Prior Stillbirth is Associated with Increased Risk of Subsequent Stillbirth

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Tweetable statement: Prior stillbirth is associated with more than double the recurrence risk, rising 6-fold when due to placental insufficiency.

Objective:

Stillbirth remains a major cause of perinatal mortality and has profound implications for patients planning future pregnancies[1]. Counseling after stillbirth is challenging because recurrence risk estimates vary widely due to differences in study populations, definitions, and etiologic classification[2]. Some causes of stillbirth reflect persistent or recurrent placental and maternal disease processes that may confer increased risk in subsequent pregnancies[3]. The objectives of this study were to quantify the risk of recurrent stillbirth in a subsequent pregnancy and to determine whether stillbirth attributed to placental insufficiency is associated with a disproportionately elevated recurrence risk.

Study Design

We conducted a retrospective cohort study of individuals with two consecutive singleton deliveries at a single academic institution between 2000 and 2023. The study population included 77,689 individuals, of whom 508 experienced a stillbirth in the index pregnancy. Stillbirth was defined according to institutional criteria at the time of delivery. Prior to January 1, 2020, this was based on birthweight ≥500 g. On or after January 1, 2020, stillbirth was defined as gestational age ≥20 weeks, or birthweight ≥350 g if a dating ultrasound was unavailable.

All stillbirth cases underwent standardized evaluation by a multidisciplinary review committee. This process included detailed review of maternal clinical history, laboratory and imaging data, placental pathology, autopsy findings when available, and genetic testing results to assign a

primary etiology. The committee composition and structured review process are described in detail in Supplementary Appendix, Figure 1.

Placental insufficiency was defined as placental pathology demonstrating maternal vascular malperfusion as classified using the Amsterdam criteria by a dedicated perinatal pathologist[4]. Morphologic features used to identify maternal vascular malperfusion included accelerated villous maturation, villous infarction, decidual arteriopathy, perivillous fibrin deposition, and distal villous hypoplasia, in conjunction with supportive clinical findings, in the absence of an alternative cause of stillbirth. Perinatal pathologists actively participated in the multidisciplinary stillbirth review committee to adjudicated cases with diagnostic uncertainty.

The study period represented a convenience sample of all consecutive singleton deliveries at our institution; therefore, a prospective sample size calculation was not performed. Rates of stillbirth in the subsequent pregnancy were compared between those with and without a prior stillbirth in the index pregnancy. A prespecified subgroup analysis evaluated recurrence risk among individuals whose index stillbirth was attributed to placental insufficiency. Relative risks (RR) with 95% confidence intervals (CI) were calculated using Pearson chi-square testing. Statistical significance was defined as $p<0.05$. This study (STU#20251288) was determined to be exempt from Institutional Review Board review due to its retrospective cohort design.

Results

Among the 508 stillbirths, placental pathology was completed in 87.0% of cases and perinatal autopsy was performed in 45.3% of cases. Maternal characteristics associated with index stillbirth included older maternal age, Black race, pregestational diabetes, and chronic

hypertension, while nulliparity was less common among stillbirths compared with live births (Table 1).

In the subsequent pregnancy, individuals with a prior stillbirth experienced a significantly higher rate of stillbirth compared with those whose index pregnancy resulted in a live birth (1.2% versus 0.5%; RR 2.44, 95% CI 1.10-5.45; p<0.02) (Table 1). Among those whose index stillbirth was attributed to placental insufficiency, recurrence risk was markedly elevated. Subsequent stillbirth occurred in 2 of 69 individuals (2.9%) in this subgroup, corresponding to a six-fold increased risk compared with those without a prior stillbirth (RR 6.00, 95% CI 1.15-23.59; p<0.01) (Table 1). Elevated recurrence risk remained significant after adjustment for maternal age, nulliparity, and pregestational diabetes (Supplemental Table 1). The absolute risk difference in subsequent stillbirth was 0.7% between individuals with and without a prior stillbirth in the index pregnancy, and 2.4% among those with a placental insufficiency-attributed index stillbirth.

Conclusion

In this cohort, a prior stillbirth was associated with an increased risk of stillbirth in a subsequent pregnancy, with the highest recurrence risk observed when the index stillbirth was attributed to placental insufficiency. Additionally, chronic medical conditions such as chronic hypertension and pregestational diabetes, which may serve as supportive clinical criteria for placental insufficiency classification, may persist in subsequent pregnancies and independently contribute to recurrence risk.

The highly protocolized nature of fetal surveillance and stillbirth evaluation at our institution minimizes the potential for differential ascertainment across time and represents a strength of this study; however, unaccounted for temporal changes in clinical practice over the 23-year study

period such as the implementation of routine antenatal ultrasound and advances in genetic evaluation represent a limitation.

A comprehensive analysis of adverse outcomes in subsequent pregnancies, including preterm birth, preeclampsia, and small-for-gestational age neonates, stratified by stillbirth etiology, represents an important direction for future investigation. Our findings suggest that the etiologic determination of stillbirth is an important determinant of recurrence risk and underscores the value of comprehensive evaluation following stillbirth, including placental pathology and multidisciplinary review.

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Table 1. Obstetric Characteristics of Index Pregnancy and Risk of Subsequent Stillbirth

	Stillbirth (n = 508)	**Liveborn (n = 77, 181)**	**P-value**	**RR (95% CI)***
Maternal Characteristics				
Age (years), mean ± SD	25.2 ± 5.9	23.7 ± 5.2	<0.001	1.41 (0.89, 1.92)
Race			<0.001	
Black	87 (17.1)	8,143 (10.6)		1.62 (1.34, 1.97)
White	15 (3.0)	1,736 (2.2)		1.31 (0.80, 2.17)
Hispanic	397 (78.1)	65,809 (85.3)		0.92 (0.88, 0.96)
Other	9 (1.8)	1,493 (1.9)		0.92 (0.48 ,1.75)
Nulliparous	277 (54.5)	46,504 (60.3)	<0.01	0.90 (0.84, 0.98)
Diabetes mellitus	35 (6.9)	3,603 (4.7)	0.02	1.48 (1.07, 2.04)
Gestational	26 (5.1)	3,157 (4.1)	0.24	1.25 (0.86, 1.82)
Pregestational	9 (1.8)	567 (0.7)	<0.01	2.41 (1.26, 4.63)
Body mass index, mean ± SD	31.0 ± 6.3	31.1 ± 5.5	0.75	-0.09 (-0.68, 0.49)
Obese (BMI ≥ 30)	243 (53.9)	38,226 (53.2%)	0.77	1.01 (0.93,1.10)
Chronic hypertension	9 (1.8)	552 (0.7)	<0.01	2.48 (1.29,4.76)
Subsequent Stillbirth in Next Pregnancy †				
All prior stillbirths (n = 508)	6 (1.2)	373 (0.5)	**0.02**	**2.44** (1.10, 5.45)
Prior stillbirth due to placental insufficiency (n = 69)	2 (2.9)	373 (0.5)	**<0.01**	**6.00** (1.15, 23.59)

Data displayed as frequency (%) or mean +/- standard deviation.

*****RR (95% CI) for categorical variables from Pearson chi-square; for continuous variables, effect size is the mean difference (95% CI).

† Comparison group for subsequent stillbirth rows in patients with a prior livebirth (n = 77,181), representing primary stillbirth risk. The denominator for the placental insufficiency subgroup is the 69 patients whose index stillbirth was attributed to placental insufficiency. See Supplemental Table 1 for adjusted risk estimates.