Placental lesions associated with stillbirth by gestational age, according to feature importance: results from the Stillbirth Collaborative Research Network

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Abstract

Introduction—Previous studies have identified lesions commonly found in placentas associated with stillbirth but have not distinguished across a range of gestational ages (GAs). The objective of this study was to identify lesions associated with stillbirths at different GAs by adapting methods from the chemical machine learning field to assign lesion importance based on correlation with GA.

Methods—Placentas from the Stillbirth Collaborative Research Network were examined according to standard protocols. GAs at stillbirth were categorized as: <28 weeks (extreme preterm stillbirth [PTSB]), 28–33'6 weeks (early PTSB), 34–36'6 weeks (late PTSB), 37

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weeks (term stillbirth). We identified and ranked the most discriminating placental features, as well as those that were similar across GA ranges, using Kernel Principal Covariates Regression (KPCovR).

Results—These analyses included 210 (47.2%) extreme PTSB, 85 (19.1%) early PTSB, 62 (13.9%) late PTSB, and 88 (19.8%) term stillbirths. When we compute the KPCovR, the first principal covariate indicates that there are four lesions (acute funisitis & nucleated fetal red blood cells found in extreme PTSB; multifocal reactive amniocytes & multifocal meconium found in term stillbirth) that distinguish GA ranges among all stillbirths.

Discussion—There are distinct placental lesions present across GA ranges in stillbirths; these lesions are identifiable using sophisticated feature selection. Further investigation may identify histologic changes across gestations that relate to fetal mortality.

Keywords

Placental Lesions; Stillbirth; Intrauterine Fetal Demise; Feature Selection; Kernel Principal Covariates Regression

Introduction

Understanding placental pathology in cases of intrauterine fetal demise (IUFD/stillbirth) has significant implications for uncovering the etiologies of stillbirth and, ultimately, helping reduce the high rate of preventable stillbirths in the United States [1–3]. Placental examination has proven of great utility in identifying risk factors and causes for stillbirth since its inception, even recently uncovering patterns of vascular malperfusion in stillbirths associated with COVID-19 infection [3,4]. Therefore, understanding which placental lesions are present in stillbirths of all etiologies and gestational ages is vitally important.

Previous studies identified placental lesions present in stillbirths across a range of gestational ages (GAs) [5]. Developmental, inflammatory, and circulatory lesions were compared across placentas associated with stillbirths delivered at the following GAs: less than 24 weeks, 24 weeks to 31 weeks 6 days, 32 weeks to 36 weeks 6 days, and greater than or equal to 37 weeks. While this study comprehensively described these lesions (see supplemental table 1), analyses were limited to comparisons across groups, which does not identify lesions unique to each GA range. Tiwari et al. (2022) studied placental findings of preterm stillbirths versus livebirths and term stillbirths versus livebirths but did not compare lesions between preterm and term stillbirths [6]. Others have sought to identify lesions common within different trimesters of stillbirths and the prevalence of placental causes of death across GAs, but none have identified which lesions are unique to specific GA ranges [7,8].

Therefore, we sought to use feature importance techniques to identify placental lesions associated with stillbirths at different GAs. Feature importance refers to techniques that calculate how useful certain measures are in explaining the variance of a sample or a target variable; such methods include Exploratory Factor Analysis and Principal Components Analysis. We utilized a method borrowed from chemistry and engineering fields, Kernel Principal Covariates Regression (KPCovR), first created by Helfrecht,

Cersonsky, et al. in 2020 [9,10]. This method constructs a non-linear latent-space projection simultaneously minimizing regression error and maximizing projection variance. This is done by considering a mixing of two optimization functions; the losses used in kernel ridge regression and kernel principal components analysis. The first dimension of the resulting projection (first kernel principal covariate) contains the constructed feature for each sample resulting from this minimization. We hypothesized that, with this method, we would be able to classify which lesions best explained the variance in placental findings in stillbirths across GA ranges.

Methods

Data

Data were derived from the Stillbirth Collaborative Research Network (SCRN), a comprehensive study of stillbirths and livebirths in the United States. Data were collected at 59 hospitals across five geographic regions from 2006 to 2009 [11]. Each center's Institutional Review Board approved study procedures, as well as the Data Coordinating and Analysis Center. Participants gave written informed consent for each portion of the study, including postmortem and placental examinations. SCRN procedures, including inclusion/exclusion criteria, have been described previously [11].

For these analyses, participants were included if they delivered a singleton stillbirth of GA > 20 weeks and consented to complete placental examination and were excluded if they delivered a live birth or a singleton stillbirth of GA <20 weeks or did not have complete placental examination. Protocols for placental and postmortem examination have been described previously [12,13]. Study pathologists received centralized training in placental examinations, resulting in standardized assessments. Participants also completed surveys regarding demographics (including self-reported minority race [Black, Asian, American Indian/Alaskan Native, Pacific Islander, multiple races, other]), maternal health history, and current pregnancy history.

Placental features

Features included in these analyses encompassed those previously identified by Pinar et al. (2014), as well as a number of related lesions and gross findings [5]. Developmental, inflammatory, circulatory, findings of the placental disc, and multifocal findings (across membranes, chorionic plate, umbilical cord, etc.) were included. Specific lesions were classified as focal (present in one area on a single side), multifocal/patchy (present in more than one area on multiple sides), or diffuse (full thickness of placental disc, all sections involved). Lesions included and their definitions are described in supplemental table 2.

Statistical analyses

For the purposes of these analyses, we chose to separate stillbirths into gestational age ranges according to the American College of Obstetricians and Gynecologists: extreme preterm stillbirth (<28 weeks), early preterm stillbirth ($28 - 33^{6/7}$ weeks), late preterm stillbirth ($34 - 36^{6/7}$ weeks), and term stillbirth (37 weeks) [14,15]. Sample characteristics

were compared across groups using Chi-Square tests (categorical) or Kruskall-Wallis tests (continuous) in RStudio (version 2022.07.1, R version 4.1.3).

KPCovR (*scikit-matter v0.1*) was utilized to determine those features that best correlated and explained most variance observed in placentas associated with stillbirth at different GAs. Placental features (n = 54) were preprocessed using one-hot encoding; features were first linearly correlated to GA, then encoded into a non-linear similarity matrix (radial basis function [RBF] kernel, γ=0.1) to determine our subject similarities. We cross-validated our kernel hyperparameters using leave-one-out cross-validation on a grid search (GridSearchCV and KernelRidge, *scikit-learn v1.0*). Using this RBF kernel, we computed the correlation of the lesions with the latent space projection over 1000 random train / test draws in a 90/10 proportion.

First principal covariate was reported, which represents the feature of this data that explains the most variance (similarly to Principal Components Analysis). Once this first dimension was constructed, we then completed post-hoc analyses (in RStudio) to understand which features were more common within each gestational age range. Chi-Square tests were used to compare across and between GA ranges; p-values <0.05 were considered significant.

Results

Sample characteristics

We identified 445 placentas that met study inclusion criteria (Figure 1): 210 extreme preterm stillbirth (GA <28 weeks), 85 early preterm stillbirth (GA 28 – 33$^{6/7}$ weeks), 62 late preterm stillbirth (GA 34 – 36$^{6/7}$ weeks), and 88 term stillbirth (GA 37 weeks). The distributions of minority race and use of assisted reproductive technologies significantly differed across all GA ranges; there were no other significant differences in demographic or maternal history measures (Table 1). Fetuses delivered at earlier gestational ages were, as expected, of smaller weight.

Kernel Principal Covariates Regression

As has been suggested by literature, we chose to equally minimize the regression and projection loss, and our resulting first principal covariate maps onto gestational age with Pearson correlation coefficient of 0.89 ± 0.01. The correlation of the original parameters with this first principal covariate encodes how much their similarity across subjects delineates the different gestational age thresholds. We found that acute funisitis, multifocal meconium, and multifocal reactive amniocytes had the strongest correlations with the first principal covariate (Table 2, Figures 2&3).

Post-hoc analyses

Several lesions had significantly different distributions across all ranges. Numerous other lesions did not differ in their distributions; these lesions did not contribute to the variance observed in the sample (Table 2).

Within extreme preterm stillbirth, we identified higher rates of acute funisitis and lower rates of accelerated villous maturity and nucleated fetal red blood cells relative to all other

ranges. Acute umbilical arteritis was more common in this group than in early preterm or term stillbirth. Hemorrhage of the placental disc and retroplacental hematoma were more common in this group than in late preterm or term stillbirth.

Within early preterm stillbirth, we identified higher rates of parenchymal infarct compared to all other ranges. Increased syncytial knots of the chorionic villi were more common in this group compared to extreme or late preterm stillbirth.

There were no lesions more common in late preterm stillbirth group compared to all other groups. Diffuse terminal villous immaturity and multifocal reactive amniocytes were more common in this group than in extreme or early preterm stillbirth; decidual vasculopathy and trophoblast proliferation of the placental disc were less common comparatively. Accelerated villous maturity was more common in the late preterm stillbirth group compared to extreme preterm and term stillbirth.

Finally, there were no lesions more common within term stillbirths compared to all other groups. Decidual vasculopathy was less common in this group compared to extreme and early preterm stillbirth, whereas multifocal reactive amniocytes were present more frequently, comparatively. Multifocal calcifications and meconium were present more commonly in this group compared to extreme and late preterm stillbirth.

Discussion

Using Kernel Principal Covariates Regression, we were able to identify distinct placental lesions present across different GAs in a sample of singleton stillbirths. This method, which has not before been used in medicine, was able to identify lesions with a principal component strongly correlated with GA, with a coefficient of 0.89. These findings point to unique patterns of placental dysfunction across different GA ranges, which may offer valuable insight into stillbirth etiology.

Acute funisitis was present more commonly in extreme preterm stillbirths (13.3% of this group compared to 1.6–2.4% in other groups) without more acute chorioamnionitis (compared to other ranges), suggesting that the fetal inflammatory response is more significant in stillbirths of this GA. Funisitis has been associated with impending onset of preterm labor, neonatal morbidity, and multiorgan fetal involvement [16]. Funisitis has been frequently associated with stillbirth, particularly acute and subacute necrotizing funisitis; in many (if not all) of these cases, chorioamnionitis was coexistent with funisitis [17–19]. Funisitis, unlike histological chorioamnionitis, is also frequently associated with positive post-mortem microbiology cultures [20]. Our findings suggest that, while chorioamnionitis occurs at all gestational ages, funisitis is a unique feature of late second-trimester gestation that might contribute more commonly to stillbirths in these cases. This is consistent with the literature, which has identified infection-related stillbirth at these earlier gestational ages in high-resource settings [21–23].

Lower rates of accelerated villous maturity and nucleated fetal red blood cells were also observed in the extreme preterm stillbirth group compared to other ranges. As both findings are known to be associated with fetal hypoxia or placental malperfusion, this result is

suggestive of a lower rate of hypoxic causes of death among earlier stillbirths [24,25]. Accelerated villous maturity is higher in late preterm stillbirth relative to extreme preterm and term stillbirth, implying the converse: hypoxic causes of fetal death may be more common among late preterm stillbirths compared to extreme preterm and term stillbirths. While nucleated fetal red blood cells were observed more often in association with extreme preterm stillbirth, we did not have data for the percent of the total fetal red blood cells that were nucleated, which can vary across gestational ages. Further analyses of the identified cause of death in these stillbirths may further elucidate this difference.

Parenchymal infarcts were found more commonly in early preterm stillbirths compared to other groups. Such infarcts are known to be associated with hypertensive disorders of pregnancy, particularly in more severe disease [26]. However, in our cohort, there were no differences in hypertensive disease across GA ranges. This may point to the presence of more severe disease in early preterm stillbirths, or, alternatively, more preterm deliveries in fetuses of GA 34 weeks. Such deliveries may be expected in, for example, preeclampsia with severe features, given current ACOG guidance [27].

While those lesions identified above were significant in differentiating between stillbirths of different GA ranges, there are a number of previously identified lesions that did not significantly differ in prevalence among GA ranges [5]. Among these were single umbilical artery, velamentous or furcate cord insertion, chorioamnionitis, acute umbilical cord phlebitis, chorionic vascular degeneration, acute or chronic villitis, intervillous thrombus, avascular villi, and edema. We can determine from the absence of differences in these lesions that, possibly, structural differences in the umbilical cord (both single umbilical artery and abnormal insertion) might contribute to stillbirths at many GA ranges; as suggested previously, this might indicate a need for closer surveillance of pregnancies with these findings. Other lesions listed here might be more significant in differentiating stillbirth versus livebirth, thus related to the etiologies of many stillbirths, but may also not be specific to GA ranges.

Our study has several strengths, including our novel methodology. By using a method of feature importance that allows for correlation with a continuous variable such as GA, we were able to identify features that vary along this range or delineate different GA ranges. Additionally, we utilized this method for the first time in medical analyses, therefore introducing this technique, with source code available on GitHub, as a viable option for other clinical researchers, particularly when the relationship between measurements and observables requires a non-linear approach to mapping and regression.

Our study should also be interpreted in the context of several limitations. Our data were collected from 2006–2009; therefore, more recent patterns in pregnancy outcomes are not accounted for in our analyses, such as findings related to the ongoing COVID-19 pandemic [28]. The SCRN data was also collected prior to the release of the Amsterdam consensus, thus excluding several important lesions that were not commonly reported in our sample (i.e., villous chorangiosis, villous agglutination, meconium-associated vascular necrosis). Furthermore, though placental examination was standardized across SCRN hospitals, it is possible that inter-examiner differences may introduce bias into our placental

data, especially given that not all pathologists were subspecialty-trained. However, all placental sampling and examinations were overseen by the primary SCRN pathologists, who maintained quality with the help of the SCRN steering committee.

Using a novel analytic method, we identified unique placental features associated with stillbirth at differing gestational ages. Further studies may link these features to specific etiologies and therefore validate these associated conditions. Specifically, we intend to investigate the relationships between lesions identified by our analyses and Initial Causes of Fetal Death (INCODE) assessment [29]. Understanding of the conditions leading to stillbirth at different gestational ages may be of benefit for obstetricians in seeking to reduce preventable stillbirths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding details

Abbreviations:

GA	gestational age
IUFD	intrauterine fetal demise
KPCovR	Kernel Principal Covariates Regression
RBF	radial basis function
SCRN	Stillbirth Collaborative Research Network

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Highlights:

- SCRN contains comprehensive placental examination data for stillbirths.

- Lesions are found in association with stillbirth at different gestational ages.

  – Funisitis and nucleated fetal red cells are found in extreme preterm stillbirth.

  – Multifocal reactive amniocytes and meconium are found in term stillbirth.

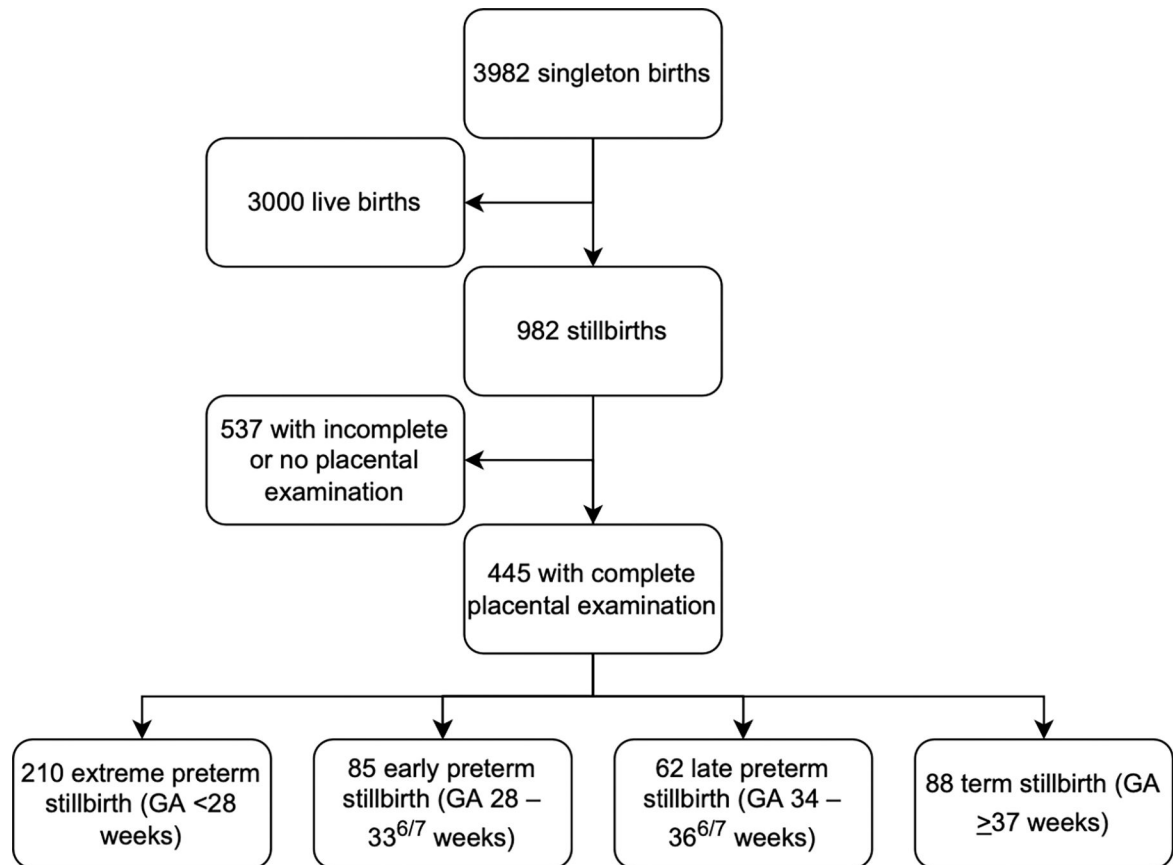- Kernel Principal Covariates Regression can delineate placental features.

Figure 1:
Sample derivation. A flowchart of included and excluded participants in this study. 3982 participants were considered; 445 were ultimately included.
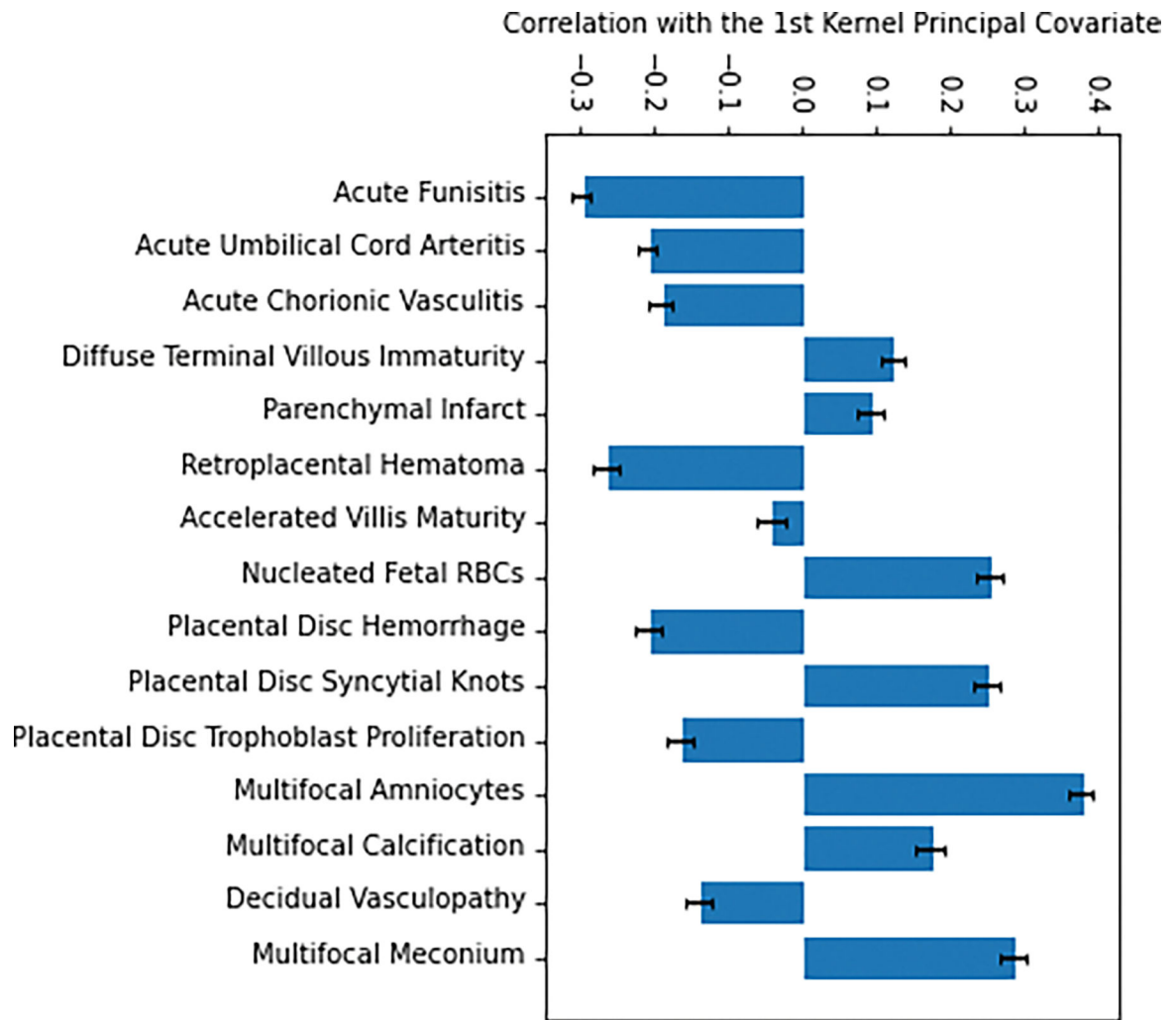
Figure 2:

Feature correlation with first principal covariate. Correlation coefficient with 1st Kernel principal covariate for various lesions shown with standard error bars.
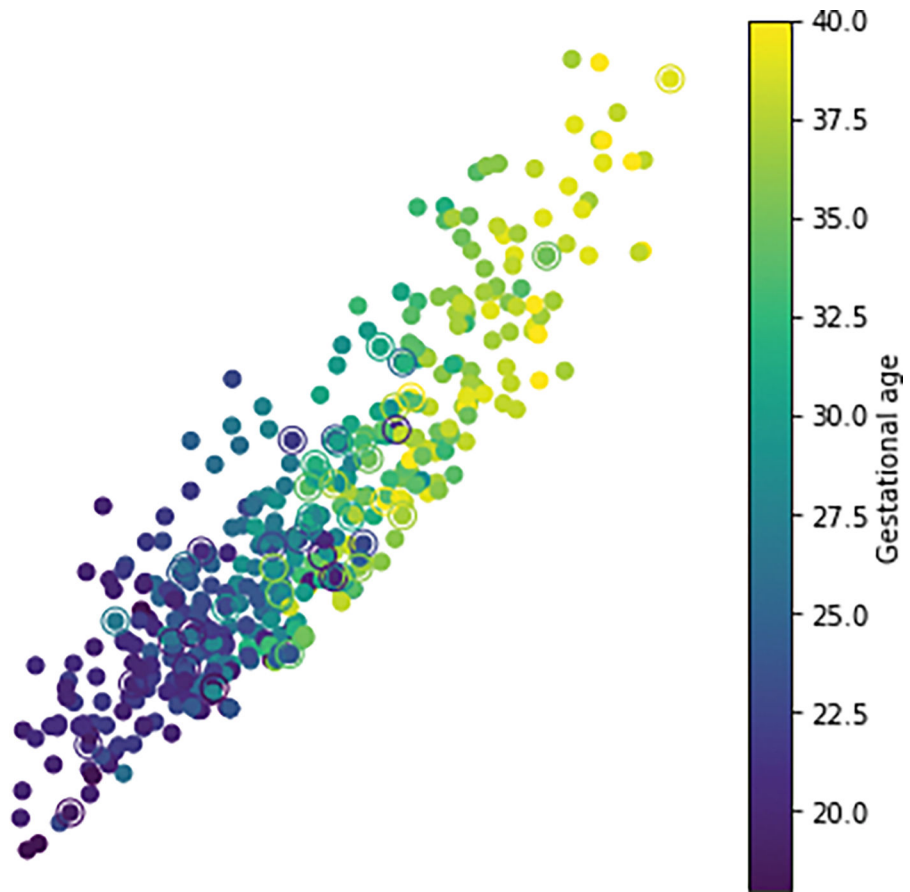
Figure 3:
Feature mapping across gestational ages. Each dot represents a lesion, color coded according to approximate gestational age to which it is mapped.

Sample characteristics

Table 1:

	Extreme Preterm Stillbirth (n = 210)	Early Preterm Stillbirth (n = 85)	Late Preterm Stillbirth (n = 62)	Term Preterm Stillbirth (n = 88)	p-value [*]
Maternal age (years)	27.0 ± 6.7	28.3 ± 7.2	27.1 ± 6.2	28.2 ± 7.0	0.4
Race (minority)	94 (44.8)	35 (41.2)	20 (32.3)	25 (28.4)	**0.038**
Ethnicity (Hispanic)	58 (27.8)	30 (35.3)	21 (33.9)	32 (36.4)	0.4
Education (years)	12.8 ± 2.9	12.8 ± 3.2	12.6 ± 3.6	12.9 ± 2.9	0.9
Any chronic illness	144 (68.6)	52 (61.2)	43 (69.4)	65 (73.9)	0.3
Diabetes	7 (3.6)	3 (3.8)	3 (5.1)	9 (11.1)	0.1
Hypertension	23 (12.0)	14 (17.7)	10 (16.9)	15 (18.5)	0.4
Cardiovascular disease	121 (57.6)	47 (55.3)	35 (56.5)	53 (60.2)	0.9
Gastrointestinal disease	100 (47.6)	37 (43.5)	31 (50.0)	38 (43.2)	0.8
Mental health condition	24 (11.4)	9 (10.6)	9 (14.5)	17 (19.3)	0.3
Obesity	58 (27.6)	23 (27.1)	17 (27.4)	20 (22.7)	0.8
Obstetric history					
Past IUFD	38 (18.1)	9 (10.6)	10 (16.1)	14 (15.9)	0.5
Number of pregnancies	2.6 ± 1.6	2.6 ± 1.6	2.4 ± 1.7	2.8 ± 1.9	0.7
Assisted reproductive technology	49 (23.3)	29 (34.1)	13 (21.0)	10 (11.4)	**0.005**
Fetal characteristics					
Sex (female)	78 (37.1)	31 (36.5)	19 (30.6)	39 (44.3)	0.4
Weight (g)	425 ± 363	1181 ± 530	2246 ± 671	3120 ± 680	**<0.001**

All values listed as number (percent) or mean ± standard deviation.

[*] Chi-Square difference test (categorical) or Kruskall-Wallis test (continuous); p<0.05 significant.

Table 2:

Correlations and post-hoc analyses of placental lesions

	Correlation Coefficient[1]	Extreme Preterm Stillbirth	Early Preterm Stillbirth	Late Preterm Stillbirth	Term Stillbirth	p-value[2]
Acute funisitis	−0.30 ± 0.01	28 (13.3)[y]	2 (2.4)	1 (1.6)	2 (2.3)	<0.001
Acute umbilical arteritis	−0.21 ± 0.01	10 (4.8)[yy]	0 (0.0)	1 (1.6)	0 (0.0)	0.030
Acute chorionic vasculitis	−0.19 ± 0.02	22 (10.5)	1 (1.2)	2 (3.2)	4 (4.5)	0.012
Diffuse terminal villous immaturity	0.12 ± 0.02	6 (2.9)	3 (3.5)	8 (12.9)[yy]	5 (5.7)	0.022
Parenchymal infarct	0.09 ± 0.02	44 (21.0)	37 (43.5)[y]	16 (25.8)	20 (22.7)	<0.001
Retroplacental hematoma	−0.26 ± 0.02	52 (24.8)[yy]	17 (20.0)	9 (14.5)	5 (5.7)	0.001
Accelerated villous maturity	−0.04 ± 0.02	40 (19.0)[y]	28 (32.9)	23 (37.1)[yy]	0 (0.0)	<0.001
Nucleated fetal red blood cells	0.26 ± 0.02	45 (21.4)[y]	29 (34.1)	28 (45.2)	31 (35.2)	0.001
Placental disc						
Hemorrhage	−0.21 ± 0.02	83 (39.5)[yy]	26 (30.6)	15 (24.2)	19 (21.6)	0.009
Syncytial knots	0.25 ± 0.02	22 (10.5)	29 (34.1)[yy]	8 (12.9)	25 (28.4)	<0.001
Trophoblast proliferation	−0.17 ± 0.02	45 (21.4)	16 (18.8)	4 (6.5)[yy]	9 (10.2)	0.012
Decidual vasculopathy	−0.14 ± 0.02	41 (19.5)	19 (22.4)	5 (8.1)[yy]	7 (8.0)[yy]	0.009
Multifocal						
Reactive amniocytes	0.38 ± 0.02	16 (7.6)	6 (7.1)	14 (22.6)[yy]	32 (36.4)[yy]	<0.001
Calcifications	0.17 ± 0.02	1 (0.5)	3 (3.5)	0 (0.0)	7 (8.0)[yy]	<0.001
Meconium	0.29 ± 0.02	41 (19.5)	29 (34.1)	16 (25.8)	43 (48.9)[yy]	<0.001

[1] Pearson correlation with first principal covariate.

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[2] Chi-Square difference test; p<0.05 significant.

[y] Post-hoc analysis indicates significantly higher/lower relative to all other ranges.

[yy] Post-hoc analysis indicates significantly higher/lower relative to 1–2 other ranges.

Lesions not significantly different across ranges (did not contribute to variance explained in sample): thrombi of or disrupted fetal vessels, chorionic vascular degeneration, chorioamnionitis, chorangioma, chorangiomatosis, chorangiosis, chorionic or disc karyorrhexis, acute umbilical phlebitis, umbilical vascular lesion, punctate or gross umbilical hemorrhages, true knot, single umbilical artery, umbilical degeneration, irregular disc lobulations, disc inclusion bodies, deciduitis, amniotic bands, disc fibrin deposition, avascular villi, terminal villous hypoplasia, intravillous thrombus, diffuse villous fibrin deposition, intervillitis, acute or chronic villitis, abnormal membrane insertion, abundant blood clots, or multifocal edema, hemosiderin, amnion nodosum, or necrosis.