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Interpregnancy Interval After Pregnancy Loss and Risk of Repeat Miscarriage

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Abstract

Objective—To assess whether interpregnancy interval length after a loss is associated with risk of repeat miscarriage.

Methods—This analysis includes pregnant women participating in the *Right from the Start* (2000–2012) community-based prospective cohort study whose most recent pregnancy prior to enrollment ended in miscarriage. Interpregnancy interval was defined as the time between prior miscarriage and last menstrual period of study pregnancy. Miscarriage was defined as pregnancy loss prior to 20 weeks of gestation. Cox proportional hazard models were used to estimate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between different interpregnancy interval lengths and miscarriage in study pregnancy. Adjusted models included maternal age, race, parity, body mass index, and education.

Results—Among the 514 study participants who reported miscarriage as their most recent pregnancy outcome, 15.7% had a repeat miscarriage in the study pregnancy (n=81). Median maternal age was 30 (interquartile range 27 to 34) and 55.6% of participants had at least one previous live birth (n=286). When compared to women with interpregnancy intervals of 6–18 months (n=136), women with intervals of less than 3 months (n=124) had the lowest risk of repeat miscarriage (7.3% versus 22.1%; adjusted-HR 0.33, 95% CI 0.16 to 0.71). Neither maternal race or parity modified the association. Attempting to conceive immediately was not associated with increased risk of miscarriage in next pregnancy.

Conclusions—An interpregnancy interval after pregnancy loss of less than 3 months is associated with the lowest risk of subsequent miscarriage. This implies counseling women to delay conception to reduce risk of miscarriage may not be warranted.

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Introduction

Miscarriage is the most common adverse pregnancy outcome with an estimated 17% of clinically recognized pregnancies ending in loss.[1] Most women who experience a miscarriage want to know if they can do anything to prevent a future miscarriage from occurring and many couples seek counsel from health care providers on how long they should wait before trying to conceive again.[2] No consensus for optimal spacing after a miscarriage exists. The World Health Organization (WHO) is the only advisory body to put forth formal guidelines, but they note their recommendation to wait at least six months is limited since it is based on a single cross-sectional study that did not differentiate between induced and spontaneous abortions.[3, 4] Many physicians recommend waiting at least 3 months after a miscarriage to reduce the chance of another miscarriage.[5] As age at first pregnancy rises in developed countries, recommendations for delaying future pregnancies need to be balanced with risk associated with increasing maternal age.[6]

The objective of this study is to evaluate the relationship between length of interpregnancy interval after a loss and risk of subsequent miscarriage in the *Right from the Start* community-based prospective cohort study.

Materials and Methods

Right from the Start is a prospective cohort study that recruited women who were pregnant or planning a pregnancy from eight metropolitan areas in North Carolina, Tennessee, and Texas between 2000 and 2012.[7] To be eligible for the study, women had to be age 18 or older, English- or Spanish-speaking, and not using assisted reproductive technologies to conceive. Women who were planning a pregnancy could pre-enroll and were fully enrolled at first positive pregnancy test. Informed consent was obtained from all study participants upon enrollment. The cohort was designed to enroll participants early in gestation to optimally study miscarriage. Median gestational age at enrollment for this sample was 39 days (interquartile range 34 to 48). All women were enrolled prior to 12 weeks of gestation. This study was approved by Vanderbilt University's Institutional Review Board (070037).

Study participants completed a baseline interview at time of enrollment and an extensive computer-assisted telephone interview at the end of the first trimester. These interviews collected information on maternal demographics, obstetric history, lifestyle characteristics, and health behaviors around time of conception. All participants also underwent a study ultrasound in the first trimester to confirm gestational dating. Maternal anthropometric measurements taken at time of ultrasound were used to calculate maternal body mass index (BMI).

This analysis was restricted to women who were fully enrolled, consented, and pregnant. Of the 5,780 women who met these criteria, 530 reported miscarriage as their most recent pregnancy outcome. We excluded women who had induced abortions, ectopic or molar pregnancies, or pregnancies with unknown outcome, resulting in a sample population of 514 women (Figure 1). Interpregnancy interval was defined as the time between prior miscarriage and self-reported last menstrual period (LMP) of the study pregnancy. Self-

reported LMP is validated in *Right from the Start* participants (average difference of 0.8 days between LMP-based and ultrasound-based dating).[8] We classified miscarriage in the study pregnancy as loss prior to 20 weeks of gestation (n=81). The comparison group included participants with a pregnancy surviving past 20 weeks of gestation (n=431 live births, n=2 stillbirths). Pregnancy status at 20 weeks of gestation was determined by maternal report validated by vital records.

Statistical Analysis

We modeled the relationship between interpregnancy interval and miscarriage risk in the study pregnancy in two ways. First, we divided interpregnancy interval into four categories to compare common recommendations (<3 months, 3 to 5.99 months, 6 to 17.99 months, and ≥ 18 months). We also modeled interpregnancy interval as a continuous variable using restricted cubic splines to more specifically characterize the underlying relationship. We plotted the expected value of the proportion of pregnancies to end in miscarriage by interpregnancy interval length using a logistic regression model including restricted cubic spline terms for interpregnancy interval adjusted for selected covariates.

Difference in study participant characteristics by interpregnancy interval category were evaluated using Pearson's chi-squared test. We used Cox proportional hazard models to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between interpregnancy interval and miscarriage risk. Survival time was defined as days of gestation in the study pregnancy and accumulated to time of miscarriage or 20 weeks' gestation, whichever came first. Assumptions of proportional hazards were met. Participants missing any covariate data (maternal age, BMI, education, parity, or ethnicity) were excluded from the survival analysis (n=3). The interpregnancy interval of 6 to17.99 months was used as the referent category since this range coincided with the WHO recommended interval. Potential confounders consisted of variables known or suspected to associate with risk of miscarriage and interpregnancy interval length. All adjusted models included the following *a priori* selected covariates: maternal age (years), ethnicity (non-Hispanic White, non-Hispanic Black, other), BMI (kg/m^2), parity (0, 1, 2+ prior births), and education (high school or less, some college, college or more). We also present a model adjusted for number of prior miscarriages. We tested for effect modification by race and parity using the likelihood ratio test for the inclusion of interaction terms. Interaction terms were retained in the model for p-values less than 0.20.

Interpregnancy interval is made up of two time periods: wait time (the time after loss a couple waits before trying to conceive again) and time to pregnancy (the time a couple spends trying to conceive). At the first trimester interview, women were asked to recall the amount of time they spent trying to conceive. We used this information and the calculated interpregnancy interval to approximate wait time. In a secondary analysis, we used logistic regression to quantify the adjusted relationship between wait time (modeled using restricted cubic splines) and repeat miscarriage risk. The secondary analysis was limited to women who had time-to-pregnancy data (n=471). All analyses were completed in Stata statistical software version 14.0 (StataCorp LP, College Station, TX).

Results

Among the women enrolled and consented in *Right from the Start*, 514 reported miscarriage as their most recent pregnancy outcome prior to study pregnancy. The average maternal age was 30 (inter-quartile range 27 to 34) and 20.4% of study participants were 35 or older. Nine percent of women had three or more consecutive miscarriages at time of study enrollment and 55.6% of participants had at least one previous live birth (n=286). The study population was predominantly white (76.8%) and 12.3% of participants were black.

More than half of the study participants had an interpregnancy interval less than six months (58.9%) and 24.3% had interpregnancy intervals of less than 3 months. Less than 15% of participants had an interpregnancy interval of greater than 18 months. Maternal age and number of previous miscarriages were not associated with interpregnancy interval length. Women with short interpregnancy intervals tended to be white, married, and college-educated (Table 1). Women with long interpregnancy intervals were most likely to be obese and to come from low-income households.

The overall prevalence of repeat miscarriage in the study pregnancy was 15.7% in this sample (median gestational age: 9 weeks, inter-quartile range: 7 to 11 weeks). No effect modification by race or parity was detected, so we present unstratified models. When compared to women who had interpregnancy intervals between six and 18 months, women with interpregnancy intervals less than 3 months had the lowest risk of repeat miscarriage (7.3% versus 22.1%; adjusted-HR 0.33, 95% CI 0.16 to 0.71; Table 2). This trend was consistent when modeling interpregnancy interval as a continuous variable, with risk of subsequent miscarriage in pregnancy being the lowest for women with short interpregnancy intervals and steadily increasing with interval length until peaking at six months (Figure 2). The time a woman waited before trying to conceive again did not associate strongly with risk of miscarriage in the next pregnancy. However, miscarriage risk slightly increased with wait time up to 3 months and then plateaued (Figure 3).

Discussion

Women with an interpregnancy interval after miscarriage of less than 3 months have a significantly reduced risk of subsequent miscarriage compared to women with intervals between six and eighteen months. We did not observe effect modification by race or parity. Attempting to conceive immediately after miscarriage was not associated with increased risk of miscarriage in next pregnancy.

These findings are not consistent with recommendations to delay conception by at least six months, but align with recent studies.[9–17] In a Scottish health database study, women who conceived within six months of a miscarriage were at lower risk for subsequent miscarriage than women with an interval of six to twelve months (adjusted-odds ratio [OR] 0.66, 95% CI 0.57 to 0.77).[13] Similarly, a study in Egyptian women whose first pregnancy ended in miscarriage showed women with an interpregnancy interval longer than twelve months had twice the risk of miscarriage than those with an interval less than six months.[17] A study of the Demographic Surveillance System in Bangladesh reported interpregnancy intervals of

less than 3 months after loss were associated with the highest probability of live birth in next pregnancy.[14]

A secondary analysis of the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial demonstrated women with an interpregnancy interval of less than 3 months after a miscarriage were not at increased risk of peri-implantation or clinically confirmed loss when compared to women with longer intervals (adjusted-risk ratios 0.95, 95% CI 0.51 to 1.80 and 0.75, 95% CI 0.51 to 1.10, respectively).[15] Further, the proportion of pregnancies to end in live birth were similar between groups. In our study, women with intervals less than 3 months had twice the odds of live birth than women with longer intervals (adjusted-OR 2.05, 95% CI 1.03 to 4.08). Couples from the EAGeR trial who waited less than 3 months before trying to conceive were more likely to have a pregnancy ending in live birth than couples who waited longer.[16] In our cohort, a non-significantly higher proportion of live births occurred among couples who waited less than 3 months before attempting to conceive compared to those who waited longer (85.8% compared to 79.9%, chi-squared p-value = 0.10).

Short interpregnancy interval after a loss may be associated with reduced risk of repeat miscarriage for several reasons. The first trimester of pregnancy involves many physiologic changes. A time may exist after miscarriage before a woman's body returns to its pre-pregnancy state when it is "primed" for pregnancy. While physiologic priming is used to explain increase in adverse pregnancy outcomes associated with long interpregnancy intervals after a live birth,[18, 19] there is an absence of studies evaluating such changes post-miscarriage. Conception prior to the body's return to baseline may promote next pregnancy's success. Also, short time to pregnancy associates with favorable outcome independent of when a couple tries to conceive.[16, 20] Study participants with short interpregnancy intervals are necessarily those who achieved pregnancy quickly. The women who conceived within 3 months after loss had high fecundity and were less likely to be obese then women with longer intervals. Therefore, increased representation of women with high reproductive fitness may drive low risk seen in this group. Our evaluation of wait time focuses on the time under a couple's control, not time to pregnancy. The decreased risk associated with short wait time was less drastic than that with a short interpregnancy interval.

Right from the Start is well-suited to study this association between interpregnancy interval after miscarriage and subsequent miscarriage risk. Many prior studies determine eligibility and measure interpregnancy interval using healthcare records or surveillance data. This method is vulnerable to exposure and outcome misclassification since it requires women to engage the healthcare system for every miscarriage to be valid. Further, this study enrolled women across three states very early in gestation, allowing us to precisely assess interpregnancy interval and research outcome in a varied population. Additionally, we collected information on how long a couple waited before trying to conceive and were thus able to characterize how both interpregnancy interval and wait time associate with miscarriage risk. We were limited by our inability to account for the role of emotional preparedness. Miscarriage can be emotionally devastating and this analysis does not measure

the potential impact of emotional preparedness on the relationship between interpregnancy interval and pregnancy success.[21]

In summary, short interpregnancy interval after a loss is not associated with increased risk of miscarriage in next pregnancy. This implies counseling women to delay conception to prevent a repeat miscarriage is not warranted.

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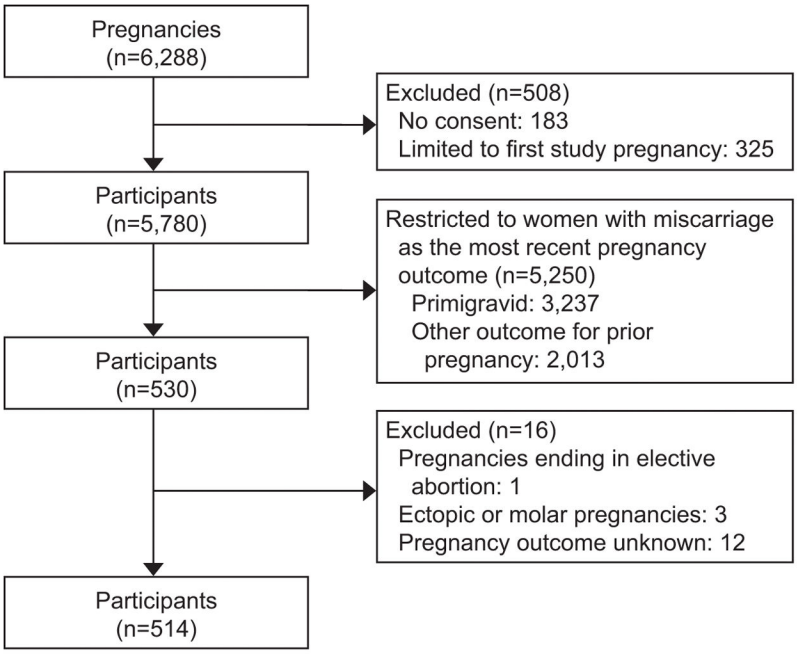

Figure 1.
Flow diagram showing inclusion and exclusion criteria for study sample.

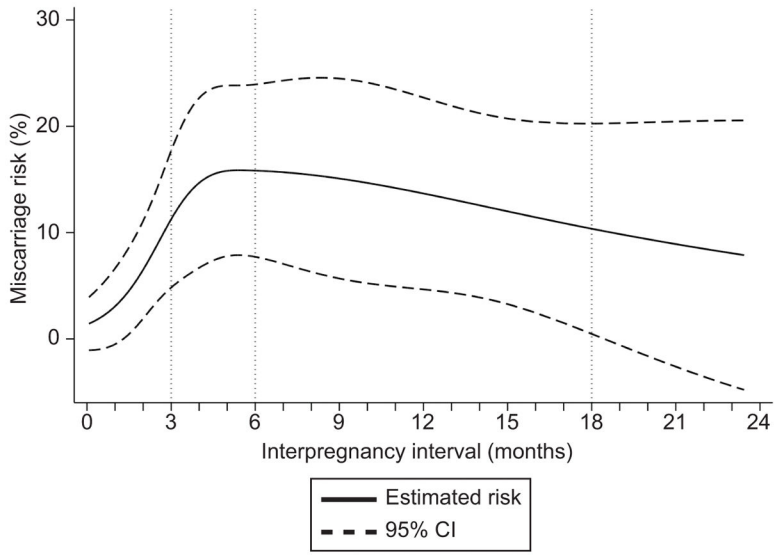

Figure 2.

Predicted probability of repeat miscarriage and 95% CIs by interpregnancy interval length after a loss (n=511). *Vertical lines* represent boundaries used for interpregnancy interval groups in the categorical analysis.

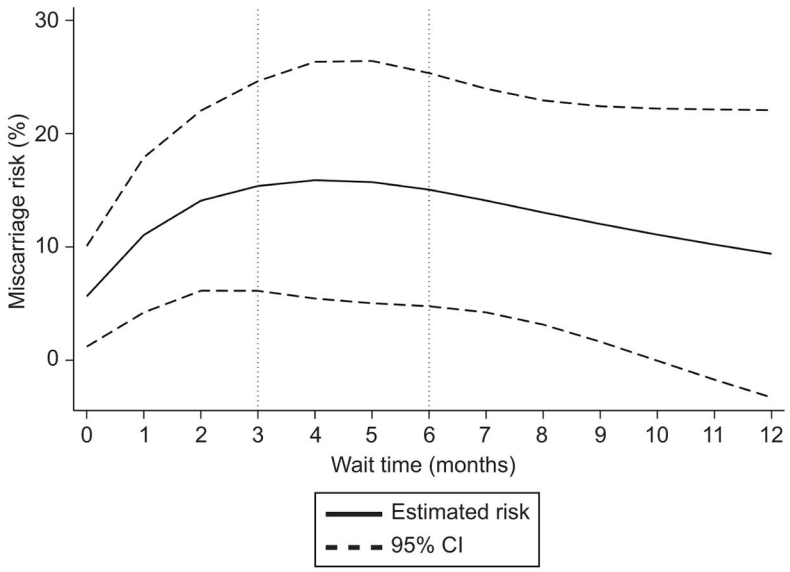

Figure 3.

Predicted probability of repeat miscarriage and 95% CIs by the length of time a couple waited after a loss before trying to conceive again (n=471). *Vertical lines* represent boundaries used for interpregnancy interval groups in the categorical analysis.

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Table 1

Characteristics of participants from *Right from the Start* with previous pregnancy ending in miscarriage by length of interpregnancy interval, 2000–2012 (n=514)

Characteristics Categorical	<3 months (n=125)		3–5.99 months (n=178)		6–17.99 months (n=137)		≥ 18 months (n=74)		p-value*
	N	%	N	%	N	%	N	%	
Maternal age, years									0.18
19 or younger	2	1.6	4	2.2	2	1.5	0	0.0	
20–24	15	12.0	18	10.1	14	10.2	10	13.5	
25–29	40	32.0	48	27.0	32	23.4	26	35.1	
30–34	51	40.8	65	36.5	63	46.0	19	25.7	
35 or older	17	13.6	43	24.1	26	19.0	19	25.7	
Race									<0.01
White, non-Hispanic	107	85.6	146	82.0	97	70.8	45	60.8	
Black, non-Hispanic	10	8.0	15	8.4	18	13.1	20	27.0	
Other	8	6.4	17	9.6	21	15.3	9	12.2	
Missing	0	0.0	0	0.0	1	0.7	0	0.0	
BMI, kg/m^2									<0.01
<18.5	2	1.6	4	2.2	0	0.0	3	4.1	
18.5–24.9	75	60.0	92	51.7	67	48.9	30	40.5	
25–29.9	33	26.4	50	28.1	35	25.5	16	21.6	
≥30	14	11.2	31	17.4	35	25.5	25	33.8	
Missing	1	0.8	1	0.6	0	0.0	0	0.0	
Education									<0.01
High school or less	12	9.6	15	8.4	18	13.1	10	13.5	
Some college	24	19.2	20	11.2	28	20.4	23	31.1	
College or more	89	71.2	143	80.3	91	66.4	41	55.4	
Marital status									<0.01
Married or cohabiting	118	94.4	170	95.5	128	93.4	60	81.1	
Other	7	5.6	8	4.5	9	6.6	14	18.9	
Household income, $									0.01
≤ 40,000	22	17.6	31	17.4	38	27.7	26	35.1	

Characteristics Categorical	<3 months (n=125)		3–5.99 months (n=178)		6–17.99 months (n=137)		≥ 18 months (n=74)		p-value*
	N	%	N	%	N	%	N	%	
40,001 to 80,000	55	44.0	69	38.8	45	32.9	20	27.0	
> 80,001	43	34.4	74	41.6	50	36.5	25	33.8	
Missing	5	4.0	4	2.2	4	2.9	3	4.1	
Parity									<0.01
Nulliparous	48	38.4	85	47.8	48	35.0	47	63.5	
1 prior delivery	50	40.0	65	36.5	59	43.1	17	23.0	
2+ prior deliveries	27	21.6	28	15.7	30	21.9	10	13.5	
Past miscarriage									0.09
1	86	68.8	133	74.7	97	70.8	60	81.1	
2	24	19.2	32	18.0	23	16.8	13	17.6	
3–7	15	12.0	13	7.3	17	12.4	1	1.4	
Smoking status †									0.05
Never or distant quit	119	95.2	167	93.8	128	93.4	63	85.1	
Current or recent quit	6	4.8	11	6.2	9	6.6	11	14.9	
Pregnancy Intention									<0.01
Intended	107	85.6	154	86.5	117	85.4	47	63.5	
Not intended	10	8.0	19	10.7	13	9.5	17	23.0	
Missing	8	6.4	5	2.8	7	5.1	10	13.5	

Abbreviations: BMI, body mass index.

*P-values derived from chi-square test (if any cell has less than five observations, Fisher's exact test is used)

†Quitting within the four months prior to the end of first trimester interview is considered a recent quit. Quitting before that time is considered a distant quit.

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Table 2

Association between interpregnancy interval length and risk of miscarriage in subsequent pregnancy (n=511)*

Interpregnancy interval length	N	Miscarriage	Crude HR	95% CI	Adjusted HR†	95% CI	Adjusted HR‡	95% CI
< 3 months	124	9	0.31	0.15–0.65	0.33	0.16–0.71	0.34	0.15–0.72
3–5.99 months	177	31	0.79	0.48–1.30	0.77	0.46–1.29	0.79	0.47–1.33
6–17.99 months	136	30	1.00	[referent]	1.00	[referent]	1.00	[referent]
≥ 18 months	74	10	0.59	0.29–1.20	0.53	0.25–1.12	0.56	0.26–1.19

Abbreviations: HR, hazard ratio; CI, confidence interval.

*n=3 participants missing covariate data excluded

†Adjusted for maternal age, BMI, education, parity and ethnicity

‡Adjusted for maternal age, BMI, education, parity, ethnicity, and number of prior miscarriages

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