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Original Investigation

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Pediatric and Developmental Pathology
2022, Vol. 25(3) 285–291
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DOI: 10.1177/10935266211063118
journals.sagepub.com/home/pdp
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Abstract

Introduction: Heterogeneous patterns of placental lesions in stillbirth signal important variations in placental histopathology that may be diagnostic in stillbirth. We explore placental heterogeneity and its associations with maternal characteristics (including HIV) using latent class analysis.

Methods: Placental and maternal data and slides were assessed retrospectively for 122 confirmed stillbirths (gestational age ≥ 28 weeks) delivered at a major South African academic hospital between January 2016–July 2018. The slides were reviewed by 2 pathologists and classified using the Amsterdam Consensus Classification System. Latent class analyses were conducted on raw data.

Results: We identify 5 latent placental classes in stillbirth based on similarity in patterns of observed diagnostic criteria and their associations with maternal characteristics. Three classes bear similarity to generalized patterns of placental injury identified previously. Our study shows that intrauterine infection was the commonest histopathological condition associated with stillbirth in our setting. Novel findings include 2 classes, distinguished by high placental RPH and maternal HIV, respectively, and the non-emergence of a class distinguished by VUE.

Conclusion: The size and content of the latent classes and their similarity/dissimilarity to the more generalized patterns identified previously suggest potential new avenues for investigation and theory development concerning the role of the placenta in stillbirth and the impact of HIV.

Keywords

placental pathology, stillbirth classification systems, Amsterdam Consensus Classification System, latent class analysis, HIV

Introduction

The important role of the placenta in stillbirth is becoming clearer. Recent progress is due, at least in part, to programmatic research initiatives, such as the Stillbirth Collaborative Research Network and the Prenatal Alcohol in SIDS and Stillbirth (PASS) Research Network. Collaborative international networks are encouraging interdisciplinarity and convergence and sharpening the focus on longstanding obstacles to progress. The increasing research rigor and synthesis[1-3] and development of new standardized approaches (e.g., stillbirth classification systems)[4,5] are important examples of the fruit of this work. A striking and consistent finding in this recent body of research concerns the heterogenous nature of stillbirth. This is particularly true of the patterns of multiple concurrent placental lesions that can have adverse effects in stillbirth. This heterogeneity remains an unexplored but important consideration, making placental heterogeneity an important research topic in its own right.[5]

The goals of this exploratory study are 2-fold: (1) to classify stillbirth placentas into an ideally small number of relatively homogeneous subgroups (i.e., latent classes) based on pattern similarity in observed diagnostic criteria of the placenta and (2) examine the associations of these latent

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classes with relevant maternal characteristics (i.e., covariates), especially maternal HIV. To achieve these goals, we explore placental heterogeneity in stillbirth and its relations to fetal and maternal exogenous characteristics using latent class analysis (LCA), a rigorous model-based statistical procedure that can be used to classify placentas into relatively homogenous subgroups based on similarities and differences in diagnostic criteria. We include exogenous maternal characteristics in the model as covariates that help explain variations in the latent classes, but do not affect the associations between the placental diagnostic criteria directly.

The research makes theoretical, empirical, and practical contributions. *Theoretically*, heterogeneity in patterns of concurrent placental lesions implies the varied presence/absence of possibly associated placental diagnostic criteria. Placental pathology in stillbirth research is at an early stage. Thus, identifying patterns in placental diagnostic criteria and relating these patterns to exogenous maternal characteristics can yield important information for theory development. *Empirically*, there remains an important need to understand the impact of HIV/AIDS on stillbirth. We collected data in South Africa, a country with one of the world's highest HIV infection rates. Our results revealed important new insights into the relationship of maternal HIV infection to other placental diagnostic criteria. *Practically*, many healthcare professionals struggle to explain stillbirth to grieving parents and other interested parties. The knowledge of associated patterns of diagnostic criteria in stillbirth can be very helpful in this regard.

Table 1. A Summary of the Maternal and Fetal Characteristics of the Study Cohort.

	N	Mean ± SD	Range
Maternal characteristics	122		
Maternal age (yrs)		28 ± 6	18–41
Gestational age (wks)		34 ± 4	28–42
Parity		1 ± 1	1–3
Gravidity		2 ± 1	1–5
HIV positive	32	26.2 (%)	
T pallidum serology positive	1	0.8 (%)	
PROM	6	4.9 (%)	
Diabetes mellitus	5	4.1 (%)	
APH	19	15.6 (%)	
Maternal hypertension	43	35.2 (%)	
Anemia	0	0.0 (%)	
Maternal infection	3	2.5 (%)	
Placental characteristics			
Placental weight (g)		323.8 ± 236.2	77–702
Placental weight < 10th centile	69	56.6 (%)	
Tumors (Chorangiomas)	5	4.1 (%)	
CAM	49	40.2 (%)	
CAF	19	15.7 (%)	
FVM	42	34.4 (%)	
MVM	42	34.4 (%)	
Hematogenous infection	0	.0 (%)	
VUE	19	15.6 (%)	
RPH	27	22.1 (%)	
DVM	6	4.9 (%)	
MFI/MPFD	5	4.1 (%)	
MAVN	4	3.3 (%)	

PROM, premature rupture of membranes; APH, antepartum hemorrhage; DVM, delayed villous maturation; MFI/MPFD, maternal floor infarction/massive perivillous fibrin deposition; MAVN, meconium associated vascular necrosis of the umbilical cord.

Methods

Sample

We performed a retrospective assessment of placentas from stillbirths delivered at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a South African tertiary academic hospital in Gauteng Province, for the period January 2016–July 2018. Placental and maternal data and slides were assessed retrospectively for 122 confirmed stillbirths (maternal age ≥ 18, gestational age ≥ 28 weeks, see Table 1). The mean placental weight was 323.8 ± 236.2 g (range 77–702 g). As most placentas were below the 10th centile for gestational age, this was expressed as relative to the 10th centile (Ratio 10). Maternal HIV status was reported as seropositive in 32 (26.2%) cases. Hypertension and maternal infection were reported in 43 (35.2%) and 3 (2.5%), respectively.

Procedure

All slides were reviewed by 2 pathologists (ZM and CW) and reclassisfied into the Amsterdam Consensus Classification System.[5] Live births and records with incomplete data that made it difficult to classify the pathology were excluded. Maternal data was extracted from the hospital records and clinical information regarding the fetus was cross-referenced from the maternity registers and hospital records, but this was minimal and was not included in the data analyzed. Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC): Clearance Certificate Number M180909. Medical and institutional approval was granted by CMJAH.

Data Analysis

Placental heterogeneity and its relations to maternal characteristics were explored using latent class analysis (LCA). LCA flexibly accommodates exploratory models with covariates and mixed mode data (i.e., nominal and ratio scaled data), as in the current research.[6-8] In the current research, observed stillbirth placental variables, viz. weight placenta as a proportion of 10th centile (Ratio10), chorioamnionitis maternal response (CAM) chorioamnionitis fetal response (CAF), fetal vascular malperfusion (FVM), maternal vascular malperfusion (MVM), villitis of unknown etiology (VUE),

retroplacental hemorrhage (RPH), and delayed villous maturation (DVM), were assumed to be indicators of a single unobserved categorical latent variable that has an unknown number of relatively homogeneous, mutually exclusive, and exhaustive latent classes. Local independence was assumed for the placental indicator variables conditional on class membership and no local dependencies were allowed. Thus, a placenta is a member of one class, and class membership explains the associations among the observed variables for that placenta. Nine exogenous stillbirth maternal characteristics (e.g., maternal age (MA), gestational age (GA), parity (Para), gravidity (Grav), maternal HIV serostatus (HIV), premature rupture membranes (PROM), diabetes mellitus (DM), antepartum hemorrhage (HAEM), and hypertension (HT)) are included as covariates in the LCA model. The covariates have direct effects on the latent variable but no direct effect on the endogenous placental diagnostic indicator variables, the associations of which are explained by the latent variable.

LCA models were fit incrementally to the raw dataset with no missing values in Latent Gold 5.1.[9] Beginning with a 1-class model, the number of latent classes was increased to determine the best fitting model. Since latent class models can converge at suboptimal local maxima, the analyses began from 250 random starting values, which ran for 200 iterations. Of these, the best 10% were run for an additional 2 iterations and the best solution was selected as the starting point for the current analysis. All analyses converged normally without warning messages or boundary condition warnings. There were no missing data, and no local dependencies were allowed.

Comparative model fit was assessed using the bootstrap likelihood ratio tests (500 iterations). The Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC) statistics, and bivariate residuals (BVRs) also were examined. Based on the results summarized in the Supplementary Appendix Table A1, the 5-class result was chosen. Of 84 BVR test results, only 2 exceeded the critical value (i.e., > 3.84), suggesting that the final model may not explain the association of Ratio10 with HT and VUE with PROM completely. *Class separation* was confirmed by significant Wald test results for all indicator variables across the 5 latent classes ($P \leq .05$ in all cases, see Supplementary Appendix Table A2 in the Supplementary Appendix for details). Wald statistic tests of paired class comparisons also supported separation ($P \leq .05$ in 83% of indicator comparisons). Thus, the results show that the model distinguishes between classes well. Overall, these results suggest that the model fits these data well.

Results

Latent Class Analysis

Detailed results and technical details for the 5-class LCA model are reported in the Web Appendix. Figure 1 summarizes results for each latent class, which include the within-class probabilities for the placenta indicator variables and the associated maternal characteristic covariates. For criteria not measured on a binary scale (present/absent) scale (viz. Ratio10, MA, GA, Para, Grav), Figure 1 reports class-specific means re-scaled to lie within the 0–1 range.[9] Table 2 reports distinctive characteristics for each latent class, which were determined by examining the within-class probabilities and re-scaled class-specific means. These were considered distinctive when near 1.0 or 0.0 (i.e., homogeneous for that class, which was operationalized as ≥ .70 or ≤ .30).[6]

Distinctive Class Characteristics

The analysis identified 2 large classes comprising 69% of the placentas. At least 3 placental characteristics were distinctive for each latent class. To make our summary of these results tractable, we refer to high/low within-class probabilities as "high" or "low."

Class 1: FVM (35%)

This class is high in FVM and includes 67% of the placentas showing FVM in the sample (Figure 2). RPH was not observed. MVM and CAF also are low. Placentas tend to be near the 10th centile. Associated covariates include very low DM, HAEM, HT, and PROM. MA (mean = 25.3) is the youngest of all classes, and GRAV and HIV also are low.

Class 2: MVM (34%)

Class 2 is high in MVM, including 74% of placentas showing MVM in the sample (Figure 3). RPH is absent, and CAF is very low. Placental weight is more likely to fall short of the 10th decile than any other class. CAM, FVM, and VUE also are low. Associated covariates are very low DM and HAEM, and low PROM. Mean MA is 29.7. Although the probability of HIV is 33%, it is noteworthy that the class includes 42% of HIV+ mothers (i.e., 1.24 times class size).

Class 3: RPH (19%)

Placentas in this class have a 99% probability of RPH (Figure 4). CAF is very low and placenta weight, CAM, FVM, MVM, and VUE are low. Class 3 includes 81% of placentas with RPH. Associated covariates are high HT, very low DM and PROM, and low PARA and GRAV. Although not distinctive characteristics, 52% show antepartum hemorrhage and 38% with hypertension. In existing studies, this triad of features are traditionally associated.[9]

Class 4: CAM (10%)

This smaller class is distinguished by high CAM (Figure 5). Placental weight, FVM, MVM, VUE, RPH are low. The

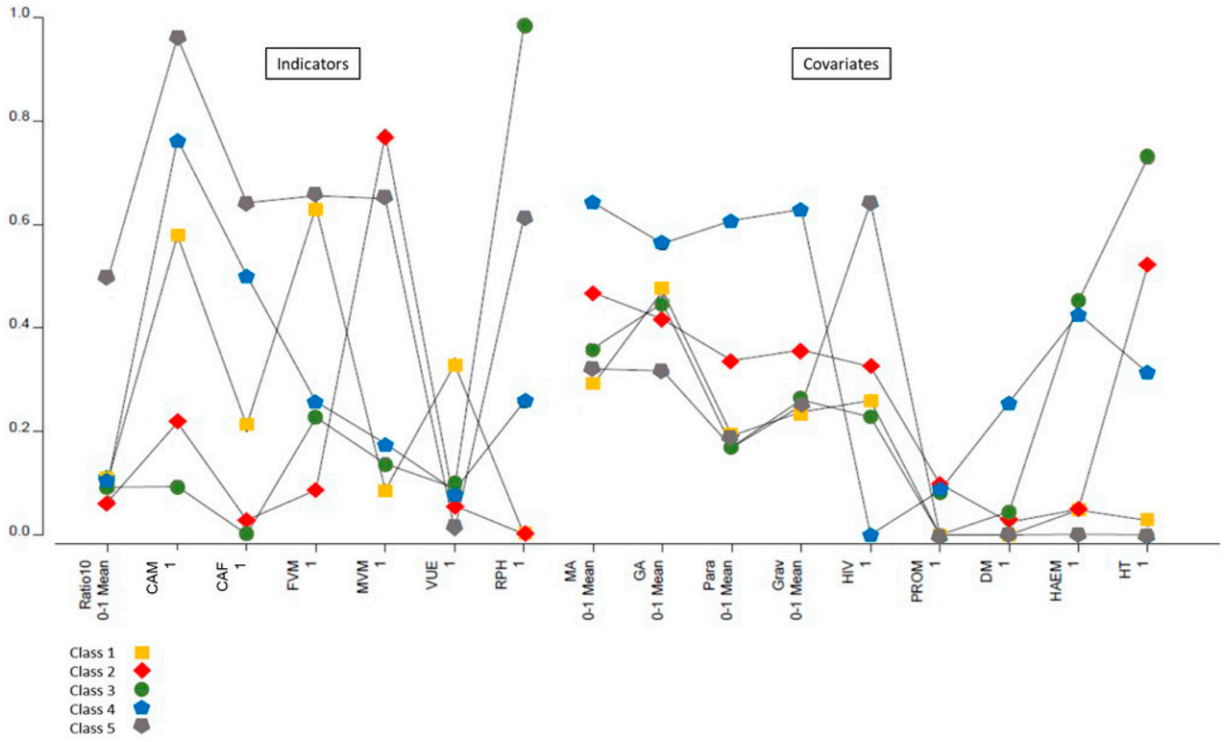


Figure 1. Latent class profile plot.

Table 2. Distinctive Latent Class Characteristics.

	Distinctive latent class characteristics			
	Indicator variables		Covariates	
Class size	High	Low	High	Low
Class 1: FVM (35%)	*FVM*	*RPH, RATIO10, CAF, MVM*		*DM*, *HAEM*, *HT*, *PROM*, MA, GRAV, HIV
Class 2: MVM (34%)	MVM	*CAF, RPH, RATIO10, CAM, FVM, VUE*		*DM*, *HAEM*, PROM
Class 3: RPH/HT (19%)	RPH	*CAF, RATIO10, CAM, FVM, MVM, VUE*	HT	PARA, GRAV, HIV, *PROM*, *DM*
Class 4: CAM (10%)	CAM	*RATIO10, FVM, MVM, VUE, RPH*	MA, *GA*, PARA, GRAV	*HIV*, PROM, DM
Class 5: HIV (3%)	*CAF*, *FVM*, *MVM*, *RPH*, CAM	*VUE*	*HIV*	*PROM*, *DM*, *HAEM*, *HT*, MA, GA, PARA, GRAV

High refers to within-class probabilities exceeding 0.70 except when in italics, which exceed 0.60. **Low** refers to within-class probabilities below 0.30.

associated covariates include high GA and MA, and PARA and GRAV also are high. There is no maternal HIV seropositivity, and DM and PROM also are low.

Class 5: HIV (3%)

The incremental addition of this small class greatly reduced the level of unacceptable bivariate residuals and significantly improved model fit. CAF, FVM, MVM, and RPH are very high. CAM also is high. VUE is very low. However, this cluster appears to be distinguished most by the associated covariate of high HIV (66% probability). PROM, DM, HAEM, and HT are very low and MA, GA, PARA, GRAV are low.

In summary, ascending intrauterine infection was the most common histopathologic condition associated with stillbirth in our setting. Among maternal clinical conditions, hypertension (n = 43; 35.3%) and HIV infection (n = 32; 26.2%) were most prevalent. Chorioamnionitis was the most frequently observed pathological process in placentas, particularly in HIV-positive

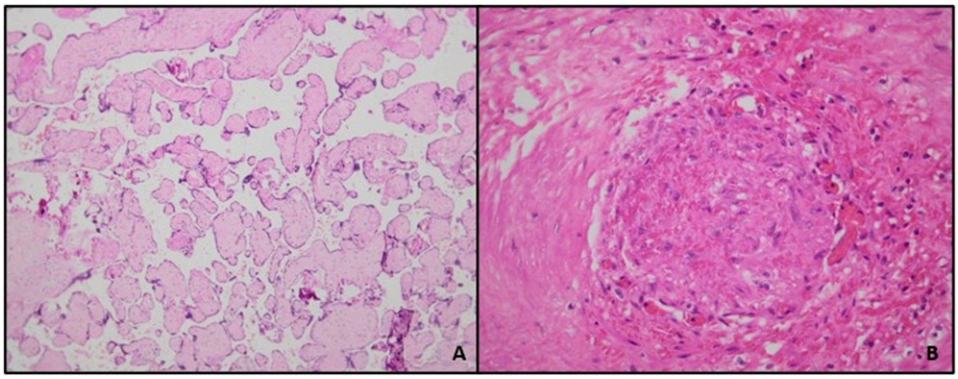


Figure 2. FVM: A: discrete focus of villi with loss of capillaries and hyaline fibrosis H&E ×100 B: organizing thrombus within a vessel H&E ×400.

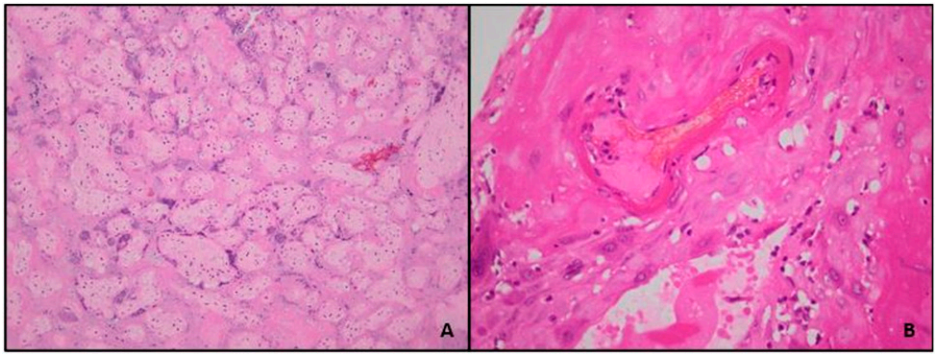


Figure 3. MVM: (A) Infarction with necrosis and loss of trophoblast nuclear staining H&E ×200. (B) Decidual arteriopathy with fibrinoid necrosis H&E ×400.

individuals. LCA confirmed placental heterogeneity as expected in our stillbirth population.

Discussion

Latent class analysis (LCA) is a technique that permits identification of clusters or groups of patients with similar clinical characteristics, disease risk factors, comorbidities, and pathology that may not be immediately evident. The goals of this exploratory study were to classify stillbirth placentas into a small number of relatively homogeneous latent classes based on similarity in patterns of observed diagnostic criteria and examine the associations of these latent classes with relevant maternal characteristics (i.e., covariates), especially maternal HIV infection. The placental coding procedure was compatible with the Amsterdam Consensus system[5] and the latent class analyses in accordance with accepted best practice.[6] The 5-class LCA distinguished among the endogenous effects of placental diagnostic criteria on placental heterogeneity and the effects of maternal covariates and provided a good fit to the data.

Our research makes theoretical, practical, and empirical contributions. *Theoretically*, we identify the size and content of 5 placental classes in stillbirth. Three classes (MVM, FVM, and CAM) bear similarity to the generalized patterns of placental injury identified by Redline et al.[5] The 4 major patterns of placental pathology as defined by the Amsterdam Consensus system and clarified by Redline are MVM, FVM, VUE, and Acute Chorioamnionitis (ACA). In stillbirths, caution needs to be taken when diagnosing FVM, as secondary involutional changes such as avascular villi and villous stromal karyorrhexis occur postmortem. However, thrombi, intramural fibrin and discrete foci of avascular villi suggest the FVM is a cause of the stillbirth. A notable difference in our results is the emergence of 2 classes distinguished by high placental RPH and maternal HIV, respectively, and the non-emergence of a class distinguished by VUE. The size and content of the latent classes and their similarity/dissimilarity to the more generalized patterns identified by Redline et al.[5] suggest potential new avenues for investigation and theory development concerning the role of the placenta in stillbirth.

Empirically, we collected data in an emerging African country with high HIV infection rates. The emergence of a distinct 5th class is a potentially important finding that may be replicated in countries with high HIV infection rates focusing on unanswered questions around the impact of HIV in stillbirth.

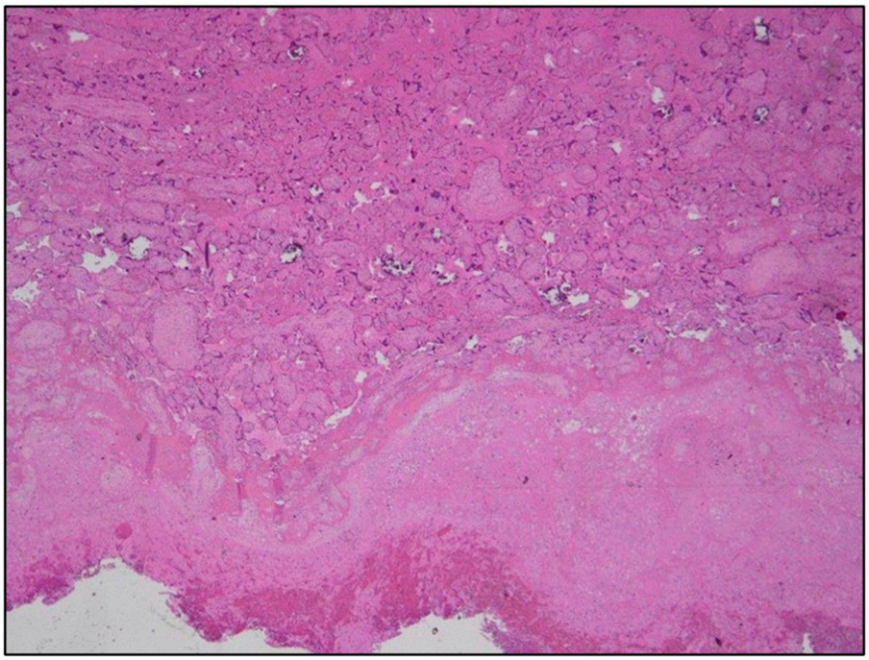


Figure 4. Retroplacental hemorrhage H&E ×40.

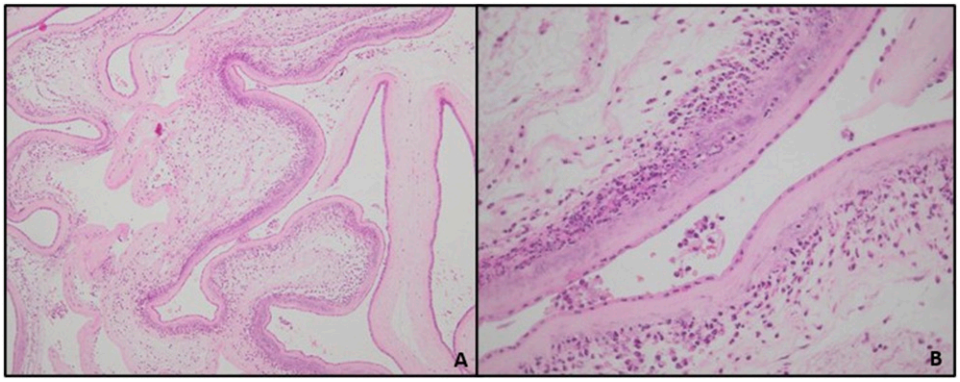


Figure 5. CAM: A: Acute inflammation extending into the amnion H&E ×100. B: Diffuse band of acute inflammation extending into the amnion. H&E ×400.

Practically, the identification of placental classes and their relations to exogenous maternal characteristics provides clinicians with new guidance that can help explain adverse outcomes and predict possible recurrences. In this vein, there is an increasing awareness of the role placental pathology can play in understanding stillbirth. In the SCRN study,[4] a specific placental cause was identified as the leading cause of antepartum stillbirth (25%). Roescher et al.'s 2014 review of 135 papers examining placental lesions and perinatal mortality found that placental lesions cause stillbirths in 12–65% of cases.[10]

More generally, we noted that two-way communication with clinicians is pivotal. In practice, an accurate histopathological diagnosis may be greatly improved by clinical information. Gestational age is essential and maternal comorbidities may contribute to an understanding of the pathological processes present in the placenta. Communication can be improved by a specific request form for placentas. Also, the macroscopic and microscopic examination of the placenta should be recorded on a standardized placental template. These communication tools help ensure the obstetric and maternal disease processes, and the placental pathology diagnoses are seamlessly integrated and the reports are standardized.[11] This makes it easier for the clinician to communicate more effectively with parents.

We close with a recommendation for future research. There is a need for more research that implements structured approaches, such as in this study. The rigorous identification of patterns in placental lesions and their relations to maternal and fetal characteristics in stillbirth can be an important next

step in expanding our understanding of the role of the placenta in stillbirth and our understanding of the impact of HIV.

Acknowledgments

SM would like to acknowledge the South African Midcareer scientist award.

Author Contributions

Nompumelelo Z. Mtshali and Colleen A. Wright carried out data retrieval and analysis.Steven M. Burgess performed the latent class analyses.All authors conceived the study and were involved in writing the paper and had final approval of the submitted and published versions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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