cases where, despite an exhaustive investigation regarding clinical, fetal-pathologic and placental aspects, no cause can be ascertained for late stillbirth.

In our study, 24.5% of all stillbirths were unexplained, which is consistent with previous studies. We believe that a complete pathological and serological work-up can be helpful in identifying a trend in the incidence of unexplained late stillbirth.

In this study, unexplained stillbirth was associated with nulliparity but other factors can be related; a large study of

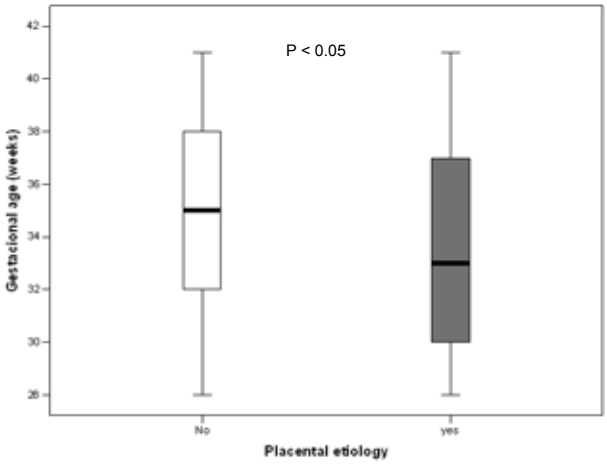

Figure 2: Overall placental factors in relation to gestational age.

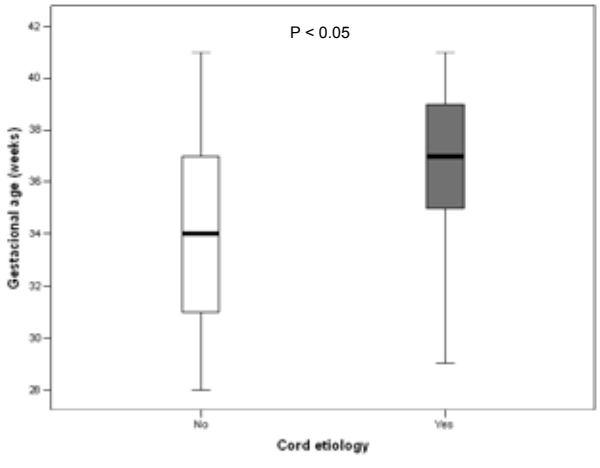

Figure 3: Overall cord factors in relation to gestational age.

unexplained stillbirth reported the following characteristics as independent risk factors: maternal pre-pregnancy weight greater than 68 kg, birth weight ratio (defined as *ratio* of birth weight to mean weight for gestational age) between 0.75 and 0.85 or over 1.15, parity of three or more, primiparity and low socioeconomic status.[7]

Maternal diseases associated with uteroplacental insufficiency, placental infarction, or abruptio placentae, like hypertension, diabetes mellitus, renal disease and some vasculitides are associated with an increase in late stillbirth. Hypertensive disorders of pregnancy are one of the major causes of maternal and fetal morbidity and mortality, complicating 10% to 16% of all pregnancies[8] and are likely to be the best known cause of fetal death in western countries. The stillbirth rate associated with mild essential hypertension is low and similar to the rate in the general population although the risk of stillbirth is increased in chronic hypertension when there is associated placental insufficiency.[9]

Stillbirth is strongly associated with fetal growth restriction (FGR).[10,11] The risk factors and potential causes of stillbirth and FGR largely overlap. FGR is associated with a number of maternal, fetal and placental risk factors and, for some authors, not a real cause of stillbirth but a highly relevant associated condition. In our study, using the ReCoDe system, FGR represents an important fetal condition associated with stillbirth that doesn't require a clear demonstration of a causal relation and that leads to a relevant reduction of the incidence of unexplained deaths.[12] It is a fact that in our series SGA has been found in a significant proportion of cases, half of them being the only relevant condition without any other feto-maternal disease. This reinforces the importance of regular antenatal care attendance. Identification of SGA may be one of the reasons why adequate antenatal care reduces stillbirth.

Several studies have identified an association between fetal death in late pregnancy and advanced maternal age[11,13] that remains after adjusting for medical disease, parity, and race.[14] In our study, an important number of patients were over 35 years of age although the small size of the sample didn´t allow us to make an isolated analysis of this risk factor.

Umbilical cord abnormalities account for 3.4 - 15% of stillbirth.[15] It must be emphasized that umbilical cord accidents are a pathological diagnosis that requires demonstrable cord occlusion, with resultant hypoxic tissue injury, in the absence of other clear causes of fetal death. This was shown in 17 cases in our study and in a further 3 cases, cord etiology was suspected but unproven. In face of our results and according to the available data in the literature, it appears that umbilical cord accidents make a significant contribution to the overall incidence of fetal demise at late gestational pregnancies.

This is a particularly important aspect, as the categorization of the cause of the initial stillbirth will allow for better estimates of individual recurrence risk, counselling affected parents and treatment of previously undiagnosed medical conditions.

CONFLICT OF INTERESTS

None stated.

FUNDING SOURCES

None stated.

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