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## Research Article

# Previous Preterm Birth and Current Maternal Complications as a Risk Factor of Subsequent Stillbirth

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**Purpose.** To examine the association between previous preterm birth and the risk of stillbirth. **Methods.** This population-based retrospective cohort study analyzed live births and stillbirth records in Missouri (1989–1997). The main outcome of interest was stillbirth occurrence while the exposures were prior preterm birth. Adjusted odds ratios and 95% confidence intervals were computed using logistic regression. **Results.** Women who had a previous preterm birth have 63% increased odds of stillbirth in singleton pregnancies and 75% increased odds in twins as compared to those who did not have a preterm birth in a prior pregnancy (AOR = 1.63, 95% CI = 1.41–1.88 and AOR = 1.75, 95% CI = 1.20–2.56), respectively. The most significant risk factor for stillbirth in singleton pregnancies was uterine bleeding (AOR = 5.89, 95% CI = 5.13–6.76). In twin pregnancies, it was the condition hydramnios/oligohydramnios (AOR = 4.72, 95% CI = 3.70–6.02). Eclampsia was associated with a heightened risk of stillbirth in singletons (AOR = 2.45, 95% CI = 1.41–4.12), but not in twins (AOR = 0.96, 95% CI = 0.13–7.00). Black mothers were more likely than white to experience stillbirth (AOR = 2.10, 95% CI = 1.99–2.22 for singletons and AOR = 1.51, 95% CI = 1.27–1.79 for twins). **Conclusion.** Stillbirth is a vital public health issue and its etiology is not well understood. Previous history of preterm birth was found to be associated with future stillbirth. Targeted early medical and obstetric care and interventions among women with preterm birth history may potentially reduce the likelihood of stillbirth.

## 1. Introduction

Stillbirth (defined as fetal death at 20 or more weeks of gestation) affects one in 160 births in the United States [1], with a global estimate of 3.2 million stillbirths annually [2], half of which occur before 28 weeks of gestation [3]. With the introduction of interventions for preeclampsia, Rh isoimmunization, and diabetes, the stillbirth rate has declined since the 1950s [4]. However, racial disparities in stillbirth rates persist [5–7], as rates among blacks are almost twice that of whites [4, 6]. Since 2003, the stillbirth rate has remained at about 26,000 stillbirths each year [8].

Factors previously associated with increased risk for stillbirth include adolescent or advanced maternal age [4, 5, 9],

low socioeconomic status [9], low birth weight, lack of prenatal care [10, 11], prenatal smoking [12], stillbirth in first pregnancy [13], preeclampsia, gestational diabetes, eclampsia [10], placental abruption, nulliparity, and smoking [14]. Other known risk factors for stillbirth are delayed and obstructed labor, maternal infections, hypertensive disorders that occur during pregnancy [15, 16], and anemia [10, 17]. Prior research has revealed that the risk of stillbirth increases as gestational age progresses towards 42 weeks, with most occurring at 41–42 weeks [4, 9, 18, 19]. An in-depth report on preterm birth and stillbirth has been established [20].

Adverse pregnancy events in a prior pregnancy have been associated with negative outcomes in subsequent

pregnancies. For example, women with three or more previous spontaneous abortions in previous pregnancies have been shown to be at a higher risk for preterm birth in subsequent pregnancies [21]. Obstetric interventions aimed at increasing preterm gestation and infant size can play a role in preventing stillbirth, as well as infant morbidity and mortality [22]. Studies in Sweden and the US have indicated an association between previous preterm and small for gestational age births and the subsequent risk of stillbirth [23, 24]. They suggested that more studies are needed to confirm their findings.

This study aims to estimate the subsequent risk of stillbirth occurrence among mothers who experienced previous preterm birth and other risk factors using a large US population data. We further computed estimates to determine stillbirth risks associated with various maternal risk factors and pregnancy complications. Approximations that assessed the differences in stillbirth rates by maternal sociodemographic characteristics, including age, race, and educational level, were also calculated.

## 2. Methods

We conducted a population-based retrospective cohort study utilizing the Missouri maternally linked cohort data files for births between 1989 and 1997. The data file was collected by the Missouri Department of Health and Senior Services and contains individual records of live births and fetal deaths. Infants were linked with their biological mothers by the use of unique identifiers and were also verified to be from the second maternal pregnancy.

In this study, the exposure of interest was preterm birth (PTB) in previous pregnancies, while the outcome was stillbirth in the current pregnancy. PTB was defined as birth at less than 37 weeks of gestational age. Gestational age was calculated from the date of last normal menses minus the date of birth, in weeks. Stillbirth was defined to include both intrapartum (deaths during labor) and antepartum (deaths before labor onset) [25].

We examined maternal sociodemographic and risk factors in relation to PTB. Maternal medical risk factors were defined as any maternal health condition that could potentially be incompatible with fetal life or could cause fetal death. For this study, the maternal medical risk factors of interest included a range of pregnancy and labor complications, including uterine bleeding, eclampsia, preeclampsia, placenta previa, placental abruption, chronic hypertension, insulin-dependent diabetes and other forms of diabetes, acute/chronic lung disease, genital herpes, hydramnios/oligohydramnios, renal disease, and anemia. Demographic factors considered as likely confounders in the analysis included marital status, maternal age, prenatal smoking, number of fetuses born, maternal educational level, and maternal race. Maternal age was categorized as less than 18 years, 18 to 35 years, and above 35 years. Maternal education was classified into two groups: less than 12 years of education and 12 years or more of education. All maternal risk factors and demographic factors were based on data collected at the time of the second pregnancy.

Differences in sociodemographic characteristics by exposure status were assessed through bivariate analysis using chi-square tests. The rate of pregnancy and labor complications during the study period was computed by dividing the total number of cases by the total number of births and then multiplying by 1,000. We conducted multivariable analysis with logistic regression to compute estimates of the 95% confidence intervals and odd ratios for the likelihood of stillbirth occurrence. Analyses were conducted with the R statistical package (version 2.15.2), and all hypothesis testing was carried out with a type I error rate set at 5%. This study was approved by the institutional review board at the University of South Florida.

## 3. Results

Our study population consisted of 17,937 (1.40%) mothers who experienced preterm birth in the first pregnancy, while the remaining carried their pregnancies to term. Live births totaled 1,268,138 (99.31%) of the study population, while stillbirth comprised 8,780 (0.69%) of all births. We selected viable births (20–44 weeks of gestation) that include 1,234,951 (96.71%) singletons and 41,967 (3.29%) twins.

Sociodemographic characteristics of the population under study at the time of the second pregnancy are represented in Table 1. Significant differences were observed in age, race, infant sex, maternal education level, paternal education level, marital status, prenatal smoking status, and parity among mothers who experienced stillbirth, as compared to those with a live birth ( $p < 0.0001$ ). Mothers who experienced stillbirth were more likely to be black, unmarried, smokers, and of adolescent (<18 years) or advanced age (>35 years) with less than 12 years of education. Additionally, multiple gestation pregnancies were more common among women who experienced stillbirth.

The pregnancy and labor complication rates (per 1,000 births) experienced in the population during the second pregnancy are described in Table 2. Apart from maternal lung disease and preeclampsia, which showed no statistically significant difference among mothers, all other rates were higher for women who experienced stillbirths, as compared to those with live births, with the exception of genital herpes and other forms of diabetes mellitus. The most elevated rate among mothers with live births was observed for other forms of diabetes mellitus (17.37/1000,  $p = 0.005$ ) while the highest rate amongst mothers with stillbirths was observed for placenta abruption (75.74/1000,  $p < 0.0001$ ).

Adjusted odds ratios and 95% confidence intervals from logistic regression analysis are presented in Table 3. Previous preterm birth was associated with 63% increased odds of stillbirth, as compared to live birth among singletons (AOR = 1.63, 95% CI = 1.41–1.88) and 75% increased odds of stillbirth among twins (AOR = 1.75, 95% CI = 1.20–2.56). Furthermore, pregnancy and labor conditions for the second pregnancy, including hydramnios/oligohydramnios, chronic hypertension, and uterine bleeding, were associated with increased odds of stillbirth occurrence in both groups, while eclampsia and insulin-dependent diabetes are associated with increased odds among singletons and reduced odds in twins

TABLE 1: Sociodemographic characteristics of study population at the time of the second pregnancy.

	Stillbirth <sup>a</sup> n (%)	Live birth <sup>a</sup> n (%)	<i>p</i> value <sup>b</sup>
Maternal age			<b>&lt;0.0001</b>
Less than 18 years	532 (6.11)	52064 (4.15)	
18 to 35 years	7278 (83.59)	1115315 (88.85)	
Above 35 years	897 (10.30)	87917 (7.00)	
Maternal race			<b>&lt;0.0001</b>
White	6220 (71.91)	1041145 (84.44)	
Black	2429 (28.08)	191852 (15.56)	
Infant sex			<b>&lt;0.0001</b>
Male	4798 (53.09)	662673 (51.22)	
Female	4239 (46.91)	631160 (48.78)	
Maternal educational level			<b>&lt;0.0001</b>
Less than 12 years	2040 (25.10)	247616 (19.87)	
12 years or more	6086 (74.90)	998390 (80.13)	
Paternal educational level			<b>&lt;0.0001</b>
Less than 12 years	882 (16.05)	135495 (13.37)	
12 years or more	4613 (83.95)	877774 (86.63)	
Marital status			<b>&lt;0.0001</b>
Married	5361 (61.23)	901026 (71.80)	
Not married	3395 (38.77)	353932 (28.20)	
Maternal prenatal smoking			<b>&lt;0.0001</b>
Yes	2536 (30.18)	283699 (22.69)	
No	5867 (69.82)	966767 (77.31)	
Number of fetuses			<b>&lt;0.0001</b>
Singleton	7944 (90.48)	1227007 (96.76)	
Twins	836 (9.52)	41131 (3.24)	

<sup>a</sup>Columns do not total due to missing data.

<sup>b</sup>Significant *p* values are in bold font. *p* values of 0.05 or less were considered significant.

TABLE 2: Rates of pregnancy and labor complications experienced during the second pregnancy within the study population.

Rates expressed per 1,000	Stillbirth n (‰)	Live birth n (‰)	<i>p</i> value <sup>a</sup>
Previous preterm	34094 (26.70)	18031 (14.12)	<b>&lt;0.0001</b>
Uterine bleeding	39483 (30.92)	6679 (5.23)	<b>&lt;0.0001</b>
Eclampsia	2184 (1.71)	894 (0.70)	<b>&lt;0.0001</b>
Placenta previa	8160 (6.39)	3908 (3.06)	<b>&lt;0.0001</b>
Placenta abruption	96714 (75.74)	8186 (6.41)	<b>&lt;0.0001</b>
Chronic hypertension	20840 (16.32)	8939 (7.00)	<b>&lt;0.0001</b>
Other forms of diabetes	17200 (13.47)	22181 (17.37)	<b>0.005</b>
Insulin-dependent diabetes	13702 (10.73)	6896 (5.40)	<b>&lt;0.0001</b>
Preeclampsia	43569 (34.12)	43071 (33.73)	0.840
Acute/chronic lung disease	10931 (8.56)	9296 (7.28)	0.160
Genital herpes	5976 (4.68)	9616 (7.53)	<b>0.002</b>
Hydramnios/oligohydramnios	50273 (39.37)	16025 (12.55)	<b>&lt;0.0001</b>
Renal disease	4955 (3.88)	2503 (1.96)	<b>&lt;0.0001</b>
Anemia	24926 (19.52)	16013 (12.54)	<b>&lt;0.0001</b>

<sup>a</sup>Significant *p* values are in bold font. *p* values of 0.05 or less were considered significant.

TABLE 3: Adjusted odd ratios from logistic regression analysis for prediction of stillbirth by maternal risk factors.

Predictor variables	OR (95% CI) <sup>b</sup> Singletons	OR (95% CI) <sup>b</sup> Twins
Previous preterm	1.63 (1.41–1.88)	1.75 (1.20–2.56)
No previous preterm	1.00	1.00
Eclampsia present	2.45 (1.41–4.25)	0.96 (0.13–7.00)
Eclampsia absent	1.00	1.00
Insulin-dependent diabetes	1.74 (1.38–2.19)	0.67 (0.27–1.63)
No insulin	1.00	1.00
Hydramnios/oligohydramnios	2.28 (1.99–2.62)	4.72 (3.70–6.02)
No hydramnios	1.00	1.00
Chronic hypertension	2.04 (1.70–2.45)	1.25 (0.70–2.25)
No chronic hypertension	1.00	1.00
Uterine bleeding	5.89 (5.13–6.76)	4.19 (2.75–6.38)
No uterine bleeding	1.00	1.00
Black	2.10 (1.99–2.22)	1.51 (1.27–1.79)
White	1.00	1.00
No smoking	0.64 (0.61–0.68)	1.01 (0.83–1.22)
Smoking	1.00	1.00
Maternal education level < 12 years	1.00	1.00
Maternal education level ≥ 12 years	0.93 (0.88–0.99)	0.66 (0.54–0.80)
Maternal age < 18 years	1.30 (1.17–1.44)	1.01 (0.66–1.55)
Maternal age 18–35 years	1.00	1.00
Maternal age > 35 years	1.66 (1.54–1.80)	1.36 (1.08–1.71)

<sup>a</sup>Model included all maternal sociodemographic factors and pregnancy and labor complications examined in this study, including marital status, maternal age, prenatal smoking, number of fetuses born, maternal educational level, maternal race, previous preterm and small for gestational age births, uterine bleeding, eclampsia, preeclampsia, placenta previa, placental abruption, chronic hypertension, insulin-dependent diabetes and other forms of diabetes, acute/chronic lung disease, genital herpes, hydramnios/oligohydramnios, renal disease, and anemia. Only those variables with significant findings in our analysis are presented in this table.

<sup>b</sup>OR = odd ratios, 95% CI = 95% confidence intervals.

for insulin-dependent diabetes. The most elevated risk factor for stillbirth in current singleton pregnancies was uterine bleeding, which was associated with almost 6-fold increased odds (AOR = 5.89, 95% CI = 5.13–6.76). In twin pregnancies, it was the condition hydramnios/oligohydramnios (AOR = 4.72, 95% CI = 3.70–6.02). Black mothers were at least 50% more likely to experience stillbirth as compared to whites (AOR = 2.10, 95% CI = 1.99–2.22) in singletons and (AOR = 1.51, 95% CI = 1.27–1.79) in twins. Additionally, there was an elevated risk of stillbirth in women of both advanced age (>35 years, AOR = 1.66, 95% CI = 1.54–1.80 in singletons and AOR = 1.36, 95% CI = 1.08–1.71 in twins) and adolescent age (<18 years, AOR = 1.30, CI = 1.17–1.44 in singletons). Nonsmokers have reduced odds of stillbirth in singletons (AOR = 0.64, CI = 0.61–0.68) and no statistically significant difference in odds for stillbirth is found among twins pregnancies. Having at least 12 years of education is associated with reduced odds of stillbirth among both singletons (AOR = 0.93, 95% CI = 0.88–0.99) and twins (AOR = 0.66, CI = 0.54–0.80).

#### 4. Discussion

An important finding in our study was that women whose previous infant was born preterm had an increased risk of

stillbirth in their subsequent pregnancy. To our knowledge, this is the first time such a finding is reported in the US among twin pregnancies. And for singletons, this is the first time a large population data is used. This corroborates previous findings in Scotland and Sweden, which have shown that women whose previous infant was born at preterm and was small for gestational age had a higher risk of stillbirth in their second pregnancy [23, 25]. Environmental or genetic factors that play a role in the progression of intrauterine asphyxia and fetal growth retardation could actually result in a higher risk of having infants that are small for gestational age and could also explain the relationship between the risk of having stillbirth and the delivery of a previous small for gestational age infant in subsequent pregnancies [23].

Our study reinforces previous research findings that repeatedly highlight the influence of multiple maternal sociodemographic factors on birth outcomes, such as stillbirth. As with our study, previous studies have shown that stillbirth rates are higher at the extremes of maternal age (i.e., young [<18 years] and advanced maternal age [>35 years]) [4, 5]. Similar to previous research [4, 6], our analysis revealed racial disparities in the rate of stillbirth, as black mothers experienced around twofold higher odds of stillbirth compared to white mothers. We also observed a decreased risk

of stillbirth occurrence among mothers who did not smoke while pregnant, compared to those who did, providing further support for maternal smoking as an important risk factor for both antepartum and intrapartum stillbirth [12, 23, 26].

This study has some limitations. There is the possibility of underreporting of medical risk factors and labor complications in the birth certificate data used as well as recall bias of certain exposures, such as prenatal smoking [27, 28]. Additionally, maternal self-report of smoking instead of the use of indicators for exposure, such as biomarkers, could be subject to errors generated from misclassification as a result of the chances of underreporting [26]. Although our findings provided further evidence that various pregnancy and labor conditions are associated with stillbirth, including eclampsia, placenta abruption, hypertension, diabetes, and multiple gestations [10, 14, 28–30], genetic factors, which are known to affect the stillbirth occurrence [31], were absent in the data and could not be examined. As the study covers a nine-year period (1989–1997), it is possible that infants and women in the study population could have been subject to different obstetric procedures and practices that could have impacted fetoinfant morbidity and mortality outcomes. Additionally, unlike the Swedish and Scotland studies, our dataset lacks information on previous pregnancy SGA information.

Despite these limitations, our study has some key strengths. The population-based nature of the data used in analysis decreases the potential for our results to be affected by selection bias, making our findings more generalizable. Additionally, the reliability of the Missouri maternally linked cohort data files used in this study is well-documented, as it has been recognized as the “gold standard” in various validation studies of national datasets in the United States that require linking and matching procedures [32, 33].

In conclusion, stillbirth is a critical public health issue. While the etiology is not well understood, substantial medical risk factors and labor complications have been associated with stillbirth. This study builds on the existing public health knowledge regarding stillbirth with strong evidence that prior preterm birth and SGA play an important role in its occurrence. The findings may aid in the elucidation of the causal pathway between prior childbirth experiences and subsequent birth outcomes, such as stillbirth. Furthermore, our study underscores the importance of interconception care as a vital part of the comprehensive strategy to improve fetoinfant outcomes [34]. Targeted medical and obstetric care that takes into account a woman’s childbirth history has the potential to reduce stillbirth occurrence and increase the likelihood of fetoinfant survival.

## Conflict of Interests

The authors attest that there are no financial interests, commercial affiliations, or possible conflict of interests involved.

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