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Infant Mortality and the Risk of Small Size for Gestational Age in the Subsequent Pregnancy: A Retrospective Cohort Study

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Abstract

To examine the association between prior infant mortality and subsequent risk for small for gestational age (SGA). This population-based, retrospective cohort study used the Missouri maternally linked, longitudinal dataset (1989–2005). Analyses were restricted to women who had two singleton pregnancies during the study period. Logistic regression was conducted to obtain adjusted odds ratios (AOR) and 95 % confidence intervals (CI) for the association between infant mortality in the first pregnancy and SGA in the second pregnancy. Women with a prior occurrence of infant death were more likely to be black and obese and had lower educational levels and had higher rates of pregnancy-related complications ($p < 0.01$). White women with previous infant mortality were at 1.46 times greater risk for SGA in the subsequent pregnancy (AOR = 1.46, 95 % CI = 1.24–1.71). For black women with prior infant death, the risk for SGA increased to 2.77 times (AOR = 2.77, 95 % CI = 2.19–3.51). White mothers who experienced infant mortality coupled with SGA in the first pregnancy had a nearly threefold heightened risk for SGA in the second pregnancy (AOR = 2.89, 95 % CI = 2.21–3.78), whereas black women with this history were more than four times as likely to have an infant with SGA (AOR = 4.60 95 % CI = 3.05–

6.96). Prior occurrence of infant mortality is associated with increased risk for subsequent SGA. This finding has important implications for health professionals, as targeted inter-conception strategies for women who have experienced infant death, as well as SGA, may be warranted.

Keywords

Infant mortality; Small for gestational age; Birth outcomes; Pregnancy; Health disparities

Introduction

Small for gestational age (SGA) (generally defined as a birth weight less than the 10th percentile, according to population birth weights) [1] is a significant adverse pregnancy outcome. SGA has been associated with increased mortality risk during the first year of life [2, 3], reduced neurodevelopmental outcomes [4], and increased risk of subsequent stillbirth [5, 6], preterm labor [7], and maternal age [8]. Some studies have examined the relationship between poor pregnancy outcomes and the risk of SGA in the subsequent pregnancy; however, results are conflicting [1]. Although rates for SGA have declined by approximately one-fifth over the past two decades in the United States (US) [7, 8], little is understood regarding its etiology.

Infant mortality is recognized as a critical factor for overall health and wellness and has been associated with access to and quality of health care, maternal health, and socioeconomic conditions [9, 10]. Although the US infant mortality rate has decreased by 5–8 % between 1997 and 2007 [11], it ranks unfavorably relative to other industrialized nations [10, 12]. In 2009, the US infant mortality rate (6.8 per 1,000 live births) was roughly twice that of France (3.2), Italy (3.4), and Germany (3.5) [13].

Previous studies regarding infant mortality have focused on the identification of risk factors and interventions to prevent and reduce its occurrence. However, minimal research has investigated the influence of prior experiences of infant death on subsequent pregnancy outcomes. Pregnancy following a fetal loss can carry with it a heightened risk for subsequent adverse events, such as preterm delivery [14, 15], stillbirth recurrence [16–18], and small size for gestational age suggesting common shared pathways [5]. To address this gap in the literature, we used a population-based data set to examine the association between infant mortality and SGA during subsequent pregnancies across racial groups.

Methods

This study utilized data on births in the state of Missouri during the period of 1989 through 2005 (N = 1,035,547). The live birth and fetal/infant death data were longitudinally linked to the biological mothers using unique identifiers, which also links siblings. The methods and algorithm used in linking birth certificate data into sibling relationships, as well as the validation process, have previously been described in detail [19, 20]. The Missouri vital record system has been adopted as the gold standard for the validation of US datasets that involve matching and linking procedures [21]. The dataset includes maternal socio-demographic characteristics and medical history and feto-infant outcomes. For this study, we selected two consecutive, singleton births from the same mother with gestational age within 20–44 weeks. After applying further exclusion criteria, we retained a total of 317,668 sibling pairs for analysis, as depicted in Fig. 1.

The main outcome of interest was SGA in the second pregnancy, which was defined as infants weighing below the 10th percentile of birth weight for their gestational age using normalized growth curves [22]. Gestational age was determined as the interval between the

last menstrual period and the date of delivery of the baby. When the menstrual estimate of gestational age was inconsistent with the birth weight (e.g., very low birth weight at term), a clinical estimate of gestational age on the vital records was used instead [23].

The primary exposure of interest was infant mortality (death of the infant within the period from day 0 through 364) associated with the first pregnancy. Infant mortality was further examined on the basis of three subtypes: neonatal (death of newborn within the first 28 days of life), post-neonatal (death of the infant within the period from day 29 through 364), and infant death (death of the infant within the period from day 0 through 364). We also examined SGA at the first pregnancy as a secondary exposure.

To assess differences in baseline characteristics, the distribution of the following selected maternal socio-demographic characteristics at the time of the second delivery was compared between mothers with previous infant death and those who had infants who survived their first year of life: race, age, marital status, educational level, cigarette smoking during pregnancy, body mass index, inter-pregnancy interval, and adequacy of prenatal care. Maternal race was grouped into three categories: white, black, and other. Maternal age was dichotomized as women who were of advanced age (≥ 35 years old) or < 35 years old at the time of second delivery. Maternal marital status was grouped as either married or unmarried, with all persons divorced, widowed, or of unknown marital status classified as unmarried. Maternal educational level was categorized as those with at least a high school degree or its equivalent (≥ 12 years of education) and those without a high school degree (< 12 years), with mothers with missing and unknown educational information grouped under the latter category. Pre-pregnancy obesity was determined based on body mass index (BMI), which was calculated as weight (kg)/height (m^2) using height, as measured at the first prenatal visit of the second pregnancy, and pre-pregnancy weight, as reported at the first prenatal visit. Obese mothers were defined as those with a pre-pregnancy BMI of ≥ 30 . Adequacy of prenatal care was assessed using the Revised-Graduated Index (R-GINDEX) algorithm, which assesses the adequacy of care based on the trimester when prenatal care began, the number of visits, and the gestational age of the infant at birth [24]. Inadequate prenatal care utilization refers to women who either had missing prenatal care information, had prenatal care but the level was considered sub-optimal (i.e., fewer prenatal care visits as compared to the length of pregnancy), or had no prenatal care at all. The interval between the first day of the last menstrual period of the second pregnancy and the date of birth of the child in the first pregnancy was used to compute inter-pregnancy intervals in days.

We performed crude frequency comparisons for the presence of common obstetric and medical complications during the second pregnancy. These complications included: anemia (< 30 g/L hematocrit and/or < 12 g/dL hemoglobin); insulin dependent diabetes mellitus (absolute deficiency of insulin secretion); other types of diabetes mellitus (either gestational diabetes or adult-onset diabetes); chronic hypertension (an increase in systolic or diastolic pre-existing blood pressure to a level of $\geq 140/90$ mm Hg, respectively, prior to 20th week of gestation); preeclampsia (pregnancy-induced high blood pressure at $\geq 140/90$ mm Hg and excess protein in the urine after 20 weeks of pregnancy); eclampsia (pregnancy-induced hypertension associated with convulsions); abruptio placenta (premature separation of normally implanted placenta from the uterus); placenta previa (attachment of the placenta to the uterine wall close to or covering the cervix); and renal disease. We also constructed a composite variable indicating the presence of at least one of these conditions.

Statistical Analysis

Infant, neonatal, and post-neonatal mortality rates were computed by dividing the number of deaths by the total live births and multiplying by 1,000. The Chi-square test was used to conduct crude frequency comparisons with respect to socio-demographic characteristics and

pregnancy complications in the second pregnancy between the exposed and unexposed groups. The student's sample *t* test was used for comparison of parametric continuous variables (i.e., birth weight) and the Mann–Whitney–Wilcoxon test was applied for continuous, non-parametric variables (i.e., inter-pregnancy interval). We used logistic regression to derive adjusted odds ratios by loading all the variables that were considered to be potential confounders (i.e., age, marital status, educational level, cigarette smoking during pregnancy, body mass index, length of pregnancy, infant's gender, year of birth, adequacy of prenatal care, and overall complication) into the model. Overall complication is a composite variable that indicates the presence or absence of pregnancy-related clinical conditions, including: anemia, insulin dependent diabetes mellitus, other diabetes, chronic hypertension, abruptio placenta, placenta previa, renal disease, pre-eclampsia, and eclampsia.

All hypothesis tests were two tailed, with a type 1 error rate fixed at 5 %. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used to perform all analyses. This study was approved by the Institutional Review Board at the University of South Florida prior to initiation.

Results

Our study population consisted of a total of 317,668 women who had first and second consecutive singleton pregnancies with a gestational age of 20–44 weeks. Infant death in the first pregnancy was observed in 2,398 women (0.75 %) (exposed), while the remaining 315,270 women had a first pregnancy with an infant who survived the first year of life (unexposed). A total of 23,497 cases of SGA infants occurred during the second pregnancy, representing a rate of 7.4 per 1,000.

Table 1 provides a comparison of selected maternal socio-demographic characteristics and obstetric/maternal complications in the second pregnancy between women who had experienced infant death in the first pregnancy with those who had infants that survived their first year of life. Women with infant death in the first pregnancy were more likely to be black, obese, and have lower educational levels. These women also tended to smoke during pregnancy and have a higher level of adequate prenatal care. Alternatively, women who had infants surviving through their first year of life were more likely to be white and married. On average, mothers whose infants survived the first year of life had longer inter-pregnancy intervals (Median inter-pregnancy interval $\pm$ Interquartile range: 718 $\pm$ 808 days vs. 361 $\pm$ 548 days; $p < 0.0001$). When comparing the birth weights of infants from the second pregnancy, these mothers also had infants about 274 g bigger than those infants born to mothers whose infants died in the first year of life during the first pregnancy (mean birth weight: 3407 $\pm$ 542 g vs. 3133 $\pm$ 713 g; p value < 0.01).

For the study population, the incidence of pregnancy complications during the second pregnancy was 6.64 % ($n = 21,084$). Using crude rates, mothers with a prior infant death were nearly twice as likely to experience pregnancy complications, as compared to those whose infants survived their first year of life (10.60 vs. 6.61 %; $p < 0.01$). The occurrence of insulin-dependent diabetes, chronic hypertension, abruptio placenta, preeclampsia, and other types of diabetes was greater in the second pregnancy among women with prior infant death ($p < 0.01$) (Table 1).

Table 2 provides adjusted estimates for the association between the occurrence of infant death of a first child and SGA during the subsequent pregnancy. Model 1 provides odds ratios adjusted for socio-demographic variables in the second pregnancy, while Model 2 provides estimates with further adjustment for gestational age, and Model 3 shows the first two models plus adjustment for pregnancy complications. In all the three models, white

mothers with no prior infant death were used as a referent category. In Model 1, white mothers with previous infant mortality were at 1.46 times greater risk of having an SGA infant during the second pregnancy [adjusted odds ratio [AOR] = 1.46; 95 % confidence interval [CI] = 1.24–1.71] than white mothers with no previous infant death. Similarly, an elevated level of risk for SGA was observed among white women with prior neonatal death (AOR = 1.56; 95 % CI = 1.29–1.87), as compared to those with no neonatal death. Black mothers, regardless of their previous childbirth experience, showed a higher risk for SGA; however, the risk is much more pronounced among those with prior infant, neonatal, or post-neonatal death. Black mothers with previous infant mortality showed a 2.8-fold heightened risk for SGA (AOR = 2.77; 95 % CI = 2.19–3.51) and nearly three times more risk for SGA with prior neonatal death (AOR = 2.93; 95 % CI = 2.20–3.88), as compared to white mothers with no history of infant and neonatal mortality, respectively. Adjusting for length of pregnancy in Model 2 increased the overall risk for SGA in the second pregnancy among white mothers with previous infant death by 4 % (AOR = 1.50; 95 % CI = 1.27–1.79) and the risk of SGA following neonatal death by 5 % (AOR = 1.61; 95 % CI = 1.33–1.94). For black mothers, the risk for SGA increased by 20 % among those with prior infant death and 23 % with prior neonatal death. Further adjustment for pregnancy complications did not alter the risk for SGA in the analysis.

Further analysis examined the co-occurrence of SGA and infant death during the first pregnancy and the risk for SGA in the second pregnancy (Table 3). Overall, mothers who had SGA infants, regardless of infant mortality status, demonstrated a heightened risk of SGA birth in the second pregnancy (SGA and infant death: AOR = 2.34; 95 % CI = 1.91–2.86; SGA and no infant death: AOR = 3.27; 95 % CI = 3.17–3.36) compared to non-SGA infants who survived the first year of life. When the analysis was stratified by race, we found that the risk estimates among white women were similar to the overall population for SGA infants who died within their first year of life (AOR = 2.89; 95 % CI = 2.21–3.78). However, white mothers who had an SGA infant who survived the first year showed a 1.5-fold higher risk for SGA in the second pregnancy (AOR = 4.77; 95 % CI = 4.60–4.96). This approach also showed that black mothers with previous SGA infants showed a higher risk for having a SGA infant in the second pregnancy whether they lost the previous infant (AOR = 4.60; 95 % CI = 3.05–6.96) or not (AOR = 6.60; 95 % CI = 6.21–7.02), as compared to white infants who did not have SGA and infant mortality in the first pregnancy (Table 4).

Discussion

Our study found that women with a prior instance of infant death had an increased risk of SGA in their next pregnancy. Furthermore, our findings demonstrate a black–white disparity, as black women were at a more pronounced risk compared to white women. White mothers who experienced infant death in their first pregnancy were 1.46 times more likely to have SGA infants during their second pregnancy relative to white women who did not previously experience infant death. However, black women with prior infant death had a 2.8-fold elevated risk of having a SGA infant in their subsequent pregnancy. While previous research has identified prior childbirth experiences, such as miscarriage, stillbirth, and SGA, as risk factors for SGA [1, 25, 26], to the authors' knowledge, this is the first study to identify prior infant mortality as a risk factor for subsequent SGA.

When the previous pregnancy involved an SGA infant, the risk for SGA in the following pregnancy was even more heightened, regardless of the occurrence of infant mortality in the first pregnancy. In whites, if the prior occurrence of infant death was coupled with SGA, the risk for an SGA infant during the second pregnancy was nearly three times higher, whereas black women had a more than fourfold elevated risk. Regardless of race, the highest risk of having an SGA infant was noted among women who previously had an SGA infant who

survived the infancy period. This finding builds on previous research indicating that prior SGA is a marker for subsequent SGA [5, 6].

The association between previous infant mortality and risk of SGA in subsequent mortality could be explained by multiple factors. First, it could be argued that similar socio-demographic characteristics impact the occurrence of infant mortality in first pregnancy and SGA in subsequent pregnancy. Economic disadvantage is known to be associated with risky maternal behaviors, such as smoking during pregnancy, which increases the likelihood of intra-uterine growth retardation [27, 28]. Post-neonatal mortality, in particular, is sensitive to socio-demographic factors [29, 30]. However, the association between infant mortality and SGA in the subsequent pregnancy persisted, even after controlling for socio-demographic characteristics, making our first argument less plausible. A second possible explanation could be psychological stress related to previous infant loss. Unexpected adverse feto-infant outcomes present a crisis for the mother and family, which may result in fear and worry as parents and family members adapt [31, 32]. Unfortunately, we could not test this hypothesis in our analyses because of the absence of data on psychological factors in our dataset. These findings underscore the need for further studies on infant mortality and its association with the subsequent SGA.

Our study does have some noteworthy limitations. The utilization of an existing dataset results in the restriction of potential variables available for use and a possible lack of relevant information. However, the dataset used in this study, the Missouri maternally linked cohort data files, has been documented as the gold standard for comparison against other vital record sources in the US. Consequently, there were minimal concerns regarding data reliability and validity [19, 20]. Our decision to dichotomize all covariates included in the analysis may have led to the misclassification of some covariates. For instance, mothers with missing information for education were assumed to have not completed high school; likewise, mothers with missing marital status information were assumed to be unmarried. However, it is unlikely that this *a priori* decision impacted our findings, as a sensitivity analysis that excluded women with missing information for these variables yielded similar results (data not shown). Another issue that may have impacted our findings is the lack of data on pregnancy intentions within our study population. Pregnancy intention has been found to impact both maternal and feto-infant outcomes, such as low birth weight and preterm birth [33, 34]. However, these data were not available for analysis in our dataset. Despite these limitations, there are strengths to this study. The large population size provides substantial power to detect differences between groups in the analysis. Furthermore, due to the population-based nature of the data, the likelihood of selection bias is minimized compared to data collected from referrals or medical centers. Hence, the study results can be considered generalizable.

This study provides convincing evidence that prior infant mortality is a risk factor for SGA. After the death of a child, women and their families frequently have questions regarding the decision to attempt another pregnancy, which provides opportunities for crucial targeted inter-conception strategies [35, 36]. Clinicians should consider the potential risk of adverse infant outcomes, such as SGA, as they counsel affected mothers that are contemplating another pregnancy. Further research is warranted to strengthen the evidence base to support this assertion.

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Fig. 1.
Flow diagram of exclusion criteria for the study

Table 1

Distribution of selected maternal socio-demographic and pregnancy complications in the second pregnancy between women with infant mortality in the first pregnancy and those without (Missouri: 1989–2005)

Variables	Infant mortality N = 2,398 n (%)	No infant mortality N = 315,270 n (%)	p value ^a
Socio-demographic characteristics			
Advance maternal age (≥ 35 years)	262 (10.89)	34,700 (11.01)	0.86
Maternal education (< 12 years)	559 (23.24)	52,669 (16.71)	<0.01
Maternal smoking (yes)	584 (24.28)	61,315 (19.45)	<0.01
Marital status (married)	1,525 (63.41)	233,806 (74.16)	<0.01
Race			<0.01
Whites	1,811 (75.30)	265,415 (84.19)	
Blacks	557 (23.16)	43,689 (13.86)	
Other	37 (1.54)	6,159 (1.95)	
Obesity (yes)	502 (20.87)	56,866 (18.04)	<0.01
Prenatal care			<0.01
Adequate	1,563 (63.67)	167,138 (52.71)	
Inadequate	762 (31.04)	137,758 (43.44)	
No care	130 (5.30)	12,197 (3.85)	
Pregnancy complications (yes)			
Anemia	25 (1.04)	4,545 (1.44)	0.16
Insulin dependent diabetes mellitus	44 (1.83)	2,394 (0.76)	<0.01
Other types of diabetes	91 (3.78)	7,224 (2.29)	<0.01
Chronic hypertension	52 (2.16)	2,909 (0.92)	<0.01
Preeclampsia	120 (4.99)	9,255 (2.94)	<0.01
Eclampsia	2 (0.08)	180 (0.06)	0.54
Abruptio placenta	34 (1.41)	2,241 (0.71)	<0.01
Placenta previa	10 (0.42)	1,340 (0.43)	0.73
Renal disease	8 (0.33)	763 (0.24)	0.42
Overall complications	255 (10.60)	20,829 (6.61)	<0.01

^aSignificant values in bold font. *p* values < 0.05 considered significant

Table 2

Risk of small size for gestational age (SGA) among women with a history of infant, neonatal, or post-neonatal mortality during first pregnancy by race (Missouri: 1989–2005)

First pregnancy outcome	SGA at second pregnancy AOR (95 % CI) ^a		
	Model 1 ^b	Model 2 ^c	Model 3 ^d
Infant death			
White: no infant death	Ref	Ref	Ref
White: infant death	1.46 (1.24–1.71)	1.50 (1.27–1.79)	1.49 (1.27–1.75)
Black: no infant death	2.10 (2.02–2.18)	2.16 (2.08–2.24)	2.15 (2.07–2.23)
Black: infant death	2.77 (2.19–3.51)	2.97 (2.34–3.76)	2.93 (2.31–3.72)
Neonatal death			
White: no neonatal death	Ref	Ref	Ref
White: neonatal death	1.56 (1.29–1.87)	1.61 (1.33–1.94)	1.60 (1.33–1.93)
Black: no neonatal death	2.10 (2.02–2.18)	2.16 (2.09–2.24)	2.15 (2.07–2.23)
Black: neonatal death	2.93 (2.20–3.88)	3.16 (2.38–4.19)	3.15 (2.35–4.15)
Post-neonatal death			
White: no post-neonatal death	Ref	Ref	Ref
White: post-neonatal death	1.22 (0.89–1.68)	1.23 (0.90–1.70)	1.23 (0.89–1.69)
Black: no post-neonatal death	2.09 (2.02–2.17)	2.16 (2.08–2.24)	2.15 (2.07–2.23)
Black: post-neonatal death	2.46 (1.61–3.76)	2.59 (1.70–3.96)	2.56 (1.67–3.91)

Complications is a composite variable made up of one or more of the following pregnancy related clinical conditions: anemia, insulin dependent diabetes, diabetes, chronic hypertension, placenta abruption, placenta previa, renal disease, eclampsia, and pre-eclampsia

^a AOR adjusted odds ratio; 95 % CI 95 % confidence intervals; Significant values in bold font

^b Model 1: Adjusted for socio-demographic variables (maternal education, marital status, maternal age, maternal BMI, maternal smoking status, adequacy of prenatal care, gender of the infant, and year of birth) in the second pregnancy

^c Model 2: Adjusted for socio-demographic variables in the second pregnancy (indicated in model 1) plus gestational age

^d Model 3: Adjusted for socio-demographic variables in the second pregnancy (indicated in model 1), gestational age, and pregnancy complications.

Table 3

Risk of small size for gestational age (SGA) among women with a history of infant mortality and SGA (Missouri: 1989–2005)

First pregnancy outcome	SGA at second pregnancy AOR (95 % CI) ^a
Overall	
No SGA and no infant death	Ref
No SGA and infant death	1.60 (1.38–1.87)
SGA and no infant death	3.27 (3.17–3.36)
SGA and infant death	2.34 (1.91–2.86)
White women	
No SGA and no infant death	Ref
No SGA and infant death	1.68 (1.37–2.05)
SGA and no infant death	4.77 (4.60–4.96)
SGA and infant death	2.89 (2.21–3.78)
Black women	
No SGA and no infant death	2.22 (2.12–2.32)
No SGA and infant death	3.63 (2.73–4.83)
SGA and no infant death	6.60 (6.21–7.02)
SGA and infant death	4.60 (3.05–6.96)

^a AOR adjusted odds ratio, 95 % CI 95 % confidence intervals

Risk of small for gestational age (SGA) at second pregnancy among women with a history of early neonatal and late neonatal mortality during their first pregnancy (Missouri: 1989–2005)

Table 4

First pregnancy outcome	SGA at second pregnancy AOR (95 % CI) ^a					
	Early neonatal period (birth–7 days)			Late neonatal period (8–28 days)		
	Model 1 ^b	Model 2 ^c	Model 3 ^d	Model 1 ^b	Model 2 ^c	Model 3 ^d
White: no infant death	Ref	Ref	Ref	Ref	Ref	Ref
White: infant death	1.95 (1.58–2.41)	1.56 (1.26–1.93)	1.55 (1.25–1.92)	1.63 (1.21–2.19)	1.45 (1.08–1.95)	1.45 (1.08–1.94)
Black: no infant death	2.31 (2.23–2.39)	1.95 (1.88–2.02)	1.94 (1.87–2.01)	2.31 (2.23–2.39)	1.95 (1.88–2.02)	1.94 (1.87–2.01)
Black: infant death	3.71 (2.66–5.17)	2.52 (1.81–3.51)	2.51 (1.80–3.49)	3.62 (2.46–5.31)	2.93 (1.99–4.31)	2.91 (1.98–4.27)

^a AOR adjusted odds ratio, 95 % CI 95 % Confidence Intervals; Significant values in bold font

^b Model 1: Adjusted for socio-demographic variables (maternal education, marital status, maternal age, maternal BMI, maternal smoking status, adequacy of prenatal care, gender of the infant, and year of birth) in the second pregnancy

^c Model 2: Adjusted for socio-demographic variables in the second pregnancy (indicated in model 1) plus gestational age

^d Model 3: Adjusted for socio-demographic variables in the second pregnancy (indicated in model 1), gestational age, and pregnancy complications. Complications is a composite variable made up of one or more of the following pregnancy related clinical conditions: anemia, insulin dependent diabetes, diabetes, chronic hypertension, placenta abruption, placenta previa, renal disease, eclampsia, and pre-eclampsia