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Findings in Stillbirths Associated With Placental Disease

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Abstract

Objective: Placental disease is a leading cause of stillbirth. Our purpose was to characterize stillbirths associated with placental disease.

Study Design: The Stillbirth Collaborative Research Network conducted a prospective, case-control study of stillbirths and live births from 2006–2008. This analysis includes 512 stillbirths with cause of death assignment and a comparison group of live births. We compared exposures between women with stillbirth due to placental disease and those due to other causes as well as between women with term (≥ 37 weeks) stillbirth due to placental disease and term live births.

Results: 121 (23.6%) of 512 stillbirths had a probable or possible cause of death due to placental disease by INCODE. Characteristics were similar between stillbirths due to placental disease and other stillbirths. When comparing term live births to stillbirths due to placental disease, women with non-Hispanic black race, Hispanic ethnicity, lack of insurance, or who were born outside of the United States had higher odds of stillbirth due to placental disease. Nulliparity and antenatal bleeding also increased risk of stillbirth due to placental disease.

Conclusion: Multiple discrete exposures were associated with stillbirth caused by placental disease. The relationship between these factors and utility of surveillance warrants further study.

Keywords

placental disease; stillbirth; placental insufficiency; placental pathology

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Objective

Stillbirth complicates 6 per 1000 pregnancies in the United States, or approximately 1 in 160 pregnancies[1]. There are many different risk factors for and causes of stillbirth, including placental insufficiency, obstetric conditions such as cervical insufficiency, fetal genetic/structural anomalies, infection such as parvovirus, umbilical cord abnormalities, hypertensive disorders, maternal medical complications, and others.

Placental disease is a major and potentially preventable cause of stillbirth. Placental disease occurs when an abnormal placenta (either due to poor development or damage) leads to insufficient delivery of nutrients and oxygen to the fetus. This leads to adverse pregnancy outcomes such as stillbirth, preterm birth, preeclampsia, and fetal growth restriction (FGR). Placental disease also contributes to fetal programming[2–4] and leads to alterations in fetal structure and cellular function conferring increased risk of metabolic disease later in life[3,5]. The Stillbirth Collaborative Research Network (SCRN) found that 23.6% of stillbirths were attributed to placental disease in a United States cohort[6]. However, few data are available regarding details of stillbirth associated with placental disease. Thus, our objective was to characterize placenta related stillbirths in the SCRN cohort in order to inform clinical management and further research on stillbirth prevention.

Study Design

This is a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Stillbirth Collaborative Research Network (SCRN) study. The original study was a case-control study of stillbirths and representative live births in five catchment areas (Rhode Island, portions of Massachusetts, Georgia, Texas, and Utah) from March 2006 to September 2008. Catchment areas included 59 participating hospitals, which ensured access to more than 90% of births in each area. Women were recruited at the time of diagnosis of stillbirth, upon admission for delivery and/or postpartum, or prior to hospital discharge. Stillbirth was defined as birth after 20 weeks' gestation with an Apgar score of 0 at 1 and 5 minutes. Deliveries due to termination of a live fetus were excluded. Details regarding methods, study design, and sample size have been previously published[7]. The study was approved by the institutional review boards of each clinical site and the Data-Coordinating and Analysis Center, and all mothers gave written informed consent.

For this analysis, all stillbirths with complete evaluation were included. A complete evaluation included medical record abstraction and maternal interview, fetal autopsy and placental histology, attempted fetal / placental karyotype or microarray, and maternal laboratory assessment. The following laboratory tests were recommended for all stillbirths: testing for fetal-maternal hemorrhage, antibody screen, serologic test for syphilis, parvovirus serology, glycated hemoglobin, anticardiolipin antibodies, and toxicology screen), placental pathologic assessment, and fetal autopsy. Placental pathology and fetal autopsy were performed using a standardized protocol and data were reported using standardized forms[8]. Pathologists were required to participate in workshops to standardize the examination and reporting prior to initiation of the study protocol. Pathologists were not blinded to stillbirth status, as placenta and fetus were evaluated together.

SCRN developed the Initial Causes of Fetal Death (INCODE) algorithm in order to assign a level of certainty to the cause (or causes) of each stillbirth[6]. INCODE assigns cause of death as probable, possible, or condition present based on available data. Using INCODE, causes of stillbirth were broadly categorized as obstetric complications, placental disease, fetal genetic/structural anomalies, infection, umbilical cord abnormalities, hypertensive disorders, maternal medical complications, and other (such as hydrops or early amnion rupture sequence). Pathologic findings relevant to placental disease in the INCODE analysis included placental abnormalities such as fetal thrombus, villous infarct, delayed villous maturation, massive perivillous fibrin, accelerated villous maturation, decidual vasculopathy, maternal floor fibrin deposition, massive subchorionic hematoma, subamniotic hemorrhage, intraplacental thrombi, placenta previa/accreta, partial mole, and circumvallate vasculopathy. Clinical diagnoses for placental insufficiency included small for gestational age (SGA) with birthweight <10th percentile[9] with at least one of the following: oligohydramnios, abnormal Doppler velocimetry of the umbilical artery, category III fetal heart tracing, or a biophysical profile score of 6 or less[6].

We compared stillbirths with placental disease identified as cause of death per INCODE to stillbirths without placental disease as cause of death. Demographic, obstetric, and prenatal factors were compared between groups. The proportions of stillbirths complicated by gestational hypertensive disorders (GHD) and small for gestational age (SGA) fetus also were compared between groups, as these conditions are known at time of delivery and are commonly associated with placental disease. We recognize that our *a priori* definition of placental disease dictates a higher proportion of SGA in the placental disease group. GHD was defined as gestational hypertension, preeclampsia, superimposed preeclampsia, and/or HELLP syndrome[10]. SGA was defined as birth weight at less than the 10th percentile for gestational age[9]. Variables were compared by Chi-square, Fisher's exact, or Student's t-test. Odds ratios (ORs) were calculated for exposures. The same analysis was repeated for the subset of stillbirths occurring at or beyond 34 weeks. When evaluating stillbirths only, we attempted to build a multivariate model to calculate adjusted odds ratios (aORs), but no variables altered the crude OR by more than 10%, so none qualified for the model.

We then compared stillbirths due to placental disease to live births. This analysis was stratified by term or preterm birth. Preterm birth was defined as all deliveries prior to 37 weeks' gestation, regardless of reason. Demographic, obstetric, and prenatal factors were compared between groups. In the original study design, controls were oversampled for live births between 20–31 weeks' gestation and for women of African descent delivering a live birth at or beyond 32 weeks' gestation. Also, there was variable consent to complete stillbirth evaluation and placental examination. Thus, to account for oversampling and differential consent in enrollment and sampling methods, data weights were calculated and used in the analysis[7]. Crude ORs and 95% confidence intervals were calculated using univariate regression models. Adjusted ORs and 95% confidence intervals were calculated using a multivariate model. Variables were evaluated for inclusion in the multivariate model if their univariate p-value was 0.2 or less. They were included in the final model if they altered the overall OR by 10% or greater. Statistical analysis was performed using Stata, StataCorp, College Station, TX.

Results

In the primary study, 663 women experiencing stillbirth with 676 stillborn fetuses were enrolled. 500 of these women had complete evaluation with 512 stillbirths. These 512 stillbirths were reviewed by two physicians as previously described[6] and assigned to one or more INCODE categories. Of the 512 stillbirths analyzed, 121 (23.6%) were attributed to placental disease. The distribution of stillbirths due to placental disease were as follows: fetal thrombus 42 (34.7%), villous infarct 31 (25.6%), clinical placental insufficiency 24 (19.8%), delayed villous maturation 12 (9.9%), massive perivillous fibrin 11 (9.1%), accelerated villous maturation 9 (7.4%), maternal floor fibrin deposition 9 (7.4%), massive subchorionic hematoma 8 (6.6%), intraplacental thrombi 5 (4.1%), and other 1 (0.8%). There were no cases of placenta previa/accreta, partial mole, circumvallate placenta, decidual vasculopathy, or sub-amnionic hemorrhage.

Table 1 shows demographic and prenatal characteristics of women with stillbirth attributed to placental disease and women with stillbirth due to other causes. Body mass index (BMI) of 30–34.9 kg/m^2 and ≥35 kg/m^2 were both more common in the placental disease group (OR 1.97 [95% CI 1.04–3.72] and OR 2.22 [95% CI 1.23–4.02], respectively). Hyperthyroidism was rare overall, but was more common in women with stillbirths due to placental disease than in women with stillbirth due to other causes (2.6% vs 0.3%, OR 9.88 [95% CI 1.01–95.96]).

As expected, gestational hypertensive disorders were more common in stillbirths due to placental disease than in stillbirths due to other causes (23.1% vs 11.5%, p=0.001). Similarly, SGA was also more common in stillbirths due to placental disease than stillbirths due to other causes (39.7% vs 16.4%, p<0.001). Put another way, if GHD was present, placental disease was more likely to be implicated as a cause of death (38% vs 21%, OR 2.3, 95% CI 1.3–4.0). Similarly, if SGA was present, placental disease was more likely to be implicated as a cause of death (43% vs 18%, OR 3.4, 95% CI 1.3–4.0). If both GHD and SGA were present at stillbirth, placental disease was even more likely to be implicated as a cause of death (71% vs 22%, OR 9.1, 95% CI 3.2–29.1).

Of the 155 stillbirths that occurred at or beyond 34 weeks, 35 (22.6%) were attributed to placental disease. Further, 92.9% of stillbirths at or beyond 34 weeks had accessed prenatal care. In this group, only tobacco use differed between stillbirths due to placental disease and those due to other causes (28.6% vs 10.1%, OR 3.6, 95% CI 1.2–10.1). In this late preterm, near term, and term sub-group, neither GHD nor SGA was associated with stillbirth due to placental disease (data not shown).

After weighting, there were “206.2” preterm live births to compare to “97.5” preterm stillbirths due to placental disease (data not shown). Mean gestational age at delivery was 33.2 weeks for preterm live births and 27.8 weeks for preterm stillbirths due to placental disease (p<0.001). The multivariate model for preterm births included maternal age, insurance status, BMI, nulliparity, and previous stillbirth. BMIs outside of the normal range were associated with increased risk of stillbirth due to placental disease, with aOR of 4.88 (95% CI 1.09–21.92) for women with BMI <18.5 kg/m^2 and aOR of 16.18 (95% CI 2.01–

130.34) for women with BMI ≥ 35 kg/m^2. Nulliparity was associated with increased risk of stillbirth due to placental disease (aOR 3.97, 95% CI 1.77–8.93), as was previous stillbirth (aOR 3.47, 95% CI 1.44–8.36).

After weighting, there were “1,550” term live births to compare to “25.1” term stillbirths due to placental disease (Table 2). Mean gestational age at delivery was 38.8 weeks for live births and 39.1 weeks for stillbirths (p=0.173). The multivariate model included nulliparous status, maternal birth in the United States, years of maternal education, tobacco use, asthma, diabetes, chronic hypertension, hyperthyroid disease, and antenatal bleeding. Non-Hispanic black race (aOR 5.64, 95% CI 1.47–21.58) and Hispanic ethnicity (aOR 3.73, 95% CI 1.07–13.07) were associated with increased odds of stillbirth due to placental disease when non-Hispanic white race was the referent category. Being born in another country was associated with increased risk of stillbirth due to placental disease (aOR 5.5, 95% CI 1.8–16.5). Women without insurance had much higher odds of placental disease associated stillbirth than women with insurance from the Veteran Affairs, commercial health insurance, or a health maintenance organization (aOR of 18.32, 95% CI 2.80–119.92). Medical conditions with increased risk of stillbirth due to placental disease included asthma (aOR 2.84, 95% CI 1.03–7.79), diabetes (aOR 7.22, 95% CI 1.90–27.41), and hyperthyroid disease (aOR 9.48, 95% CI 2.26–39.73). Pregnancy specific factors including nulliparity (aOR 6.85, 95% CI 2.74–17.15) and antenatal bleeding (aOR 7.80, 95% CI 2.54–23.93) also increased risk of stillbirth due to placental disease.

Conclusion

Stillbirth due to placental disease accounts for 23.6% of stillbirths at all gestational ages and 22.6% of stillbirths in the late preterm and term period. The SCRN previously reported that the frequency of placental disease was common at each gestational time period examined, ranging from 12.5% at 20–23 weeks up to 40.0% at 18–19 weeks[11]. Unfortunately, within a stillbirth population, few clinical factors predict placental disease as a cause of death.

The risk factors we identified in our analysis are consistent with previous findings. Abnormal BMI was associated with increased risk of stillbirth due to placental disease, both compared to other stillbirths as well as to live births. This is consistent with previous case-control analyses showing that increased BMI is associated with all-cause stillbirth[12[Lawn, 2016 #1273,13–15]. Our analysis is the only one to focus on placental disease, providing evidence that elevated BMI is associated with abnormal placental development and/or function. Tobacco use has also long been associated with stillbirth and other adverse pregnancy outcomes linked to placental disease such as fetal growth restriction and placental abruption[16,17]. Smoking has been linked to placental damage, leading to insufficiency. Smoking is associated with decreased mean placental weight and both maternal and fetal vascular lesions of the placenta[18]. Epigenetic changes in methylation of placental specific genes have also been found in women who smoke tobacco during pregnancy[19].

Maternal medical comorbidities such as diabetes, asthma, and thyroid disease have been previously associated with stillbirth[13,20[Flenady, 2011 #1685,21]]. However, our analysis shows these specific comorbidities to be overrepresented in stillbirths attributed to placental

disease. Moderate to severe asthma has been noted to diminish placental vascular function as measured by corticotropin releasing hormone induced vasodilation[22]. Placental morphometry was also altered in asthmatic pregnancies, with reduced absolute volumes of fetal capillaries[23]. Thus, it is plausible that asthma exacerbates the risk of stillbirth via placental disease.

Many previous analyses have focused on hypothyroid disorders (including subclinical hypothyroidism) and its association with perinatal morbidity, including stillbirth, preeclampsia, growth abnormalities, and preterm birth[24ni[Nijkamp, 2016 #1678,25]26]. However, we found hyperthyroidism to be associated with stillbirth due to placental problems while hypothyroidism was not. One previous report of 32 women with uncontrolled hyperthyroid disease during pregnancy showed a rate of stillbirth of approximately 100/1,000[27]. A population analysis of all pregnancies in Denmark from 1997 to 2008 (n=1,062,862) found an increased risk of pregnancy loss prior to 22 weeks with hyperthyroid disease treated before or during pregnancy (adjusted hazard ratio 1.22, 95% CI 1.06–1.41) and an increased risk of stillbirth (pregnancy loss at or after 22 weeks) if hyperthyroid diagnosed for the first time in the two years after pregnancy (adjusted hazard ratio 2.10, 95% CI 1.13–3.92)[28]. Our findings in this setting emphasize the importance of adequate control of maternal hyperthyroid disease in pregnancy.

Disparities in stillbirth rates are well documented but the reasons remain uncertain[29–32]. For example, reviews of stillbirth rates in the United States and other high-income countries consistently note increased risk of stillbirth in socially disadvantaged groups, including African-American women, migrants, indigenous women, low-income women, early teenagers, and women with low education[15,31]. Non-Hispanic black race, Hispanic ethnicity, lack of insurance, and non-native birth status all were associated with increased odds of placental stillbirth even after accounting for maternal medical disease. Although historically researchers have attributed these disparities to discordance in access to adequate prenatal care and antenatal testing, evidence suggests that exposure to institution, personal, and internalized racism is primary causal factor[33]. For Black women, having a higher income or more education does not ameliorate the negative affect of being exposed to racism on perinatal outcomes[34]. Our findings suggest that focusing on placental disease is a potential strategy to decrease disparities in the rate of stillbirths.

Unfortunately, very early stillbirths (<28 weeks) due to placental disease may not be preventable. Even if placental disease is detected, it is uncertain whether extreme prematurity is justified unless stillbirth seems imminent. However, in the late-preterm and term period, delivery is a viable and usually, preferable option. In cases of severe preeclampsia or severe FGR with abnormal fetal testing, delivery at 34 weeks is reasonable. Ultrasound examination of fetal growth, amniotic fluid volume, and flow and resistance to flow in maternal and fetal vessels, as well as serum biomarker assessment of FGR fetuses may be used to predict which cases of FGR are due to placental disease and at higher risk of stillbirth[35–37]. These tests show promise for assessing FGR fetuses. However, FGR pregnancies are not the only ones in which the placenta is malfunctioning. Better tests to predict a compromised placenta in late gestation are needed since current screening

(including risk factor based third trimester ultrasound) is non-specific and has poor predictive value for neonatal morbidity[38].

When placental histopathology was previously compared between stillbirths and live births in SCRN, the following lesions were associated with stillbirth: vascular degenerative changes in the chorionic plate, retroplacental hematoma, intraparenchymal thrombi, parenchymal infarction, fibrin deposition, fetal vascular thrombi, avascular villi, and hydrops[39]. Placental pathologic evaluation permits identification of these lesions and may lead to diagnosis of placental disease as a cause of death, even in the absence of a clinical phenotype of placental disease. This diagnosis provides an explanation to parents and can guide management of future pregnancies. However, it is important to be cautious when ascribing a placental cause of stillbirth in the setting of placental histologic abnormalities. Because all placental lesions found in stillbirths are also noted in a population of live births, there is no single pathologic way to distinguish stillbirths from live births. Placental pathology alone does not determine the outcome of stillbirth[39]. Further studies should determine which and to what extent specific placental abnormalities should be considered evidence of placental mediated stillbirth.

Morbidity associated with massive perivillous fibrin deposition is particularly high and includes fetal growth restriction, stillbirth, neonatal death, and neonatal neurologic damage[40[Chen, 2018 #1683,41]]. A series of 13 cases of massive perivillous fibrin deposition or maternal floor infarct noted an overall incidence of 0.028% with a recurrence rate of 18%. All infants in this series suffered FGR with a 31% fetal death rate[42]. Diagnosis is of particular import as this lesion has significant recurrence risk, ranging 12–78% in other series[43,44]. In a case-control trial of 10 placentas with massive perivillous fibrin deposition compared to 175 normal placentas from term deliveries, massive perivillous fibrin deposition was associated with complement activation, plasma cell deciduitis, maternal anti-HLA class I, and elevated maternal plasma CXCL-10, all suggesting a failure of immune tolerance[45]. Massive perivillous fibrin is associated with lower placental growth factor (PlGF), ratio of PlGF to soluble endoglin, and ratio of PlGF to soluble vascular endothelial growth factor receptor, suggesting angiogenic imbalance as a contributing cause[46].

A limitation of our analysis is a lack of systematically obtained data from serial ultrasounds and antenatal testing. This is a fundamental weakness of case-control studies. Ultrasound surveillance and antenatal testing is currently advised for women at high risk for placental disease, but these tests are not typically started until 32 or 34 weeks gestation[47]. Because of this, there may be SGA stillbirths who are not counted as due to placental disease who would have been if they had had concerning antenatal testing prior to death. Also, many women who develop placental disease and stillbirth do not have known risk factors. Our data support the need to further evaluate additional universal screening for placental function in the third trimester. Universal third trimester ultrasonography has been shown to increase detection of SGA neonates, with an area under the receiver operator curve of 0.87 suggesting good testing characteristics[38]. Another limitation is uncertainty regarding the contribution of placental histologic abnormalities that were included in the INCODE classification of placental stillbirth. Although the criteria used were conservative, robust, and based on available data and expert opinion from perinatal pathologists, the criteria remain

somewhat subjective. Additionally, a large number of stillbirths (24%) were excluded from INCODE analysis due to lack of consent to postmortem examination, including fetal autopsy and placental pathologic assessment. As previously discussed, statistical weights were incorporated into count calculations and comparison testing in an attempt to correct for this variable consent. However, there remains a possibility that there is a significant confounding factor associated with both lack of consent to postmortem examination and with placental disease causes. Notably, women who were approached but did not enroll in the original study (n=290) did not differ from those who did enroll by the demographic characteristics of age, race/ethnicity, insurance/method of payment, or gestational age at delivery[11].

An important strength of this study is the comprehensive assessment of cause of death for stillbirths using the INCODE tool. The rigor of this classification system in assigning cause of death limits ascertainment bias. Also, standardization of placental assessment in the SCRN study is important when evaluating placental histologic abnormalities. These methodologic strengths permit us to clearly define our comparison groups.

Placental disease is one of the most important causes of stillbirth, implicated in 23.6% of stillbirths at all gestational ages and 22.6% of stillbirths in the late preterm and term period. In addition, it is the largest cause of potentially “preventable” stillbirths[48]. However, it is difficult to predict based on risk factors, particularly in the late preterm and term period. Placental pathologic evaluation is helpful in diagnosing placental disease, but the information arrives too late to help the index pregnancy. Parents of stillborn infants choose tests based on their utility in informing diagnosis and predicting future pregnancy outcomes[49,50], so placental pathologic assessment is routinely recommended[51]. Meanwhile, pursuit of a test to detect a failing placenta remains ongoing.

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Table 1.

Comparison of demographic and antenatal factors between stillbirths due to placental disease (PD SB) and due to other causes (non-PD SB).

	PD SB N=121	Non-PD SB N=391	OR (95% CI)	p-value
Maternal age (years)	28.6 (6.3)	28.0 (6.7)	--	0.421
Paternal age (years)	30.1 (7.6)	29.4 (7.3)	--	0.320
Race				0.347
Non-Hispanic white	40 (33.3)	143 (36.6)	Ref	
Non-Hispanic black	22 (18.3)	93 (23.8)	0.85 (0.47–1.51)	
Hispanic	47 (39.2)	129 (33.0)	1.3 (0.80–2.11)	
Other	11 (9.2)	26 (6.7)	1.5 (0.69–3.32)	
Born outside of U.S.	26 (22.6)	86 (23.2)	0.96 (0.6–1.6)	0.888
Insurance				0.896
None	7 (5.8)	24 (6.2)	0.98 (0.40–2.42)	
Any public/private assistance	65 (53.7)	199 (51.3)	1.10 (0.72–1.68)	
VA/commercial health ins/HMO	49 (40.5)	165 (42.5)	Ref	
Maternal Education	13.0 (3.0)	12.9 (2.8)	--	0.733
Living with partner and/or married	93 (80.9)	269 (72.7)	1.59 (0.95–2.66)	0.079
Prenatal care	110 (95.7)	345 (93.5)	1.53 (0.57–4.11)	0.395
BMI (kg/m^2)	28.5 (7.1)	27.6 (6.8)	n/a	0.213
<18.5	5 (4.3)	17 (4.5)	1.33 (0.46–3.85)	0.062
18.5–24.9	36 (31.0)	163 (42.9)	Ref	
25–29.9	29 (25.0)	101 (26.6)	1.30 (0.75–2.25)	
30–34.9	20 (17.2)	46 (12.1)	1.97 (1.04–3.72)	
>35	26 (22.4)	53 (14.0)	2.22 (1.23–4.02)	
Maternal comorbidities				
Chronic hypertension	17 (14.8)	37 (10)	1.56 (0.84–2.89)	0.154
Asthma	8 (7.0)	38 (10.3)	0.65 (0.30–1.44)	0.289
Seizure disorder	0 (0)	6 (1.6)		0.344
Diabetes mellitus	7 (6.1)	20 (5.4)	1.13 (0.47–2.75)	0.781
Hyperthyroid disease	3 (2.6)	1 (0.27)	9.88 (1.01–95.96)	0.043
Hypothyroid disease	2 (1.7)	8 (2.2)	0.80 (0.17–3.83)	1.000
Kidney disease	1 (0.9)	6 (1.6)	0.54 (0.06–4.51)	1.000
Sickle cell disease	0 (0)	4 (1.1)		0.577
Autoimmune disease	2 (1.8)	0 (0)		0.055
Mental illness	11 (9.6)	26 (7.0)	1.40 (0.67–2.93)	0.370
UTI	23 (20)	49 (13.2)	1.64 (0.95–2.83)	0.075
ART	4 (3.4)	14 (3.7)	0.93 (0.30–2.87)	1.000
Alcohol use	3 (2.5)	10 (2.6)	0.96 (0.26–3.56)	1.000

	PD SB N=121	Non-PD SB N=391	OR (95% CI)	p-value
Tobacco use	20 (16.8)	42 (10.9)	1.65 (0.92–2.93)	0.089
Recreational drug use	4 (3.4)	11 (2.9)	1.20 (0.37–3.83)	0.759
Abuse (physical, sexual, or emotional)	2 (1.9)	5 (1.6)	1.16 (0.22–6.06)	1.000
Nulliparous, never pregnant or only elective terminations	48 (39.7)	128 (32.7)	1.33 (0.82–2.17)	0.77
Nulliparous with previous losses	8 (6.6)	47 (12.0)	0.60 (0.266–1.39)	
Multiparous with no previous losses or stillbirths	38 (31.4)	135 (34.5)	Ref	
Multiparous with no stillbirth but previous losses at <20 wk	14 (11.6)	59 (15.1)	0.84 (0.43–1.67)	
Multiparous with stillbirth	13 (10.7)	22 (5.6)	2.10 (0.97–4.55)	
Antenatal bleeding	11 (9.6)	35 (9.5)	1.01 (0.50–2.06)	0.980
Intrapartum demise	6 (5.5)	38 (11.0)	0.37 (0.18–0.73)	0.086

HTN=hypertension; DM=Diabetes mellitus; SLE=Systemic Lupus Erythematosus; APS=Antiphospholipid syndrome; Autoimmune disease=systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, ulcerative colitis, and/or Crohn's disease; UTI=urinary tract infection; ART=Assisted Reproductive Technology

Data are reported as n (%) or mean (SD). P-values are generated via t-test, chi-square test, or Fisher's exact test.

Table 2.

Comparison of demographic and antenatal factors between term live births and term stillbirths due to placental disease (PI stillbirth).

	Live birth 1550	PD SB 25.1	OR (95% CI)	P-value	aOR (95% CI)
Maternal age at delivery, y	26.9 (0.2)	27.9 (1.3)		0.421	
<20	181.7 (11.7)	3.72 (14.8)	1.28 (0.37–4.45)	0.923	0.75 (0.21–2.71)
20–34	1170 (75.5)	18.6 (74.1)	Ref		Ref
35–39	172.6 (11.1)	2.8 (11.1)	1.02 (0.29–3.53)		0.57 (0.11–3.05)
≥40	26.1	0	--		--
Maternal race/ethnicity			0.070		
Non-Hispanic white	704.3 (45.4)	6.4 (25.4)	Ref	0.105	Ref
Non-Hispanic black	176 (11.4)	6.1 (23.9)	3.77 (1.12–12.64)		5.64 (1.47–21.58)
Hispanic	550.9 (35.5)	12.0 (47.7)	2.4 (0.87–6.63)		3.73 (1.07–13.07)
Other	118.8 (7.7)	0.76 (3.0)	0.71 (0.08–5.96)		0.75 (0.08–6.76)
Born outside of U.S.	285 (19.0)	10.3 (40.8)	2.9 (1.3–6.9)	0.013	5.5 (1.8–16.5)
Maternal education, grade	13.3 (0.1)	12.3 (0.5)		0.05	
0–11	295.3 (19.7)	7.4 (30.5)	2.14 (0.76–6.05)	0.349	0.59 (0.08–4.23)
12	400.7 (26.8)	7.4 (30.8)	1.59 (0.56–4.50)		0.90 (0.24–3.40)
≥13	801.2 (53.5)	9.3 (38.7)	Ref		Ref
Living with a partner and/or married	1262 (84.0)	25.1 (100)	--	0.037	--
Insurance **None** **Any public/private assistance** **VA/commercial health ins/HMO**	49.6 (3.2) 811.5 (52.4) 687.8 (44.4)	4.6 (18.3) 16.8 (66.7) 3.8 (15.0)	16.89 (3.96–72.11) 3.76 (1.2–11.8) Ref	0.0007	18.32 (0.280–119.92) 3.08 (0.72–13.24) Ref
Tobacco use	125.6 (8.2)	8.2 (32.7)	5.4 (2.2–13.6)	0.0003	9.91 (2.94–33.45)
Alcohol use	21.6 (1.4)	0 (0)	--	0.569	--
Recreational drug use	45.5 (3.0)	0 (0)	--	0.416	--
Prenatal care accessed	1494 (99.3)	25.14 (100)	--	0.651	--
BMI	26.5 (0.2)	26.7 (1.0)		0.760	
<18.5	51 (3.3)	0 (0)	--	0.254	--
18.5–24.9	757.8 (49.8)	9.7 (38.6)	Ref		Ref
25–29.9	365.6 (24.0)	7.9 (31.4)	1.68 (0.62–4.53)		1.29 (0.41–4.13)
30–34.9	178.4 (11.7)	6.2 (24.7)	2.71 (0.91–8.09)		3.78 (1.11–12.88)
≥=35	168.8 (11.1)	1.3 (5.4)	0.62 (0.08–4.93)		1.20 (0.16–9.14)
Chronic hypertension	172.6 (11.5)	1.4 (5.4)	0.44 (0.06–3.27)	0.420	0.32 (0.04–2.82)
Asthma	128.1 (8.5)	5.5 (21.7)	2.97 (1.06–8.31)	0.038	2.84 (1.03–7.79)
Seizure disorder	9.96 (0.66)	0 (0)	--	0.723	--
Diabetes mellitus	37.7 (2.5)	3.7 (14.7)	6.69 (1.89–23.76)	0.003	7.22 (1.90–27.41)
Hyperthyroid disease	17.7 (1.2)	2.5 (10.1)	9.36 (2.04–42.94)	0.004	9.48 (2.26–39.73)
Hypothyroid disease	31.3 (2.1)	0 (0)	--	0.469	--

	Live birth 1550	PD SB 25.1	OR (95% CI)	P-value	aOR (95% CI)
Kidney disease	8.5 (0.6)	1.3 (5.4)	9.95 (1.21–81.58)	0.032	12.98 (0.68–247.86)
Sickle cell disease	7.1 (0.5)	0 (0)	--	0.723	--
Mental illness	140.3 (9.3)	0.91 (3.6)	0.36 (0.05–2.74)	0.327	0.19 (0.02–2.25)
Autoimmune disorder	26.7 (1.8)	0 (0)	--	0.535	--
UTI	255.2 (17.0)	6.0 (23.8)	1.53 (0.56–4.19)	0.413	0.91 (0.32–2.54)
Abuse (physical, sexual, or emotional)	50.2 (4.6)	0 (0)	--	0.367	--
Nulliparous	556.3 (35.9)	14.7 (58.6)	2.53 (1.07–5.95)	0.0338	4.52 (1.97–10.37)
Nulliparous, never pregnant or only elective terminations	471.4 (30.4)	14.7 (58.6)	2.65 (1.05–6.70)	0.039	6.85 (2.74–17.15)
Nulliparous with previous losses	84.9 (5.5)	0 (0)	--		--
Multiparous with no previous losses or stillbirths	700.9 (45.2)	8.3 (32.9)	Ref		Ref
Multiparous with no stillbirth but previous losses at <20 wk	279.1 (18.0)	1.2 (4.7)	0.36 (0.04–2.91)		0.45 (0.06–3.51)
Multiparous with stillbirth	13.3 (0.9)	1.0 (3.9)	6.24 (0.72–53.78)		8.52 (0.79–92.17)
ART	36.3 (2.4)	0.8 (3.0)	1.27 (0.16–9.89)	0.820	1.74 (0.21–14.63)
Multifetal pregnancy	14.9 (1.0)	0 (0)	--	0.723	--
Antenatal bleeding	47.0 (3.1)	4.6 (18.1)	6.85 (2.2–21.66)	0.001	7.80 (2.54–23.93)
Gestational age at delivery	38.8 (0.03)	39.1 (0.2)		0.173	

VA=Veteran's Affairs; HMO=Health Maintenance Organization; BMI= body mass index; ART= assisted reproductive technology; UTI=urinary tract infection

Multivariate model includes nulliparous status, born in the United States, years of maternal education, tobacco use, asthma, diabetes, hypertension, hyperthyroid disease, and antenatal bleeding.