Placenta 129 (2022) 77–83

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

The key role of examining the placenta in establishing a probable cause for stillbirth

Hein Odendaal [a,*], Robert Pattinson [b], Pawel Schubert [c], Deidré Mason [a], Lucy Brink [a], Stefan Gebhardt [a], Coenraad Groenewald [a], Colleen Wright [c,d]

[a] Department of Obstetrics and Gynecology, Stellenbosch University, P O Box 241, 8000, Cape Town, South Africa
[b] SAMRC/UP Maternal and Infant Health Care Strategies Unit, University of Pretoria, Private Bag X20, Hatfield, 0028, South Africa
[c] Division of Anatomical Pathology, Tygerberg Hospital, National Health Laboratory Service, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
[d] Lancet Laboratories, Johannesburg, South Africa

ARTICLE INFO

Keywords:
Stillbirth
Classification
Placental histology
Autopsy
WHO ICD PM

ABSTRACT

Introduction: Autopsy is regarded as the "gold standard" to determine probable causes of stillbirths. However, autopsy is expensive and not readily available in low- and middle-income countries. Therefore, we assessed how the clinical cause of death is modified by adding placental histology and autopsy findings.

Method: Data from the Safe Passage Study was used where 7060 pregnant women were followed prospectively. Following a stillbirth, each case was discussed and classified at weekly perinatal mortality meetings. This classification was later adapted to the WHO ICD PM system. Clinical information was presented first, and a possible cause of death decided upon and noted. The placental histology was then presented and, again, a possible cause of death, using the placental and clinical information, was decided upon and noted, followed by autopsy information. Diagnoses were then compared to determine how often the additional information changed the initial clinical findings.

Results: Clinical information, placental histology, and autopsy results were available in 47 stillbirths. There were major amendments from the clinical only diagnoses when placental histology was added. Forty cases were classified as due to M1: complications of placenta, cord, and membranes, when placental histology was added compared to 7 cases with clinical classification only, and M5: No maternal condition identified decreased from 30 cases to 3 cases. Autopsy findings confirmed the clinical and placental histology findings.

Discussion: Clinical information together with examination of the placenta revealed sufficient information to diagnose the most probable cause of death in 40 of 47 cases of stillbirth (85%).

Stillbirth is the delivery of a fetus which shows no signs of life at birth at a gestational age of at least 22 weeks [1]. As stillbirth rates are declining slower than infant or maternal mortality rates [2], more attention should be focussed on this global problem. Numerous classification systems of stillbirth have been proposed [3]. Clinical information prior to and at the time of the demise, is essential for the full utilization of these classification systems. Although autopsy has traditionally been regarded as the gold standard to determine the probable cause of death in clinically unexplained stillbirth, placental pathology has increasingly been utilized as an alternative or supplementary tool to determine the cause of stillbirth. Hirst et al. studied more than 60,000 births of which 533 were stillborn, including 445 antepartum deaths [4]. After adjustment for site, the most common risk factors were infants not suspected to have been growth restricted antenatally (HR 5.0), birthweight <3rd centile (HR 4.6), HIV/AIDS (HR 4.3) and essential hypertension (HR 4.0). These risk factors are associated with placental insufficiency. Pinar et al. studied placentas from 518 stillbirths and 1200 live births. In comparison to live births, placentas of stillbirths were more commonly associated with velamentous cord insertion, diffuse distal villous hypoplasia, inflammation, vascular degenerative changes in the chorionic plate, retroplacental hematomas, intraparenchymal thrombi, parenchymal infarction, fibrin deposition, fetal vascular thrombi, avascular villi and hydrops [5]. These findings illustrate the value of histological examination of the placentas of stillbirths. Gibbins

Abbreviations: WHO, World Health Organization; ICD, International Classification of Diseases; PM, Perinatal Mortality.

* Corresponding author.
E-mail address: hjo@sun.ac.za (H. Odendaal).

https://doi.org/10.1016/j.placenta.2022.10.001
Received 12 January 2022; Received in revised form 28 September 2022; Accepted 2 October 2022
Available online 13 October 2022

Abbreviations

FHR	Fetal Heart Rate
FVM	Fetal Vascular Malperfusion
HR	Hazard Risk
ICD	International Classification of Diseases
MVM	Maternal Vascular Malperfusion
PM	Perinatal Mortality
RCT	Randomized Controlled trial
SPS	Safe Passage Study
VUE	Villitis of Unknown Etiology
WHO	World Health Organization

et al. examined 512 stillbirths and found that 23.6% had a possible or probable cause of death due to placental pathology [6].

The Stillbirth Collaborative Research Network prospectively examined stillbirths in 500 women. An autopsy was done on 512 neonates. A probable cause of death was found in 60.9% of stillbirths and a possible or probable cause in 76.2%. The most common causes were obstetric conditions (29.3%) and placental abnormalities (23.6%) [7].

Observations from another prospective study in 354 stillbirths born to 350 women highlighted the most common causes were maternal medical conditions (21%) and placental or fetal infections (19%), as well as pathological placental conditions (19%). No cause of death could be found in 18% of stillbirths [1].

A further retrospective study also used placental histopathological information and autopsy to find probable causes of stillbirths, focussing on 140 stillbirths [8]. The most common fetal finding was intrauterine growth restriction (48.54%), while after autopsy and placental histology 27.1% of the causes were attributed to placental insufficiency and 40.0% were unexplained.

Autopsy rates are declining globally [9]. Many mothers who declined autopsy believe that limited additional information could be gained from autopsy [10]. Consent to autopsy is also negatively affected by the understandably emotional response to stillbirth [11]. The need for immediate burial in many communities further hamper the performance of perinatal autopsies [12]. Verbal autopsies, where cause of death is determined from information supplied by the health care workers attending the delivery [13], have been introduced to address the lack of essential information. This method is associated with generalizations and infrequent causes of stillbirths would unlikely be identified.

As the placenta is readily available and as placental conditions are the main cause of stillbirth [6,14,15], it is necessary to determine what additional information the autopsy contributes to determining cause of death if placental histopathology has been performed.

In South Africa, where histological examination of the placenta is infrequently requested and autopsy even more infrequently, the cause of stillbirth is unexplained in 22.8% of births despite careful clinical evaluation [16]. Limited resources should therefore be utilized very carefully to obtain maximum benefit. The question therefore arises as to what additional information regarding the cause of stillbirth could be obtained by doing an autopsy after placental histopathology. Information from the Safe Passage Study (SPS) offered a unique opportunity to answer this question as histological examination of the placenta and autopsy were performed whenever possible in all stillbirths in the study [17].

1. Methods

The SPS of the Prenatal Alcohol in SIDS and Stillbirth Network (PASS) was developed to test the hypothesis that prenatal alcohol exposure is associated with increased risk for stillbirth and/or sudden infant death syndrome (SIDS). Recruitment for this prospective study began on August 1, 2007 and ended on January 31, 2015. Inclusion criteria were written informed consent, singleton or twin pregnancy, maternal age of 16 years or older, gestational age of at least 6 weeks, and ability to communicate in Afrikaans or English [17]. In this study, we focused on 93 stillbirths investigated at Tygerberg Academic Hospital, Cape Town, South Africa [15].

At the recruitment visit, participants provided informed consent which included collection of the placenta for histological examination after delivery. After a fetal demise, a separate informed consent was obtained for autopsy. Research midwives checked labour ward admissions and deliveries daily to determine if a study participant had delivered. In cases of fetal demise, the social worker and senior personnel of the study were alerted to provide support and counselling and, at an appropriate time discussed consent for autopsy [18].

When a stillbirth occurred, the participant was asked to consent to fetal autopsy and to donate fetal brain tissue [19]; consent for cord blood and the placenta was obtained at the time of recruitment. For this analysis, the primary stillbirth outcome was defined as a fetal demise delivered at 22 weeks gestation or later [20].

All stillbirths before 22 weeks were excluded from the present study. We therefore followed the definition the WHO recommends for in-country national reporting [20] The gestational age at demise was estimated by considering the following: the gestational age at delivery (as established by an early ultrasound examination), the last gestational age when there was evidence of a live fetus (e.g. recording of the fetal heart rate (FHR) or observing fetal heart activity by ultrasound), measurement of the foot length at autopsy or estimation of the gestational age by the pathologist (using organ weights and degree of maceration) [21]. Gestational age, as determined by an early ultrasound examination, was accepted as the most important indication of gestational of at delivery. In cases where there was uncertainty, such as when demise had occurred long before birth, assessment of gestational age by foot length was considered as the most helpful [21]. If the gestational age at delivery was less than 22 weeks, the delivery was reclassified as a late second trimester miscarriage [22].

Examination of the placenta and the autopsy were done by experienced perinatal pathologists (CW, PS). The pathologist received no information on the conditions surrounding the stillbirth except the gestational age at delivery. Details on examination of the placenta and autopsy are given in a previous publication [15]. Guidelines of the Amsterdam conference, as published by Khong at al. [23], and a review by Redline [24] were followed to identify placental lesions.

Placentas and selected samples of fetal organs taken at autopsy, were placed in 10% buffered formalin. The placentas were examined macroscopically, photographed, and described at the pathology laboratory according to standardised protocols (Appendix A-placenta). Placental and fetal tissues were sampled and routinely processed to Haematoxylin and Eosin-stained slides for examination. Two experienced perinatal pathologists (CW, PS) examined the slides and reported following standard templates (Appendix B - placenta). To prevent bias the only clinical information that was provided was the GA at delivery.

Diagnosis of MVM was based on a constellation of macroscopic and microscopic findings, not all of which were present in an individual case. A minimum of three items were required for the diagnosis (Fig. 1A and B). **Macroscopic findings of MVM** included placental weight for gestation, infarction and retroplacental hemorrhage. The placenta was considered small if the trimmed weight was <10th centile for the gestation [25] Macroscopic infarction was defined as firm solid areas extending from the basal plate with the apex towards the fetal surface. Any infarction in a preterm placenta and >5% infarction at term was regarded as pathological. As placental abruption is a clinical diagnosis, the corresponding pathological term, retroplacental hemorrhage (RPH), was used. Macroscopic RPH was defined as an indentation of >15% of the maternal surface of the placenta often with gross intervillous hemorrhage. **Microscopic placental features of MVM** included microscopic RPH or infarction, distal villous hypoplasia, accelerated villous

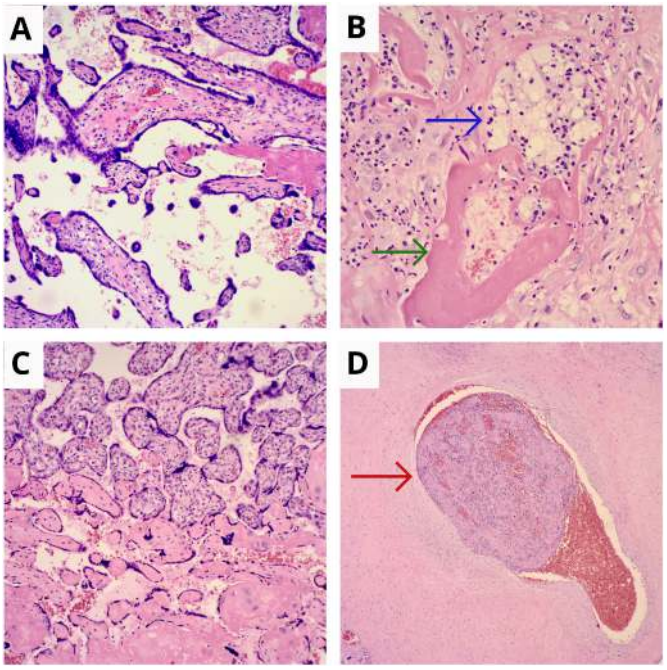

Fig. 1. A) Is a medium power image of a stem villous on top and an intermediate villous protruding from 6 o'clock. The space in the middle is taken up by very small villi with syncytial knots, a pattern called distal villous hypoplasia. B) Decidual maternal vessels showing fibrinoid necrosis (green arrow) and collection of foamy macrophages (blue arrow) with narrowing of the vessel lumen. C) A focus of avascular villi (bottom half) which contrast with the viable villi (upper half) from a case of fetal vascular malperfusion (FVM). D) Image shows a stem villous with a near-occlusive thrombus, also from a case of FVM. All images are H&E-stained sections.

maturation, decidual arteriopathy and increased syncytial knots (Fig. 1 A). Increased perivillous fibrin and increased extravillous trophoblast, previously regarded as features of MVM, are now no longer part of the Amsterdam consensus criteria for MVM but were still recorded in this study [23]. The microscopic criteria for RPH were the presence of blood beneath the decidua and dissecting into the decidua and placental parenchyma, with congestion and/or intravillous hemorrhage, sometimes with additional coagulation necrosis of the syncytiotrophoblast nuclei with overlying infarction. Distal villous hypoplasia was diagnosed when villi were small and stringy, elongated or appeared tiny, barely the size of a syncytial knot. This could be focal or diffuse and was usually only seen in placentas less than 32 weeks. Accelerated villous maturation was diagnosed when villi were hypermature for a known GA and usually associated with an increase in syncytial knots (size and number). Decidual arteriopathy refers to an absence of spiral arterial remodelling with mural hypertrophy only or with fibrinoid necrosis with foam cells (Fig. 1 B). Increased syncytial knots were reported if they were found in >33% of villi at term.

Diagnosis of FVM (see Fig. 1C and D) was based on any two of the following criteria: avascular villi, chorionic plate/stem villous thrombosis, microscopic thrombosis of the cord, or villous-stromal karyorrhexis [23].

Features of inflammation included chorioamnionitis (ascending infection), and villitis which included infectious and non-infectious villitis (villitis of unknown etiology (VUE)). Chorioamnionitis staged and graded per Redline 2003 [26] and additional features such as subchorionic micro-abscesses were noted. Villitis was recorded as acute – neutrophilic, or chronic – lymphocytic/histiocytic. If chronic features such as plasma cells or an accompanying funisitis or viral inclusions were present that might suggest a specific or infective etiology further investigations were undertaken. The remainder were recorded as VUE and graded as patchy, multifocal or diffuse and the presence of obliterative fetal vasculopathy was noted as it has prognostic significance [27,28].

All stillbirths were presented and discussed at the weekly multidisciplinary perinatal mortality meetings of the Department of Obstetrics and Gynaecology, attended by obstetricians, maternal-fetal subspecialists, neonatologists, pathologists, geneticists, ultrasonologists and midwives. The clinical information was presented first, and the most probable primary cause of death decided upon and recorded using the Perinatal Problem Identification programme (http://www.ppip.co.za/saving-babies/) The placental histology was then presented and again a probable cause of death, using the placental and clinical information, was decided upon and recorded. The same was done for the autopsy information which was presented to the meeting after the previous probable causes have been decided upon. The diagnoses were documented after each decision and kept for later analysis. At a later stage the cases were seen by two external pathologists for the SPS and presented at the SPS consensus pathology meetings for confirmation of the diagnoses. The WHO ICD PM classification of the stillbirths [29], was retrospectively applied to classify the deaths as described by Lavin et al. [30]. Stillbirths at or after a gestational age of 20 weeks were discussed at the meetings to meet the SPS definition of stillbirth. However, as South Africa uses the WHO definition of stillbirth (http://www.who.int/maternal_child_adolescent/epidemiology/stillbirth/en/),. All stillbirths before 22 weeks were excluded from the present study. We therefore followed the definition the WHO recommends for in-country national reporting [20].

Causes of demise determined according to the clinical information only or determined by combining the clinical information and the placental findings, and determined by the combination of clinical information, placental and autopsy findings were then compared to assess how often the additional information changed the initial clinical determination of the cause of the stillbirth. The SPS has been approved by the Health Research Ethics Committee of Stellenbosch University.

2. Results

There were 7110 births from 7060 pregnancies in the study. Initially 129 possible stillbirths at or after 20 weeks were identified. After the exclusion of 14 terminations of pregnancy, 14 miscarriages before 22 weeks and 8 twin pregnancies, 93 singleton stillbirths at or after 22 weeks' gestation remained for the analysis. Clinical information, placental histology, and autopsy results were available in 47 stillbirths, clinical information, and placental histology in 28, clinical information only in 15, clinical information and autopsy in 3 (Fig. 2). Placental histology was done in 75 stillbirths (80.7%) and autopsy in 50 (53.7%).

This analysis is limited to 47 stillbirths, where the information was available in all three categories (clinical information, placental histology, and autopsy). The main findings on admission for delivery of the stillbirth were suspicious placental abruption, (26%), Reduced fetal movements (19%), and preterm uterine contractions (15%) (Table 1A). The main autopsy findings were intrapartum hypoxic stress (30%), a normal fetus (21%), and poor growth/immaturity (15%) (Table 1B). The mean maternal age and parity were 24.4 years and 1.1 respectively. The mean gestational age at delivery was 214.4 days (between 30 and 31 weeks) and the mean birth weight 1316.6 g (Table 2 A). There were 49% male infants, 59% of the stillbirths were macerated and fetal death during labour occurred in 13% of participants. There were four cases of syphilis of which three were congenital syphilis at autopsy, where the women were not treated for a positive rapid precipitation reaction tests and one where the woman was successfully treated and no signs of syphilis were found at autopsy (Table 2B).Table 3A gives the causes of death using only the clinical information and Table 3B gives the causes of death with the clinical and placental histology combined. There was a marked shift in classifications from clinical only diagnoses to clinical and placental histology; 40 cases being classified as due to M1:

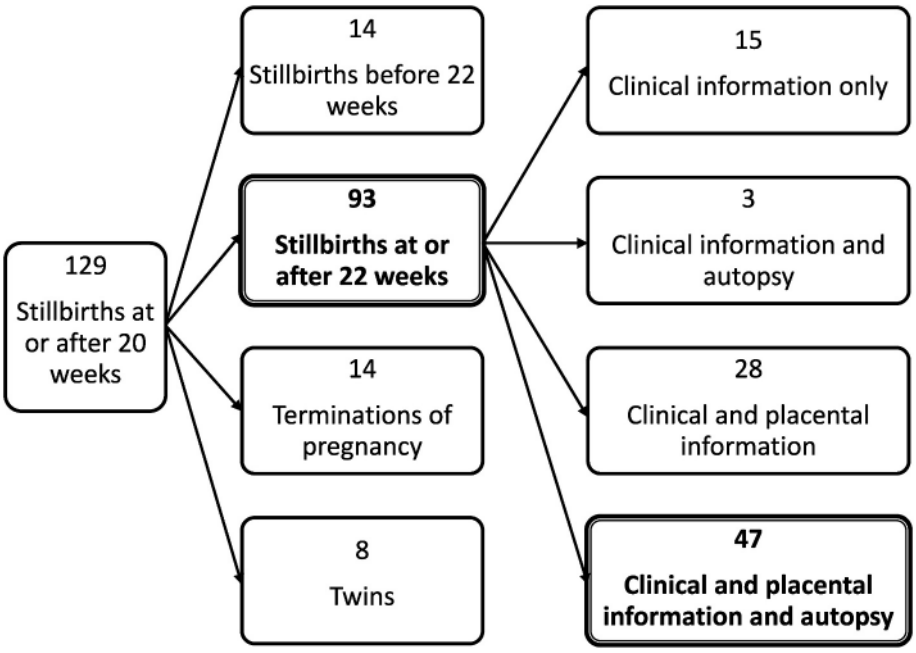

Fig. 2. Study profile.

Table 1
Main findings on admission for delivery of the stillbirth.

A: Presenting maternal clinical conditions (n = 47)		
Variable	N	%
Placental abruption suspected	12	26
Reduced fetal movement	9	19
Preterm uterine contractions	7	15
Preeclampsia	5	11
Suspected intrauterine demise	4	9
Severe fetal growth restriction	4	9
Dyspnoea	2	4
No fetal heart movement on scan (incidental)	2	4
Rupture of membranes	1	2
Normal labour at term	1	2
Diabetes	0	0
B: Fetal autopsy characteristics (n = 47)		
Variable	**N**	**%**
Intrapartum hypoxic stress	14	30
Structurally normal fetus	10	21
Poor growth/immaturity	7	15
No abnormal finding	6	13
No additional information	3	6
Congenital syphilis	3	6
Positive lung bacterial culture	2	4
Congenital abnormality	1	2
Congenital bronchopneumonia	1	2

Table 2
Background information on the stillbirths.

A: Basic statistics of stillbirths (continuous data)					
Variable	N	Mean	SD	Median	Range
Maternal age (years)	47	24.4	5.4	23	16–38
Parity	47	1.1	1.2	1	0–5
Gestational age at delivery (days)	47	214.4	42.8	215	156–300
Birthweight (g)	46	1316.6	915.3	1045	190–3500
Trimmed placental weight (g)	46	238.8	113.7	226	50–517
Birthweight z-score	39	−1.4	1.6	−1.1	−6.3–1.0
B: Basic statistics of stillbirths (categorical data)					
Variable	**Total**	**N**		**%**	
Male infants (%)	45	22		49	
Macerated stillborn (%)	46	27		59	
Fetal death during labour (%)	46	6		13	
Syphilis (%)	47	4		9	
Living with HIV (%)	47	0		0	

HIV: human immunodeficiency virus.

complications of placenta, cord, and membranes when placental histology was added compared to only 7 cases with the clinical classification only. Similarly, the category M5: No maternal condition identified decreased from 30 cases to 3 cases after placenta histology was added. A6. Fetal death unspecified cause declined from 18 cases in clinical information only, to just 3 cases when the placental histology information was added. Autopsy findings confirmed all the clinical and placental histology findings without adding any additional information or changing the diagnosis.

3. Discussion

The classification of the etiology of stillbirth, based on both clinical and placental findings, was not changed in any case when the autopsy results were included. However, the addition of placental histology to the clinical only allocation of cause of death, significantly altered the findings; unknown causes of death decreased from 18 to 3 cases, and women thought to have a normal pregnancy decreased from 30 cases to 3 cases.

Although a variety of investigations are available to identify the etiology of stillbirths, there is still uncertainty about the effectiveness of different assessments. For a Cochrane Library Review, Wojcieszec et al. searched for randomized controlled trials (RCT) on this but failed to identify any. They concluded that there is currently a lack of RCT evidence on the effectiveness regarding interventions investigating and identifying the etiology of stillbirths [31]. Although this study was not designed as an RCT, we managed to compare the conclusions on causes of stillbirths under conditions where the initial clinical history was unknown to the pathologists who examined the placenta and performed the autopsy and where the clinicians were unaware of the placental and

Table 3
Classification of stillbirths A. Classification based on clinical information.

Clinical only	A1. Congenital malformations	A2. Infection	A3. Antepartum hypoxia	A4. Other specified antepartum disorder	A5. Disorders in fetal growth	A6. Fetal death unspecified cause	Total
M1: Complications of placenta, cord, and membranes		2	5				**7**
M2: Maternal complications of pregnancy						1	**1**
M3: Other complications of labour and delivery		2					**2**
M4: Maternal medical and surgical conditions		3	4				**7**
M5: No maternal condition 1. no maternal condition identified (healthy mother)	2	2			9	17	**30**
Total	**2**	**9**	**9**	**0**	**9**	**18**	**47**

B. Classification based on clinical information and placental histology

Clinical and placental histology	A1. Congenital malformations	A2. Infection	A3. Antepartum Hypoxia	A4. Other specified antepartum disorder	A5. Disorders in fetal growth	A6. Fetal death unspecified cause	Total
M1: Complications of placenta, cord, and membranes		9	23		8		**40**
M2: Maternal complications of pregnancy							**0**
M3: Other complications of labour and delivery							**0**
M4: Maternal medical and surgical conditions		4					**4**
M5: No maternal condition 1. no maternal condition identified (healthy mother)						3	**3**
Total	**0**	**13**	**23**	**0**	**8**	**3**	**47**

autopsy findings when they decided on a cause for the stillbirth. The assigned pathologist examined both the placenta and performed the autopsy. They were provided only with the gestational age and the information on the placenta that it was a stillbirth and were blinded to all other clinical information. The clinical diagnoses were considerably refined when placental histology was added, illustrating the importance of having placental histology available. Additional information from the autopsy therefore seems to contribute very little, if any, to the final diagnosis.

In this study, the addition of placental histology reduced the etiology of fetal death to just three categories, infection, antepartum hypoxia and disorders of fetal growth. The infections were syphilis and ascending vaginal infections resulting in chorioamnionitis. Fetal growth restriction was a feature in the antepartum hypoxia group and the nine cases of fetal growth disorder. These findings can therefore guide clinicians and policy makers to implement strategies focused on improving the detection and treatment of both infection and placental insufficiency, thereby decreasing antenatal fetal death rates. Infections such as syphilis, if not treated, may recur in subsequent pregnancies and maternal vascular malperfusion[32], and isolated acute maternal inflammatory responses, such as villitis of unknown etiology [33] may also recur. These histopathological findings in the placenta may therefore be valuable to the clinician in future pregnancies to help guide aspects of maternal-fetal monitoring and timing of delivery to avoid recurrence of these conditions.

The value of placental histology is further illustrated by examining the antenatal stillbirths classified by the WHO ICD PM system for South Africa. Without placental histology M5; No maternal condition (41,0%) and A6: fetal death unspecified cause (67,5%) were the most common lesions recorded (Table 4). These were the two most common categories for the SPS clinical diagnosis only group, but when histology was added, M5: No maternal condition, declined to 6,4% and A6: Fetal death unspecified, also declined to 6,4% and M1: complications of placental, cord and membranes was the most common at 85,1% together with A3: Antepartum hypoxia 48,9%.

Table 4
Comparison of pattern of disease (in percent) between South Africa, Safe Passage Study clinical only and Safe Passage Study Clinical and placental histology.

	South Africa[30] N = 15,619	SPS Clinical N = 47	SPS Clinical and placental histology N = 47
M1: Complications of placenta, cord and membranes	17,9	14,9	85,1
M2: Maternal complications of pregnancy	3,7	2,1	0,0
M3: Other complications of labour and delivery	0,0	4,3	0,0
M4: Maternal medical and surgical conditions	37,4	14,9	8,5
M5: No maternal condition 1. no maternal condition identified (healthy mother)	41,0	63,8	6,4
	South Africa [30] N = 15,619	**SPS Clinical N = 47**	**SPS Clinical and placental histology N = 47**
A1. Congenital malformations	2,7	4,3	0,0
A2. Infection	2,9	19,1	27,7
A3. Antepartum hypoxia	0,0	19,1	48,9
A4. Other specified antepartum disorder	18,9	0,0	0,0
A5. Disorders in fetal growth	8,1	19,1	17,0
A6. Fetal death unspecified cause	67,5	38,3	6,4

Our finding that no specific cause of death could be found in 7.5% of stillbirths (3/47) compares favourably with the three studies referred to

earlier in this paragraph.

Strong points of the study are that it addressed a problem that has not yet been solved [31], that it was done in a homogeneous population and that primary examination of the placentas, and the autopsies were done by only two pathologists. In addition, as far as we know, it is the first time that a study has shown that performance of an autopsy provides little additional information to what has been found by placental information.

A possible weak point are the small numbers as only 47 cases had both an autopsy and examination of the placenta. As the main causes of death were acute chorioamnionitis, acute placental abruption and maternal vascular malperfusion, placental examination may be of less value in a community where these causes of stillbirth are less prevalent and autopsy identity less frequent causes of death. Performance of fetal autopsy and examination of the placenta by the same pathologist may raise concern for observer of bias. However, the final cause of death was recorded after a discussion at the local multi-disciplinary perinatal mortality meeting, and later confirmed in the SPS consensus pathology meetings and not by the individual pathologists. If terminations of pregnancy, of which some were for congenital abnormalities, were not excluded from the analysis, the contribution of autopsy could have been better.

In countries where resource limitation necessitates a risk-based stratification for access to various levels of antenatal care, information about the cause of stillbirth will direct both the level (from basic low-risk to sub-specialist level) antenatal care and the advised gestation-specific screening investigations in subsequent pregnancies. Information on the etiology of stillbirth obtained from the placental histology is much more than that obtained from the autopsy. Examination of the placenta should therefore be prioritized. Macroscopic examination and assessment of placental weight may be of great help as we have found in a previous study, using the data of the SPS, that a small placenta and macroscopic infarction correlated significantly with the z-score of the birthweight for gestational age. A small placenta also correlated significantly with the pulsatility indices of the uterine and umbilical arteries at 20–24 and 34–38 weeks and with the pulsatility index of the middle cerebral artery at 34–38 weeks (Odendaal, unpublished information). Macroscopic placental infarcts correlated significantly with the pulsatility index of the uterine artery at 20–24 weeks. Doppler studies of the umbilical artery should therefore be routinely offered as a screen in women where histological examination of the placenta has demonstrated MVM in a previous pregnancy or when poor fetal growth is suspected in an index pregnancy. Screening with Doppler ultrasound might detect a considerable number of fetuses at risk of antenatal stillbirth[34].

When availability of pathologists is limited, priority should be given to examination of the placenta, rather than to performing an autopsy. As placental examination is not time-sensitive, specimens can be fixed and transported to facilities where examination of the placenta is feasible. To facilitate shipment, H and E stained sections of the umbilical cord, placental bed and membranes could be sent rather than the complete placenta.

In conclusion, clinical information together with histological examination of the placenta revealed sufficient information in most of the stillbirths, refining the probable cause of death, whereas autopsy provided little additional information. Performance of an autopsy is therefore not required to confirm the cause of death when histological examination of the placenta has been done.

Financial Support

The study was funded by the National Institute on Alcohol Abuse and Alcoholism, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institute on Deafness and Other Communication Disorders: U01 HD055154, U01 HD045935, U01 HD055155, U01 HD045991, and U01 AA016501. The funding body had no role in conducting the research or writing the paper.

Declaration of competing interest

None.

Acknowledgement

We wish to thank all the personnel of the Safe Passage Study; without their dedicated and precise work, this study would not have been possible.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2022.10.001.

References

[1] J.E. Lawn, H. Blencowe, P. Waiswa, A. Amouzou, C. Mathers, D. Hogan, V. Flenady, F. Frøen, Z.U. Qureshi, C. Calderwood, S. Shiekh, F. Bianchi Jassir, D. You, E.M. Mcclure, M. Mathai, Ending preventable stillbirths 2 Stillbirths: rates, risk factors, and acceleration towards 2030, Lancet 387 (2016) 587–603, https://doi.org/10.1016/S0140-6736(15)00837-5.

[2] S.H. Leisher, Z. Teoh, H. Reinebrant, E. Allanson, H. Blencowe, J.J. Erwich, J. F. Frøen, J. Gardosi, S. Gordijn, A.M. Gülmezoglu, A.E.P. Heazell, F. Korteweg, J. Lawn, E.M. McClure, R. Pattinson, G.C.S. Smith, Ö. Tunçalp, A.M. Wojcieszek, V. Flenady, Seeking order amidst chaos: a systematic review of classification systems for causes of stillbirth and neonatal death, 2009-2014, BMC Pregnancy Childbirth 16 (2016), https://doi.org/10.1186/s12884-016-1071-0.

[3] J.E. Hirst, J. Villar, C.G. Victora, A.T. Papageorghiou, D. Finkton, F.C. Barros, M. G. Gravett, F. Giuliani, M. Purwar, I.O. Frederick, R. Pang, L. Cheikh Ismail, A. Lambert, W. Stones, Y.A. Jaffer, D.G. Altman, J.A. Noble, E.O. Ohuma, S. H. Kennedy, Z.A. Bhutta, The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21 st Project, BJOG An Int. J. Obstet. Gynaecol. 125 (2018) 1145–1153, https://doi.org/10.1111/1471-0528.14463.

[4] H. Pinar, R.L. Goldenberg, M.A. Koch, J. Heim-Hall, H.K. Hawkins, B. Shehata, C. Abramowsky, C.B. Parker, D.J. Dudley, R.M. Silver, B. Stoll, M. Carpenter, G. Saade, J. Moore, D. Conway, M.W. Varner, C.J.R. Hogue, D.R. Coustan, E. Sbrana, V. Thorsten, M. Willinger, U.M. Reddy, Placental findings in singleton stillbirths, Obstet. Gynecol. 123 (2014) 325–336, https://doi.org/10.1097/AOG.0000000000000100.

[5] K.J. Gibbins, H. Pinar, U.M. Reddy, G.R. Saade, R.L. Goldenberg, D.J. Dudley, C. Drews-botsch, A.A. Freedman, L.M. Daniels, C.B. Parker, R. Bukowski, R. M. Silver, HHS Public Access 37 (2020) 708–715, https://doi.org/10.1055/s-0039-1688472.Findings.

[6] The Stillbirth Collaborative Research Network Writing Group, Causes of death among stillbirths, JAMA 306 (2011) 2459–2468, https://doi.org/10.1001/jama.2011.1823.

[7] S.A. Madhi, C. Briner, S. Maswime, S. Mose, P. Mlandu, R. Chawana, J. Wadula, Y. Adam, A. Izu, C.L. Cutland, Causes of stillbirths among women from South Africa: a prospective, observational study, Lancet Global Health 7 (2019) e503–e512, https://doi.org/10.1016/S2214-109X(18)30541-2.

[8] N. Pásztor, A. Keresztúri, Z. Kozinszky, A. Pál, Identification of causes of stillbirth through autopsy and placental examination reports, Fetal Pediatr, For. Pathol. 33 (2014) 49–54, https://doi.org/10.3109/15513815.2013.850132.

[9] R. Adappa, S. Paranjothy, Z. Roberts, P.H.T. Cartlidge, Perinatal and infant autopsy, Arch. Dis. Child. Fetal Neonatal Ed. 92 (2007) 49–50, https://doi.org/10.1136/adc.2005.091447.

[10] P. Sauvegrain, M. Carayol, A. Piedvache, E. Guéry, M. Bucourt, J. Zeitlin, Low autopsy acceptance after stillbirth in a disadvantaged French district: a mixed methods study, BMC Pregnancy Childbirth 19 (2019), https://doi.org/10.1186/s12884-019-2261-3.

[11] S. Meaney, S. Gallagher, J.E. Lutomski, K. O'Donoghue, Parental decision making around perinatal autopsy: a qualitative investigation, Health Expect. 18 (2015) 3160–3171, https://doi.org/10.1111/hex.12305.

[12] A.S. Feroz, C. Paganelli, M. Bunei, B. Eshetu, S. Parveen, S. Reza, C. Sanji, S. S. Tikmani, S.S. Goudar, G. Goudar, S. Saleem, E.M. McClure, R.L. Goldenberg, A comparison of MITS counseling and informed consent processes in Pakistan, India, Bangladesh, Kenya, and Ethiopia, Reprod. Health 17 (2020) 1–7, https://doi.org/10.1186/s12978-020-00969-w.

[13] S.R. Manandhar, A. Ojha, D.S. Manandhar, B. Shrestha, D. Shrestha, N. Saville, A. M. Costello, D. Osrin, Causes of stillbirths and neonatal deaths in Dhanusha district, Nepal: a verbal autopsy study, Kathmandu Univ. Med. J. 8 (2010) 62–72, https://doi.org/10.3126/kumj.v8i1.3224.

[14] U. Fatima, R. Sherwani, T. Khan, S. Zaheer, Foetal autopsy-categories and causes of death, J. Clin. Diagn. Res. 8 (2014), https://doi.org/10.7860/JCDR/2014/9226.4920. FC05–FC08.

[15] H. Odendaal, K.A. Dukes, A.J. Elliott, M. Willinger, L.M. Sullivan, T. Tripp, C. Groenewald, M.M. Myers, W.P. Fifer, J. Angal, T.K. Boyd, L. Burd, J.B. Cotton, R. D. Folkerth, G. Hankins, R.L. Haynes, H.J. Hoffman, P.K. Jacobs, J. Petersen, N. Pini, B.B. Randall, D.J. Roberts, F. Robinson, M.A. Sens, P. Van Eerden,

C. Wright, I.A. Holm, H.C. Kinney, Association of prenatal exposure to maternal drinking and smoking with the risk of stillbirth, JAMA Netw. Open 4 (2021) 1–15, https://doi.org/10.1001/jamanetworkopen.2021.21726.

[16] The National Perinatal Morbidity and Mortality Committee, Saving Babies 2014-2016 Triennial Report on Perinatal Mortality in South Africa, 2016. https://www.westerncape.gov.za/assets/departments/health/napemmco_triennial_report_2014-2016_saving_babies.pdf.

[17] K.A. Dukes, L. Burd, A.J. Elliott, W.P. Fifer, R.D. Folkerth, G.D.V. Hankins, D. Hereld, H.J. Hoffman, M.M. Myers, H.J. Odendaal, C. Signore, L.M. Sullivan, M. Willinger, C. Wright, H.C. Kinney, The safe passage study: design, methods, recruitment, and follow-up approach, Paediatr. Perinat. Epidemiol. 28 (2014) 455–465, https://doi.org/10.1111/ppe.12136.

[18] M. Human, R.D. Goldstein, C.A. Groenewald, H.C. Kenney, H.J. Odendaal, PASS Network, Bereaved mothers' attitudes regarding autopsy of their stillborn baby, S. Afr. J. Obstet. Gynaecol. 23 (2017) 93–96, https://doi.org/10.7196/sajog.1224.

[19]] H.J. Odendaal, A. Elliott, H.C. Kinney, M. Human, D. Gaspar, D. Petersen, B. Randall, J. Dempers, Consent for autopsy research for unexpected death in early life, Obstet. Gynecol. 117 (2011) 167–171, https://doi.org/10.1097/AOG.0b013e318200cb17.

[20] K. Kelly, S. Meaney, S. Leitao, K. O'Donoghue, A review of stillbirth definitions: a rationale for change, Eur. J. Obstet. Gynecol. Reprod. Biol. 256 (2021) 235–245, https://doi.org/10.1016/j.ejogrb.2020.11.015.

[21] E. Geldenhuys, J. Coldrey, C. Wright, D. Nel, D.J. Roberts, T.K. Boyd, H. Odendaal, P. Network, Fetal foot length at delivery as a tool for determining gestation length in non-macerated stillbirths, Inernational J. Gynecol. Obstet. 138 (2017) 107–112, https://doi.org/10.1002/ijgo.12177.

[22] H. Odendaal, C. Wright, L. Brink, P. Schubert, E. Geldenhuys, C. Groenewald, Association of late second trimester miscarriages with placental histology and autopsy findings, Eur. J. Obstet. Gynecol. Reprod. Biol. 243 (2019) 32–35, https://doi.org/10.1016/j.ejogrb.2019.10.024.

[23] T.Y. Khong, E.E. Mooney, I. Ariel, N.C.M. Balmus, T.K. Boyd, M.A. Brundler, H. Derricott, M.J. Evans, O.M. Faye-Petersen, J.E. Gillan, A.E.P. Heazell, D. S. Heller, S.M. Jacques, S. Keating, P. Kelehan, A. Maes, E.M. McKay, T.K. Morgan, P.G.J. Nikkels, W.T. Parks, R.W. Redline, I. Scheimberg, M.H. Schoots, N.J. Sebire, A. Timmer, G. Turowski, J.P. Van Der Voorn, I. Van Lijnschoten, S.J. Gordijn, Sampling and definitions of placental lesions Amsterdam placental workshop group consensus statement, Arch. Pathol. Lab Med. 140 (2016) 698–713, https://doi.org/10.5858/arpa.2015-0225-CC.

[24] R.W. Redline, Classification of placental lesions, Am. J. Obstet. Gynecol. 213 (2015) S21–S28, https://doi.org/10.1016/j.ajog.2015.05.056.

[25] H. Pinar, C.J. Sung, C.E. Oyer, D.B. Singer, Reference values for singleton and twin placental weights, Pediatr. Pathol. Lab. Med. 16 (1996) 901–907, https://doi.org/10.1080/15513819609168713.

[26] R.W. Redline, The clinical implications of placental diagnoses, Semin. Perinatol. 39 (2015) 2–8, https://doi.org/10.1053/j.semperi.2014.10.002. https://doi.org/10.1002/14651858.CD012504.pub2.

[27] C. Iskender, S. Zergeroglu, O. Kaymak, S. Çelen, N. Danisman, Villitis of unknown aetiology: clinical implications in preterm population, J. Obstet. Gynaecol. (Lahore). 36 (2016) 192–195, https://doi.org/10.3109/01443615.2015.1036410.

[28] G. Boog, Chronic villitis of unknown etiology, Eur. J. Obstet. Gynecol. Reprod. Biol. 136 (2008) 9–15, https://doi.org/10.1016/j.ejogrb.2007.06.018.

[29] WHO, The WHO Application of ICD-10 to Deaths during the Perinatal Period: ICD-PM, World Heal. Organ., 2016, pp. 1–88. https://www.who.int/reproductivehealth/publications/monitoring/icd-10-perinatal-deaths/en/.

[30] T. Lavin, E.R. Allanson, L. Nedkoff, D.B. Preen, R.C. Pattinson, Applying the international classification of diseases to perinatal mortality data, South Africa, Bull. World Health Organ. 96 (2018) 806–816, https://doi.org/10.2471/BLT.17.206631.

[31] A.M. Wojcieszek, E. Shepherd, P. Middleton, G. Gardener, D.A. Ellwood, E. M. Mcclure, K.J. Gold, T.Y. Khong, R.M. Silver, J.J.H.M. Erwich, V. Flenady, Interventions for investigating and identifying the causes of stillbirth, Cochrane Database Syst. Rev. 4 (4) (2018), https://doi.org/10.1002/14651858.CD012504.pub2.

[32] L. Visser, H. van Buggenum, J.P. van der Voorn, L.A.P.H. Heestermans, K.W. P. Hollander, M.G.A.J. Wouters, C.J.M. de Groot, M.A. de Boer, Maternal vascular malperfusion in spontaneous preterm birth placentas related to clinical outcome of subsequent pregnancy, J. Matern. Neonatal Med. 34 (2021) 2759–2764, https://doi.org/10.1080/14767058.2019.1670811.

[33] Y. Mizrachi, E. Barber, M. Torem, D. Tairy, E. Weiner, J. Bar, L. Schreiber, M. Kovo, Is there a role for placental histopathology in predicting the recurrence of preterm birth? Arch. Gynecol. Obstet. 300 (2019) 917–923, https://doi.org/10.1007/s00404-019-05266-x.

[34] S. Nkosi, J. Makin, T. Hlongwane, R.C. Pattinson, Screening and managing a low-risk pregnant population using continuous-wave Doppler ultrasound in a low-income population: a cohort analytical study, S. Afr. Med. J. 109 (2019) 347–352, https://doi.org/10.7196/SAMJ.2019.v109i5.13611.