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Original article

Interpregnancy interval and risk of stillbirth: a population-based case control study

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ABSTRACT

Purpose: We examined the association between interpregnancy intervals (IPIs) and stillbirth (defined as fetal death ≥20 weeks), as both short and long IPIs have been associated with adverse perinatal outcomes. Prior pregnancy loss is also a known risk factor for stillbirth, and women who suffer a prior loss often have shorter IPIs. For these reasons, we also sought to quantify the proportion of the association between prior pregnancy loss and subsequent stillbirth risk that may be attributed to a short IPI.
Methods: We used data from the Stillbirth Collaborative Research Network, a multisite case-control study conducted in 2006–2008, restricted to singleton pregnancies among multiparous or multigravid women (985 controls and 291 cases). We accounted for complex sample design and nonparticipation with weighted multivariable logistic regression.
Results: In the adjusted models, IPIs <6 months, as compared with a reference of 18–23 months, were associated with increased odds of stillbirth (aOR 1.6, 95% CI: 0.8, 3.4). Long IPIs (60–100 months) were also associated with an increased odds of stillbirth (aOR 2.4, 95% CI: 1.2, 4.5). After control for covariates, about one-fifth (21.2%) of the association of prior pregnancy loss (stillbirth, ectopic pregnancy, molar pregnancy, or spontaneous abortion) and stillbirth may be attributable to a short IPI.
Conclusions: Our results suggest that women who experience a prior pregnancy loss may benefit from additional counseling on adequate birth spacing to reduce subsequent stillbirth risk.

Introduction

Stillbirth (fetal death ≥20 weeks gestation) [1] is a critical public health issue. Approximately, 2.6 million families around the world will be affected by stillbirth each year [1,2]. In the United States, 1 in 160 babies are stillborn [3]. In addition, the psychosocial effects of losing a child are felt by mothers, fathers, families, and communities [2].

Prior pregnancy loss is a strong risk factor for stillbirth. In fact, one study reported that women with a previous adverse birth outcome were 2–6 times as likely to have a subsequent stillbirth [4]. The literature also suggests that women who have suffered a prior pregnancy loss have shorter interpregnancy intervals (IPIs) [1,3,5]. Some countries follow the World Health Organization's recommendations regarding birth spacing after a live birth, miscarriage, or induced abortion; however, to our knowledge, the optimal interval after a stillbirth has yet to be established [6].

IPI is calculated by subtracting the date the previous pregnancy ended from the date of the last menstrual period (LMP) of the index pregnancy. Studies suggest both short (<6 months) and long

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(>60 months) IPIs may increase the likelihood of adverse birth outcomes including neonatal morbidity, preterm birth, and low birthweight, albeit for different reasons [7–26]. A short interval may not allow the mother's physiology and nutritional stores sufficient recovery time [27,28], whereas a long interval may return the mother's physiology to a state similar to primigravidity, which is known to be associated with poorer pregnancy outcomes [10].

The length of the IPI may be an independent risk factor for stillbirth. However, few studies have investigated the role of IPI on risk of stillbirth [3,6,29–32]. The results to date are conflicting, perhaps because much of the research is relatively dated and reliant on nonstandardized definitions and methodologies necessary for accurate monitoring. In fact, a comprehensive review [7–27,29–36] identified a few articles that investigated the association between IPI and risk of stillbirth [6,9].

Our primary objective was to evaluate whether IPI is an independent risk factor for stillbirth. Our secondary objective was to quantify the proportion of the association between prior pregnancy loss and subsequent stillbirth risk that may be attributed to a short IPI.

Methods

Study design and participants

The Stillbirth Collaborative Research Network (SCRN), a multisite, population-based case-control study of stillbirth conducted between 2006 and 2008, included catchment areas of Rhode Island and selected counties within four states: Massachusetts, Georgia, Texas, and Utah. Investigators identified 59 hospitals for enrollment to ensure access to at least 90% of pregnancies ending in either live birth or stillbirth to residents of the various catchment areas [16]. Study participants included those who resided in one of the catchment areas, were ≥13 years of age, and identified for participation before discharge from the study hospital.

Research objectives and modeling techniques

We used multivariable logistic regression to evaluate whether IPI was an independent risk factor for stillbirth. We conducted a mediation analysis to explore our secondary objective of quantifying the proportion of the association between prior pregnancy loss and subsequent stillbirth risk that may be explained by short IPI.

Exclusions

SCRN identified 953 eligible deliveries with stillbirths and 3088 deliveries with live births (Fig. 1). We excluded 290 cases and 1156 controls as these were not approached or refused to participate in the study, reducing the number of stillbirths to 663 and the number of live births to 1932. We further excluded cases with missing maternal interview and medical chart abstraction (49 cases and 116 controls). As we are interested in IPI, our sample was also restricted to singleton pregnancies among multiparous or multigravid women, excluding women who had a previous therapeutic abortion or fetal reduction and women with incomplete data on the estimated date of LMP and/or date the pregnancy before the index ended. Our final analysis sample included 291 cases and 985 controls.

Objective 1: Multivariable logistic regression

Outcome

Stillbirth cases were defined as all women who experienced a fetal death ≥20 completed weeks' gestation [16]. A weighted sample of controls included women with a live birth ≥20 completed weeks' gestation [16].

Covariates

Maternal characteristics were collected using a standardized maternal interview. Ten maternal characteristics were evaluated as potential effect modifiers and confounders. These were age, race, body mass index (BMI), education level, insurance status, smoking status, alcohol status, marital status, use of assisted reproductive technology, and prior pregnancy outcome. All covariates, including maternal age, were measured from the start of the interval. Prior pregnancy outcome was categorized into four groups: spontaneous abortion, ectopic pregnancy, and molar pregnancy; stillbirth; prior preterm live birth; and prior term live birth.

Exposure

IPI, a continuous variable, was calculated as the number of months between the date the pregnancy before the index pregnancy ended and the estimated date of the woman's LMP before the index pregnancy. We categorized IPI into six categories. Consistent with prior studies, the reference category for IPI is 18–23 months. Short IPIs included <6, 6–11, and 12–17 months. Long IPIs included 24–59 and 60–100 months.

Objective 2: Mediation analysis

To answer the second question, we aimed to decompose the total association between prior pregnancy loss (exposure) and stillbirth (outcome) into an “indirect effect” (the part that is mediated by a short IPI) and a “direct effect” (the portion that is not mediated through IPI). The exposure, pregnancy loss, included prior stillbirth, spontaneous abortion, ectopic pregnancy, or molar pregnancy. We included all covariates in the mediation analysis, as the mediation effects decomposition analysis is only valid when there is control for relevant confounding of the exposure-outcome, exposure-mediator (short interpregnancy interval <6 months), and mediator-outcome confounding. Effect decomposition with attention to these assumptions was achieved by implementing the causal mediation SAS macro developed by Vanderweele and Valeri [27,37]. The indicator for IPI contrasted intervals <6 months to intervals 18–23 months. We examined IPI in other forms; however, these results were not included in this article. All analyses were conducted using Statistical Analysis Software (SAS) Version 9.3 (SAS Institute Inc., Cary, NC).

Results

Descriptive statistics

A total of 1276 pregnancies were included in this analysis, with 985 controls and 291 cases (Table 1 and Fig. 1). Among cases, 68.0% of women were 20–31 years, with a mean age of 25.7 years. Mean IPI was 48.8 months. In preceding pregnancies, 64.5% were full-term live births, 21.5% were prior pregnancy losses, and 14.0% preterm live births. Significant differences in the distribution of IPI, race, marital status, maternal BMI, smoking status, and prior pregnancy outcome were observed comparing stillbirths and live births (Table 1).

Logistic models for short interpregnancy intervals

Table 2 summarizes results for the models examining the odds of stillbirth across short intervals. Model 1 examines the unadjusted relationship between IPI and stillbirth and model two examines the relationship between IPI and stillbirth, adjusting for all covariates. Because no statistically significant interactions between the exposure and covariates were identified, none of the reported models contain interaction terms. Unadjusted models (model 1) revealed a significant increase in risk of stillbirth for short intervals

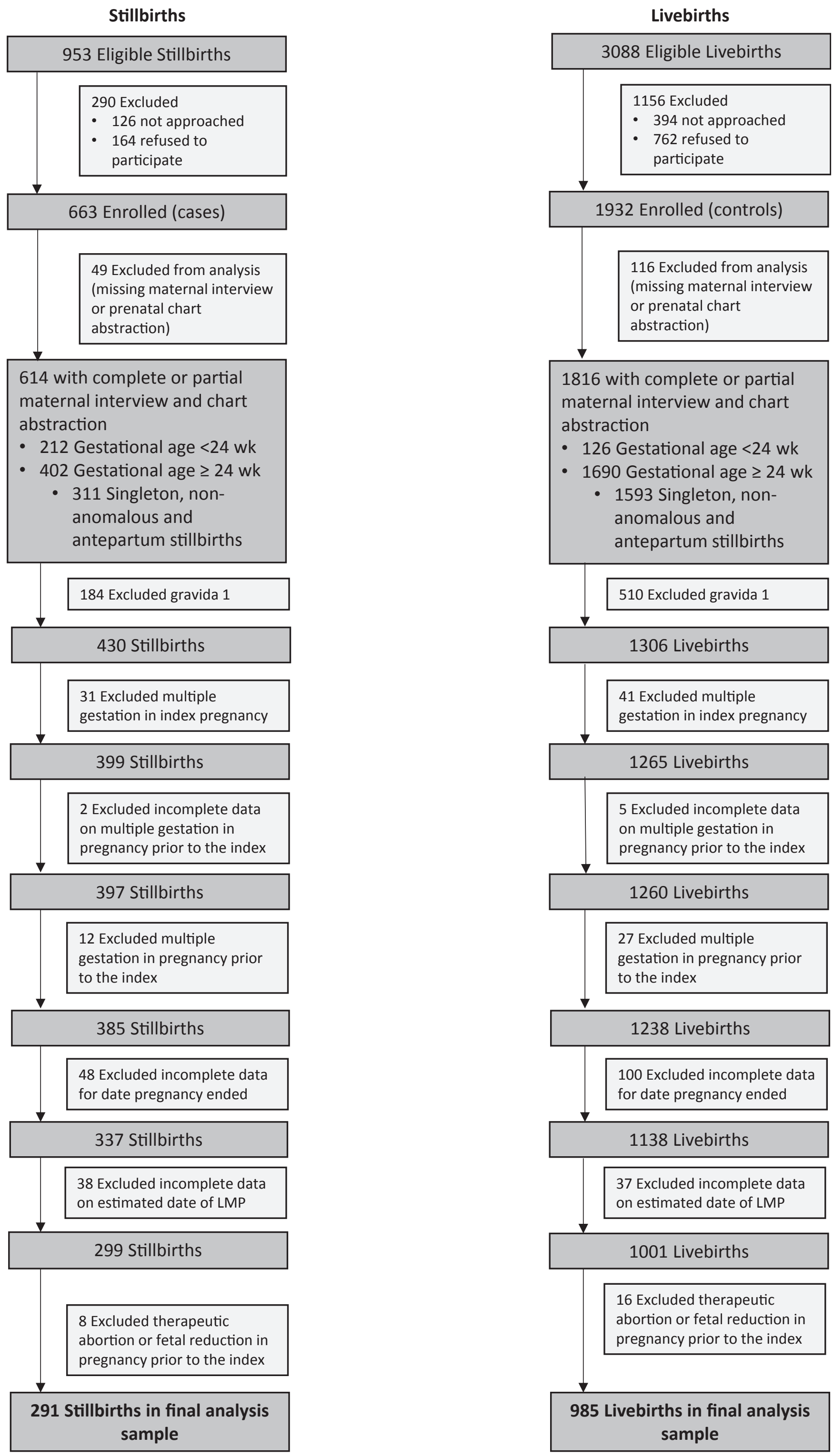

Fig. 1. Study enrollment and inclusion in regression analysis.

(<6 months). Women with IPI less than 6 months had a 3.3-fold increase in odds of stillbirth (95% confidence interval [CI]: 1.8, 6.2). The results for IPI between 6 and 17 months showed slight increases in the odds of stillbirth although the results were statistically insignificant. The adjusted models (model 2) suggested an increase in odds of stillbirth; however, the results were statistically insignificant.

Logistic models for long interpregnancy intervals

Table 3 summarizes the results for the models examining the odds of stillbirth across long intervals. Model 1 examines the crude relationship between IPI and stillbirth and model two examines the relationship between IPI and stillbirth, adjusting for all covariates. Model 1 revealed a statistically significant increase in odds of stillbirth

Table 1
Sociodemographic and pregnancy characteristics of study participants by outcome

Study population characteristics	Stillbirths		Live births		*P*-value[†]
	n (n_w)	$\%_w$	n (n_w)	$\%_w$	
	291 (294)	28	985 (757)	72	
Interpregnancy interval*					
< 6 mo	44 (44)	17.3	77 (51)	7.2	<.01
6–11 mo	33 (34)	13.3	130 (94)	13.2	
12–17 mo	37 (38)	14.9	150 (125)	17.6	
18–23 mo	23 (25)	9.9	110 (96)	13.6	
24–59 mo	73 (73)	28.6	352 (279)	39.3	
60–100 mo	43 (41)	16.0	97 (65)	9.1	
Maternal age					
<20 y	47 (48)	16.5	153 (110)	14.5	.34
20–23 ye	64 (63)	21.6	254 (194)	25.6	
24–27 y	67 (65)	22.1	252 (188)	24.9	
28–31 y	71 (71)	24.3	191 (148)	19.5	
≥32 y	42 (45)	15.4	135 (117)	15.5	
Maternal race					
NH, white	104 (99)	33.8	351 (326)	43.1	<.01
NH, black	58 (64)	21.8	148 (71)	9.4	
Hispanic	109 (111)	38.0	424 (306)	40.5	
Other	20 (19)	6.5	62 (53)	7.0	
Marital Status*					
Not married or cohabitating	58 (62)	21.0	132 (82)	10.9	<.01
Cohabitating	66 (66)	22.4	231 (161)	21.3	
Married	167 (166)	56.7	620 (512)	67.8	
Maternal education*					
0–11 y (none, primary, some secondary)	75 (75)	25.7	211 (144)	19.1	.06
12 y (completed secondary)	76 (79)	27.1	277 (204)	27.1	
≥13 (completed some college or more)	139 (138)	47.2	492 (405)	53.8	
Maternal BMI*					
< 18.5	5 (5)	1.6	27 (22)	2.9	<.01
18.5–24.9	98 (97)	33.5	427 (348)	46.3	
25.0–29.9	74 (77)	26.6	243 (177)	23.6	
30.0–34.9	58 (59)	20.2	149 (107)	14.2	
≥35.0	51 (53)	18.2	133 (98)	13.0	
Maternal insurance*					
Any public/private assistance	119 (118)	40.5	407 (359)	47.6	.13
VA/commercial health/HMO	155 (159)	54.4	531 (361)	47.8	
No insurance	15 (15)	5.1	45 (35)	4.7	
Smoking status*					
Did not smoke	235 (237)	80.8	855 (667)	88.5	.01
Smoked during 3 mo prior/during pregnancy, < 10 cigarettes	25 (25)	8.7	68 (46)	6.1	
Smoked during 3 mo prior/during pregnancy, ≥ 10 cigarettes	31 (31)	10.5	59 (41)	5.4	
Alcohol status*					
No drinking	184 (185)	62.2	640 (468)	63.8	.58
Moderate drinking	53 (53)	21.2	198 (159)	18.4	
Binge drinking	51 (52)	16.6	142 (125)	17.9	
ART use					
No	282 (285)	97.0	956 (732)	96.8	.89
Yes	9 (9)	3.1	29 (24)	3.2	
Gestational age					
< 20 wk	5 (6)	2.0	0 (0)	0	<.0001
20–23 wk	105 (109)	37.1	60 (2)	0.3	
24–27 wk	40 (39)	13.2	40 (4)	0.5	
28–31 wk	41 (37)	12.6	46 (7)	0.9	
32–36 wk	49 (53)	18.0	67 (57)	7.5	
37–42 wk	51 (50)	17.0	772 (687)	90.8	
Prior pregnancy outcome*					
SA, EP, or MP	47 (50)	17.0	90 (55)	7.3	<.01
Full-term, live birth	191 (189)	64.5	779 (637)	84.4	
Preterm, live birth	41 (41)	14.0	101 (58)	7.7	
Stillbirth	12 (13)	4.6	11 (4)	0.6	

ART = assisted reproductive technology; EP = ectopic pregnancy; HMO = health maintenance organization; MP = molar pregnancy; NH = non-Hispanic; SA = spontaneous abortion; VA = veterans affairs.
* Missing values in data set.
† *P*-value from Rao-Scott χ^2 test.

for long intervals, 60–100 months (odds ratio [OR]: 2.4; 95% CI: 1.3, 4.4). IPIs between 24 and 59 months had a null association with stillbirth (model 1). Model 2 showed a statistically significant increase in odds of stillbirth for long intervals between 60 and 100 months (OR: 2.4; 95% CI: 1.2, 4.5). Similarly, IPIs between 24 and 59 months (model 2) had a null association with stillbirth (OR: 1.0; 95% CI: 0.6, 1.7).

Examining short interpregnancy interval (<6 months vs. 18–23 months) as a mediator between prior pregnancy loss and subsequent stillbirth risk

Table 4 summarizes the results for the models examining the proportion of the association between prior pregnancy loss and

Table 2
Odds ratios for stillbirth association with short interpregnancy intervals

Inter-pregnancy interval	Model 1*		Model 2†	
	OR	95% confidence interval	OR	95% confidence interval
<6 mo	3.3	1.8, 6.2	1.6	0.8, 3.4
6–11 mo	1.4	0.7, 2.6	1.1	0.5, 2.1
12–17 mo	1.2	0.6, 2.1	1.1	0.6, 2.1
18–23 mo	Reference		Reference	

* Model contains only exposure and outcome of interest. Weighted observations in model: SB = 137, LB = 467.
† Model controls for all confounders: age, race, education, insurance, BMI, smoking, alcohol, marital status, ART, and prior pregnancy outcome. Weighted observations in model: SB = 131, LB = 462.

subsequent stillbirth risk that may be attributable to a short IPI (<6 months). Our results suggest that, after control for confounding variables, about one-fifth (21.2%) of the effect of prior pregnancy loss on stillbirth risk may be explained by shorter IPIs.

Discussion

IPIs <6 months have been associated with poor pregnancy outcomes in the subsequent pregnancy, but the association may be owing to a higher inherent risk of poor pregnancy outcome because women with a prior loss are more likely than women with a live birth to have shorter IPIs [38]. If the short interval is an independent risk, this would be of particular concern to women who have suffered a prior loss. Our results suggest that short IPIs are associated with an increased risk of stillbirth, although other maternal characteristics that are also associated with short IPIs reduce the estimate of an independent effect to nonsignificance. The mediation analysis suggests that 21.2% of the association between prior loss and stillbirth may be mediated through the rapid replacement of the prior loss.

A recent study [6] found no association between stillbirth and short IPI. That study differed from ours in three important aspects. First, Regan et al. [6] excluded stillbirths under 22 weeks' gestation. Stillbirths between 20 and 22 weeks' gestation account for nearly 20% of stillbirths in the United States. Second, their reference group was an IPI of 24–59 months. Based on prior work [6–13,16,17,19–26,28,30,32–35,38–45], we chose an IPI of 18–23 months as the reference group. The interval of 24–59 months may affect the results by omitting this "ideal" IPI and including IPIs associated with increased risk of stillbirth. However, in contrast to some prior studies, we found little difference between the odds of stillbirth for intervals of 6–17, 18–23, or 24–59 months. Finally, the analyses from this study control for gestational age in the prior pregnancy. In the study by Regan et al. [6], length of gestational age in the initial stillbirth was associated with risk of stillbirth of a similar gestational age in the subsequent pregnancy. The ORs for periviable stillbirth were similar to that of periviable live births suggesting a possible association with gestational age. It is possible that prior gestational age is a mediating factor for the IPI-stillbirth association, but we could not assess that in this study as women were not asked to remember the gestational age of their prior pregnancy. This may be a critical area of investigation for future research. Previous studies have investigated cause-specific reoccurrences of stillbirth [40–43]. Although SCRN data do not include cause of the prior stillbirth, the SCRN study may be used to estimate the association of IPI length with cause of the index (subsequent) stillbirth. We will be pursuing this in future work [45].

The results of this study also suggest that long IPIs (between 60 and 100 months) are associated with an increased risk of stillbirth. These results are complementary to the conclusions drawn by Stephansson et al. in which a statistically significant increase in risk of stillbirth was apparent among women who had IPIs ≥72 months (OR: 1.5; 95% CI: 1.1, 2.1) [9]. A recent article by Hegelund et al. also found that long IPI ≥60 months had 1.7 more stillbirths per 1000 live births than women with IPIs of 18–23 months [44].

While we included the same covariates in our adjusted models for short and long IPIs, the effect of adjustment was quite different. After controlling for age, race, education, insurance, BMI, smoking, alcohol, marital status, assisted reproductive technology, and prior pregnancy outcome, the adjusted OR for long IPI was virtually the same as the crude OR. The reasons for which long IPIs may be associated with adverse birth outcomes are disputed. Some authors suggest that parous women with long IPIs behave as nulliparous women with regard to risk of pregnancy complications and adverse birth outcomes [7,22,36,39]. This hypothesis proposes that after delivery a mother gradually loses her "childbearing" capabilities that developed during the preceding pregnancy. The results of our study may suggest that this "window of opportunity" diminishes as a woman's pregnancy interval approaches 60 months. However, it is important to consider the multitude of reasons why some women take longer to get pregnant, such as infertility or metabolic disease. Further research on the effects of long IPIs on stillbirth is needed to rule out other factors that may be associated with longer IPI.

Conversely, there was a large difference in the association of short IPI with subsequent stillbirth between the crude OR (3.3, 95% CI: 1.8, 6.2) and the OR from the adjusted model (model 2). Women who lacked health insurance were more likely to have shorter intervals than women who had some form of health insurance. We posit that insurance is a proxy for inadequate health care, including birth control (increasing chance of unintended pregnancy), which might lead not only to shorter IPI but also to poorer quality prenatal care in the subsequent pregnancy. Women who were older at the birth of the preceding pregnancy were more likely than younger women to have short IPI. Older women are known to have a higher risk of adverse pregnancy outcomes, and it is possible that they feel pressure to replace their loss quickly and before their bodies have an opportunity to recover sufficiently.

This study has many strengths. First, the data for this study were collected from a large, population-based study of stillbirth, with a diverse, multisite study design. This enabled a relatively large sample size contributing to power and possibly to the generalizability of the results. Second, the SCRN study was specifically designed to evaluate the etiology of stillbirth whereas other studies on stillbirth may rely on pooling data from multiple databases that often have fragmented information regarding maternal and obstetric characteristics. Third, detailed information from both maternal interviews and chart abstraction enabled control for prior

Table 3
Odds ratios for stillbirth association with long interpregnancy interval

Inter-pregnancy interval	Model 1*		Model 2†	
	OR	95% confidence interval	OR	95% confidence interval
18–23 mo	Reference		Reference	
24–59 mo	1.0	0.6, 1.7	1.0	0.6, 1.8
60–100 mo	2.4	1.3, 4.4	2.4	1.2, 4.5

* Model contains only exposure and outcome of interest. Weighted observations in model: SB = 139, LB = 559.
† Model controls for all confounders: age, race, education, insurance, BMI, smoking, alcohol, marital status, ART, and prior pregnancy outcome. Weighted observations in model: SB = 133, LB = 552.

Table 4
Estimates of direct and indirect effects of prior pregnancy loss on subsequent stillbirth risk mediated through short interpregnancy intervals<6 months versus 18–23 months (reference) with and without adjustment for other covariates

	Total effect		Natural direct effect		Natural indirect effect		Proportion mediated through short interpregnancy interval
	Total effect	95% confidence interval	Direct effect	95% confidence interval	Indirect effect	95% confidence interval	%
Model 1	5.4	2.6, 10.6	4.0	1.9, 8.5	1.4	1.0, 1.9	31.8
Model 2	6.6	3.0, 14.6	5.4	2.0, 15.1	1.2	0.6, 2.4	21.2

Stillbirth (binary outcome), prior pregnancy loss (exposure; prior loss vs. term live birth), interpregnancy interval binary (mediator; <6 months vs. 18–23 months).
Model 1: Exposure, mediator, and outcome. Weighted observations in model: SB = 65, LB = 137.
Model 2: Exposure, mediator, and outcome, and all covariates (including maternal age, race/ethnicity, marital status, maternal education, maternal BMI, maternal insurance, smoking status, alcohol status, ART use). Weighted observations in model: SB = 61, LB = 137.

risk factors of stillbirth to allow for a more accurate, in-depth analysis of the effect of IPI on stillbirth risk. Finally, only information regarding the most recent pregnancy was used for analysis, perhaps limiting the degree of recall bias in regard to the details of that pregnancy including but not limited to birth outcome and date of birth.

This study has several limitations. First, the SCRN retrospectively collected maternal obstetric history before the index pregnancy. Detailed information regarding pregnancy history was supposed to be recorded in chronological order; therefore, the most recent pregnancy or the pregnancy most relevant for this analysis would happen toward the end of the maternal interview. Recalling the details of previous pregnancies is time-consuming for both researchers and mothers. In addition, recalling adverse pregnancy outcomes may be emotionally exhausting for mothers. Information regarding the date the pregnancy ended, LMP, and birth outcome may all be subject to misclassification or recall bias. Finally, the sample size did not support further stratification of stillbirth risk by other covariates of interest.

Conclusion

Short IPI may account for 21.2% of the association between prior pregnancy loss and subsequent risk of stillbirth. Our findings are consistent with the American Congress of Obstetricians and Gynecologists recommendation regarding birth spacing. These results contribute to the gap in knowledge regarding risk factors for stillbirth and may be used to inform guidance regarding appropriate timing of pregnancies and identification of women at increased risk of stillbirth.

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