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Maria Pekkola, Minna Tikkanen[a], Mikko Loukovaara, Jouko Lohi, Jorma Paavonen and Vedran Stefanovic[a,*]

Postmortem examination protocol and systematic re-evaluation reduce the proportion of unexplained stillbirths

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Abstract

Background: Stillbirth often remains unexplained, mostly due to a lack of any postmortem examination or one that is incomplete and misinterpreted.
Methods: This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Helsinki University Hospital, Finland, and comprised 214 antepartum singleton stillbirths from 2003 to 2015. Maternal and fetal characteristics and the results of the systematic postmortem examination protocol were collected from medical records. Causes of death were divided into 10 specific categories. Re-evaluation of the postmortem examination results followed.
Results: Based on our systematic protocol, the cause of death was originally defined and reported as such to parents in 133 (62.1%) cases. Re-evaluation of the postmortem examination results revealed the cause of death in an additional 43 (20.1%) cases, with only 23 (10.7%) cases remaining truly unexplained. The most common cause of stillbirth was placental insufficiency in 56 (26.2%) cases. A higher proportion of stillbirths that occurred at ≥39 gestational weeks remained unexplained compared to those that occurred earlier (24.1% vs. 8.6%) (P = 0.02).
Conclusion: A standardized postmortem examination and a re-evaluation of the results reduced the rate of unexplained stillbirth. Better knowledge of causes of death may have a major impact on the follow-up and outcome of subsequent pregnancies. Also, closer examination and better interpretation of postmortem findings is time-consuming but well worth the effort in order to provide better counseling for the grieving parents.

Keywords: autopsy; placental insufficiency; postmortem examination; re-evaluation; stillbirth.

Introduction

Stillbirth complicates five per 1000 pregnancies of ≥22 gestational weeks in high-income countries [1]. In Finland, the stillbirth rate is approximately three per 1000 births [2], the rate falling to 1.8 per 1000 births with the exclusion of stillbirths of <28 gestational weeks [3]. The reduction seen in neonatal mortality is not reflected in stillbirth rate [3]. Risk factors and causes of stillbirth are poorly known, and parent counseling is often unsatisfactory [4].

Evidence of the overall performance of postmortem examinations and their impact on subsequent pregnancies is currently poor [5]. Better knowledge of the cause of stillbirth would have a major impact on quality of life and would allow better estimation of the risk for recurrence [6]. Even in high-income countries, the proportion of stillbirths undergoing systematic postmortem examination is low [7], with many stillbirths thus remaining unexplained [8].

Our primary objective was to determine the value of a postmortem examination protocol and systematic re-evaluation of the cause of stillbirth. Secondly, we defined the causes of stillbirth stratified by gestational age.

Key message

A standardized postmortem examination with re-evaluation reduced the rate of unexplained stillbirth.

[a]Minna Tikkanen and Vedran Stefanovic contributed equally to this work.

***Corresponding author: Prof. Vedran Stefanovic,** MD, PhD, Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, PO Box 140, 00029 Helsinki, Finland, Tel.: +358 50 427 1230, E-mail: vedran.stefanovic@hus.fi
Maria Pekkola, Minna Tikkanen, Mikko Loukovaara and Jorma Paavonen: Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
Jouko Lohi: Department of Pathology, University of Helsinki, Helsinki, Finland

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Materials and methods

This retrospective hospital-based cohort comprised all singleton antepartum stillbirths ≥22+0 gestational weeks or with a birthweight of ≥500 g at the Department of Obstetrics and Gynecology, Helsinki University Hospital, Finland, between 2003 and 2015. This is a tertiary teaching university hospital with a substantial proportion of high-risk pregnancy referrals. Gestational age was determined according to the last menstrual period and corrected at the first-trimester screening if discrepancy in crown-rump length exceeded 4 days. Among 62,319 children born at the unit during this period, 325 (5.2/1000) were stillborn. After excluding multiple pregnancies, intrapartum deaths, and stillbirths of unknown gestational age, 214 stillbirth cases were available for the final analysis.

All data were gathered from medical records. We recorded maternal baseline characteristics, obstetric history and pregnancy-related variables, and characteristics of the stillborns. Smoking, alcohol use, and drug abuse were self-reported at the first visit to the local antenatal clinic. Assisted reproductive technology included conception by insemination, ovulation induction, in-vitro fertilization, frozen-embryo transfer, and intra-cytoplasmic sperm injection.

Essential hypertension was defined as blood pressure over 130/90 mm Hg before 20 gestational weeks. Gestational hypertension was diagnosed if systolic blood pressure had increased more than 30 mm Hg or diastolic blood pressure by more than 15 mm Hg after the 20th gestational week, exceeding 130/90 mm Hg. Pre-eclampsia was determined as new-onset hypertension combined with proteinuria ≥300 mg/24 h or with hematological complications, renal insufficiency, or impaired liver function. Diagnostic criteria for gestational diabetes were fulfilled, if the venous plasma glucose concentration in the 2-h 75-g glucose tolerance test was ≥5.3 mmol/L (during 2003–2006, ≥5.1 mmol/L) at baseline, ≥10.0 mmol/L at 1 h, or ≥8.6 mmol/L at 2 h after glucose loading. One abnormal result justified the diagnosis. Preterm premature rupture of membranes was determined as rupture of membranes before 37 gestational weeks. Fetomaternal hemorrhage was defined as a fetal hemoglobin concentration ≥1% in maternal blood determined by high-performance liquid chromatography. Intrahepatic cholestasis of pregnancy was defined as a fasting serum bile acid concentration ≥10 μmol/L.

New Finnish growth charts (2013) determined relative birthweight in stillbirths at ≥23+0 gestational weeks [9] and international growth charts in stillbirths between 22+0 and 22+6 gestational weeks [10]. Stillborns with a relative birthweight <−2 standard deviation (SD) were considered small for gestational age (SGA). The European Concerted Action on Congenital Anomalies and Twins (EUROCAT, European surveillance of congenital anomalies) classification characterized anomalies as major or minor [11]. Chromosomal abnormalities included both aneuploidies and structural abnormalities such as deletions, duplications, and translocations. Each patient was offered a full postmortem evaluation according to the institutional standardized protocol including autopsy, fetal and placental histopathologic examinations, karyotype, and selected blood tests (Table 1).

Table 1: Protocol for stillbirth examination at Helsinki University Hospital at the time of the study.

Mother
Immediately after diagnosis
– Cervical samples (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Streptococcus agalactiae*, *Listeria monocytogenes*)
– Blood culture twice in 30 min, if fever (≥38°C)
– Blood samples for microbial antibodies: influenza, adenovirus, RSV, parainfluenza, enterovirus, parvovirus, CMV, VZV, HSV, chlamydia, mycoplasma, and toxoplasma
– Other blood samples: phospholipid antibodies, DNA antibodies, blood count, CRP, bile acids, ALAT, TSH, free thyroxin, TT, FIDD, haptoglobin, fetal hemoglobin, blood group, blood group antibodies, Coombs test, blood glucose
In 2 weeks
– Paired serums for microbial antibodies
In 2 months
– Thrombophilia screening
Stillborn
– Macroscopic examination: sex, length, weight, anomalies, maceration, digital images
– Cardiac puncture (bacterial culture, fetal blood group)
– Broad bacterial culture from ear canal
– Samples for chromosomal culture from skin and from umbilical cord insertion site
– X-ray if recommended by geneticist
– Autopsy
– Chromosomal microarray analysis if recommended by geneticist[a]
Placenta
– Macroscopic examination
– Weight
– Bacterial culture
– Chromosomal culture
– Histologic examination

[a]Since 2016. RSV, Respiratory syncytial virus; CMV, cytomegalovirus; VZV, varicella zoster virus; HSV, herpes simplex virus; CRP, C-reactive protein; ALAT, alanine transaminase; TSH, thyroid-stimulating hormone; TT, thromboplastin time; FIDD, d-dimer.

We reviewed medical records including all postmortem examination results and death certificates. Causes of death were then classified into 10 categories (fetal anomaly or disease, placental insufficiency, placental abruption, umbilical cord complication, infection, fetal anemia, other causes, unexplained death despite a full postmortem evaluation, unknown cause of death based on limited or no evaluation, and unknown cause based on missing data). Fetal anomalies and diseases included chromosomal abnormalities, fetal syndromes, and single or complex structural anomalies considered to be the cause of death. In defining placental lesions, we used the terminology agreed upon in the Amsterdam Placental Workshop Group Consensus Statement [12]. Placental insufficiency in association with SGA was the presumed cause of death in the presence of the following: maternal vascular malperfusion of the placental bed (multiple or large placental infarctions, distal villous hypoplasia, accelerated villous maturation, and decidual arteriopathy), fetal vascular malperfusion (thrombosis of the fetal vasculature, avascular villi, and widespread intramural fibrin deposition), delayed villous maturation, or villitis of unknown etiology. Placental abruption was determined as the cause of death in the presence of retroplacental hematoma combined with clinical findings matching placental abruption such as vaginal bleeding or abdominal pain. Umbilical cord complications included true knots and entanglements, abnormalities in length (<40 cm or >70 cm) or coiling (≤0.1 coils/cm or ≥0.3 coils/cm), strictures, and abnormal insertion sites. Infection was the cause of death in cases of histological chorioamnionitis, positive fetal blood culture, or significant seroconversion or in the presence of immunoglobulin M (IgM) antibodies to common pregnancy-complicating microbes, except for parvovirus (Table 1). The group "fetal anemia" comprised red blood cell alloimmunization, fetomaternal hemorrhage, and fetal anemia due to parvovirus or of unknown etiology. Other causes included macrosomia and asphyxia related to diabetes and arrhythmia related to high bile acids in intrahepatic cholestasis of pregnancy.

Finally, we estimated the added value of a systematic re-evaluation of the postmortem examination results in determining the cause of death in cases originally classified and reported to parents as unexplained deaths. Two experienced fetal medicine specialists (V.S., M.T.) analyzed cases with any discrepant clinical and postmortem data, and the most probable cause was determined by consensus. We also analyzed the causes of stillbirths by gestational age and divided them into two categories ($22+^{0}$–$27+^{6}$ vs. ≥28 and <39 vs. $39+^{0}$–$41+^{6}$ gestational weeks).

Ethical approval

The Ethics Committee of the Helsinki and Uusimaa Hospital District approved the study with permission number 92/13/03/03/2014. The parturients gave their informed consent for postmortem examinations.

Statistical analyses

Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Comparisons concerning the cause of stillbirth between women in subgroups by gestational age were evaluated using the chi-square (χ^2) test or Fisher's exact test. A two-sided P-value of <0.05 denoted statistical significance.

Results

Baseline characteristics and obstetric history variables of the mothers are presented in Table 2 and pregnancy-related variables and characteristics of the stillborns in Table 3. Of the 214 cases of singleton antepartum stillbirth, 74 (34.6%) occurred before 28 gestational weeks and 140 (65.4%) at 28 gestational weeks or later. Of the mothers, 124 (57.9%) had visited the antenatal clinic of the maternity hospital for various reasons after 22 gestational weeks.

A total of 170 (79.4%) stillborns underwent autopsy, and 189 (88.3%) had placental histology available. The autopsy rate was 77.0% vs. 80.1% in stillbirths <28 and ≥28 gestational weeks. In full-term stillbirths ($39+^{0}$–$41+^{6}$ weeks of gestation), the autopsy rate was 69.0%. Overall, 44 (20.6%) stillborns underwent no autopsy. Of these, the diagnosis was evident based on clinical or pregnancy-related findings in 18 (40.9%) cases (eight placental abruptions, four umbilical cord complications, one Rh-immunization, four cases of trisomy 18, and one case of triploidy). The entire blood-test panel included in the protocol was performed in 147 (69.0%) women. When the

Table 2: Selected baseline characteristics and obstetric history variables.

	Total (n = 214)
Age, years	32.1 ± 5.6
≥35	73 (34.0)
BMI, kg/m^2[a]	24.2 ± 5.0
Parous women	115 (53.7)
Substance abuse	
Tobacco[a]	24 (11.8)
Alcohol[a]	2 (1.1)
Drugs	3 (1.4)
ART	13 (6.1)
Maternal comorbidities	
DM type 1	13 (6.1)
Essential hypertension[a]	10 (4.7)
Thrombophilia[a]	
Diagnosed either before or after pregnancy	15 (8.2)
	Total (n = 115)[b]
Prior	
Stillbirth	9 (7.8)
Placental abruption	2 (1.7)
SGA	11 (9.6)
Pre-eclampsia	11 (9.6)

Data are presented as mean ± SD or n (%). [a]Missing data: BMI n = 18; tobacco n = 11; alcohol n = 32; essential hypertension n = 4; thrombophilia n = 32. [b]Parous women. BMI, Body mass index; ART, assisted reproductive technology; DM, diabetes mellitus; SGA, small for gestational age.

Table 3: Pregnancy-related variables and characteristics of stillborns.

	Total (n = 214) n (%)
Bleeding during pregnancy	37 (17.3)
Fetomaternal hemorrhage	17 (8.7)
PPROM	23 (10.7)
Infection	22 (10.3)
Gestational diabetes	15 (7.1)
Pre-eclampsia	19 (9.0)
Gestational hypertension	15 (7.1)
Intrahepatic cholestasis of pregnancy	7 (4.1)
Sex	
Male	109 (50.9)
Female	103 (48.1)
Unknown	2 (0.9)
Relative birthweight	
< −2 SD	73 (34.1)
−2 SD – +2 SD	120 (56.3)
>2 SD	21 (9.8)
Anomaly[a]	
Major[b]	34 (18.8)
Minor	5 (2.8)
Chromosomal abnormality[a b]	13 (7.1)

[a]Missing data: fetomaternal hemorrhage n = 19; gestational diabetes n = 3; pre-eclampsia n = 2; gestational hypertension n = 2; intrahepatic cholestasis of pregnancy n = 44; anomaly n = 33; chromosomal abnormality n = 32. [b]Major anomaly cause of stillbirth n = 25; chromosomal abnormality cause of stillbirth n = 9. PPROM, Premature preterm rupture of membranes.

cause of death was obvious, not all the blood tests were considered necessary. Karyotype was assessed by the culturing of fetal tissue or placenta or both and was successful in 182 (87.4%) stillbirths.

The cause of death was defined by our examination protocol in 133 (62.1%) cases. Clinical findings revealed the cause in 36 (16.8%), postmortem findings in 23 (10.7%), and both in 71 (33.2%). The cause was discovered despite discrepant clinical and postmortem findings in three (1.4%) cases. In 81 (37.9%) cases, the cause of death was either unknown or unexplained or the data were missing (Figure 1). The systematic re-evaluation of postmortem examination results revealed the cause of death in an additional 43 (20.1%) cases, making the total number of explained causes of death 176 (82.2%). Despite the systematic postmortem examination and re-evaluation of results, the cause of death remained unexplained in 23 (10.7%) cases. In 13 (6.1%) cases, the cause of death remained unknown based on limited or no postmortem examination, and two (0.9%) cases were unavailable for analysis (Figure 1).

Re-evaluation of postmortem examination results revealed an additional 22 cases of placental insufficiency, making it the most common cause of death with 56 (26.2%) cases. In other groups, re-evaluation uncovered a total of 21 cases (Table 4). Causes of death differed by gestational age. Placental insufficiency was more common in stillbirths before 28 gestational weeks (40.5%) than at 28 weeks or thereafter (18.6%) (P = 0.001). On the other hand, umbilical cord complications were more common at or after 28 weeks (17.1% vs. 6.8%, P = 0.04); 29 (13.6%) stillbirths occurred at or after 39 gestational weeks. Comparing these full-term stillbirths ($39+^{0}$–$41+^{6}$ weeks of gestation) to those occurring earlier, a higher proportion of full-term stillbirths remained unexplained despite systematic postmortem examination and re-evaluation of postmortem results (24.1% vs. 8.6%, respectively) (P = 0.02) (data not shown).

Discussion

Our principal finding was that, in the large majority of the cases, the cause of death was possible to determine. Without postmortem examination, however, the cause of death would have been determinable in less than 20%. Systematic re-evaluation of the postmortem examination results provided significant additional value and revealed the cause of death in two-thirds of cases originally reported as unexplained stillbirths.

The strength of our study was its standardized postmortem examination protocol with detailed evaluation of the placenta and with review both of medical records and of fetal death certificates. Earlier studies have shown that this approach yields more accurate data and fewer discrepancies [13]. Our re-evaluation of the findings case by case had added value and improved the results.

Several limitations of the study have to be acknowledged. Although we included more than 60,000 deliveries over 13 years, our sample size still was rather small. Our simple clinical classification ensured its suitability for evaluation of this particular cohort with antepartum stillbirths.

Reinebrant et al. collected 85 stillbirth reports from 50 countries including 489,089 stillbirths and found the reports to be inconsistent with differing definitions of stillbirth. Also, these reports were often of poor quality, only a small number of them basing on high-quality perinatal mortality audit [14]. They concluded that implementation of the ICD-PM (International Statistical Classification of Diseases and Related Health Problems-Perinatal Mortality) classification as part of the World Health Organization (WHO) Perinatal Audit and Review Guide [15] would be a

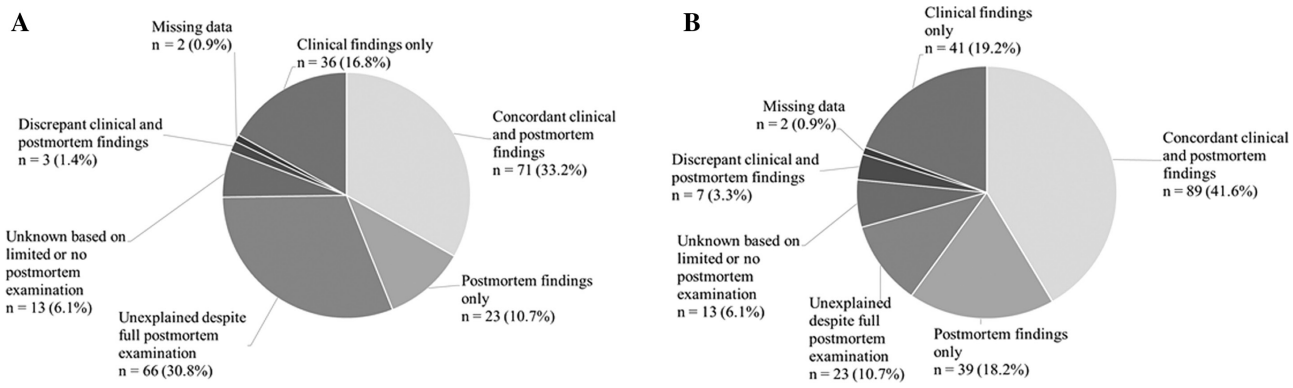

Figure 1: Added value of re-evaluation of causes of stillbirth after systematic postmortem examination. Proportions of explained and unexplained cases before (A) and after (B) re-evaluation.

Table 4: The most probable cause of death based on clinical and histopathological diagnosis.

	Before re-evaluation	After re-evaluation
Cause of death	n (%)	n (%)
Fetal anomaly or disease	27 (12.6)	29 (13.6)[a]
Placental insufficiency	34 (15.9)	56 (26.2)
Placental abruption	26 (12.1)	28 (13.1)
Umbilical cord complication	25 (11.7)	29 (13.6)
Infection	12 (5.6)	13 (6.1)
Fetal anemia	7 (3.3)	15 (7.0)
Other causes	2 (0.9)	6 (2.8)[b]
Unexplained or unknown cause of death	81 (37.9)	38 (17.8)
Total	214 (100.0)	214 (100.0)

[a]Major anomaly n = 25; dilating cardiomyopathy n = 3; incontinentia pigmenti without karyotype analysis n = 1. [b]Intrahepatic cholestasis of pregnancy n = 2 (arrhythmia related to high bile acids); type 1 diabetes n = 3; gestational diabetes n = 1 (macrosomia and asphyxia related to diabetes).

remarkable improvement. However, good quality reports from high-income countries using clinical classification systems reflect the fact that classification system requirements alternate across different settings [14].

A minor limitation of the study was that during the study period, in determining the maternal fetal hemoglobin level, we applied high-performance liquid chromatography, not the more accurate flow cytometry analysis which is nowadays standard [16]. Karyotype analysis that was used at the time of the study was of limited value compared to chromosomal microarray analysis, a method not available at our unit before 2016. Our stillbirth evaluation currently involves this technique, which is beneficial in unexplained stillbirths, in stillbirths with structural anomalies, and in intrauterine growth restriction (IUGR)-associated stillbirths [17, 18].

Comparison of figures on baseline characteristics to figures provided by the Finnish Medical Birth Register [2] showed that our case women did not differ from pregnant women in the general population by age, body-mass index, smoking habits, or by incidence of gestational diabetes. The incidence of congenital anomalies was higher in our study population (22.1%) than in the Medical Birth Register population (4.4%), as could be expected. Our stillbirth rate was 5.2/1000, much higher than the Finland's norm of 3/1000 [2]. This reflects the substantial proportion of high-risk pregnancies referred to our tertiary unit. The incidence of placenta-related pregnancy complications (pre-eclampsia, placental abruption, fetal growth restriction) in our cohort differed from that seen in earlier studies of Finnish pregnant women, such as pre-eclampsia of 2.5% [19], SGA of 2.0% [20], and placental abruption of 0.4% [21]. In our current study population, the rates were nearly four-fold for pre-eclampsia, nearly 40-fold for placental abruption, and 16-fold for SGA.

The autopsy rate in earlier studies has ranged from 12% to 72%, with the highest autopsy rate actualizing in a

tertiary center [22–24]. Our relatively high autopsy rate of 79% reflects the quality of our debriefing care; all parents were offered a face-to-face appointment with an obstetrician. In one recent study, the proportion of unexplained stillbirths fell from 76% after clinical and laboratory assessment to 39% after placental examination, and after autopsy to 26% [24], reflecting the importance of a comprehensive postmortem examination protocol. According to a recent report from the Stillbirth Collaborative Research Network, the most useful diagnostic tests in the workup for causes of stillbirth involved placental pathology, autopsy, and genetic testing [25].

Re-evaluation of postmortem results revealed the cause of death in two-thirds of the cases previously determined as unexplained. This is an important finding emphasizing the role of a systematic examination protocol. In a recent study that compared medical certificates of stillbirth and the adjudicated cause of stillbirth, 49% of the certificates contained major errors. After re-evaluation, causality could be assigned in 78% of previously unexplained stillbirths [26].

In a Dutch cohort of 750 stillbirths, the main cause of death before 32 weeks of gestation was placental bed pathology [27], in line with our data. In one systematic review of placental pathology and stillbirth, the proportion of placental causes, depending on the classification system, ranged from 11% to 65% [28]. In our study, placental insufficiency combined placental hypoxic-ischemic lesions with fetal growth impairment. We found that severe growth impairment led to intrauterine demise already during the second trimester, with placental insufficiency playing a major role. Umbilical cord complications were more frequent after 28 gestational weeks than in earlier stillbirths, in line with earlier findings [29, 30].

A recent study from Sweden [30] showed similar distribution of causes of death in regard to placental insufficiency, placental abruption, umbilical cord complication, and unexplained stillbirth compared to our cohort. Infection, in contrast, was the cause of death in 22% in the Swedish study vs. only 6% in ours. The Swedish study used the Stockholm classification, which also includes intrapartum stillbirths. We, however, excluded all intrapartum deaths, many of which were caused by delivery of prenatally detected fatal trisomy, fetuses with severe IUGR, and premature rupture of membranes with chorioamnionitis at extremely low gestational age. Such fetuses were alive before the onset of labor but were not monitored as the intrapartum or early neonatal death was an expected outcome.

Depending on the classification system, the proportion of unexplained fetal deaths in earlier studies has ranged from 9.5% to 50.2% [31]. Our proportion of unexplained deaths was 10.7%, which is strikingly low. Full-term stillbirths remained unexplained in 24%, compared to 9% of stillbirths at earlier gestational ages. A recent study from Australia showed similar results [32]. In our study, autopsies were performed in 69% of full-term stillbirths compared to 81% of earlier stillbirths. This may explain the greater proportion of unexplained deaths at full term.

The results and conclusions of our study may not be generalizable but could be applicable for other high-income countries with low perinatal mortality and stillbirth rate and a well-organized and universally accessible publicly funded maternity health care.

Conclusion

A standardized systematic postmortem examination and a re-evaluation of the results reduced the rate of unexplained stillbirth. Close examination of postmortem findings is time-consuming but well worth the effort in order to provide better counseling for the grieving parents.

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