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Post-partum interval and time to pregnancy in a prospective preconception cohort

Sydney K. Willis[1] | Elizabeth E. Hatch[1] | Amelia K. Wesselink[1] | Kenneth J. Rothman[1,2] | Ellen M. Mikkelsen[3] | Katherine A. Ahrens[4] | Lauren A. Wise[1]

[1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

[2]RTI International, Research Triangle Park, Durham, NC, USA

[3]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark

[4]Muskie School of Public Service, University of Southern Maine, Portland, ME, USA

Correspondence
Sydney K. Willis, Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA.
Email: siwillis@bu.edu

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Abstract

Background: Little is known about the influence of the post-partum interval—defined as the time between giving birth and attempting to conceive again—on subsequent fecundability.

Objectives: We evaluated the association between the post-partum interval and fecundability in Pregnancy Study Online (PRESTO), a web-based prospective preconception cohort of pregnancy planners from the United States and Canada.

Methods: Eligible women were aged 21-45 years, attempting pregnancy, and not using fertility treatment. Women completed a baseline questionnaire to ascertain information on demographics, life style factors, and reproductive history, including detailed information on all previous pregnancies. They completed bi-monthly follow-up questionnaires for up to 12 months to update pregnancy status over time. We used proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs) adjusted for sociodemographic and reproductive history covariates. Analyses were restricted to multiparous women who had been attempting pregnancy with the same male partner for ≤6 menstrual cycles at enrolment.

Results: During 2013-2019, 1489 female participants contributed 959 pregnancies and 5003 cycles. The median post-partum interval was 18 months. Compared with a 12- to 23-month post-partum interval, FRs for post-partum intervals of <12, 24-47, and ≥48 months were 0.89 (95% CI 0.77, 1.04), 1.06 (95% CI 0.91, 1.23), and 0.81 (95% CI 0.62, 1.05), respectively. When restricting to women without a history of subfertility, results were consistent for long post-partum interval and attenuated for short post-partum interval.

Conclusions: Among North American pregnancy planners, long post-partum intervals (≥48 months) were associated with slightly reduced fecundability. Short post-partum intervals (<12 months) were weakly associated with reduced fecundability in some subgroups including women with a history of caesarean delivery and planned pregnancies.

KEYWORDS

fecundability, interpregnancy interval, post-partum interval, prospective cohort, time to pregnancy

1 | BACKGROUND

For women planning to space their births, the interpregnancy interval (IPI)—the time between the delivery of a livebirth and the start of a subsequent pregnancy—is a function of the desired interval between births and any additional time it takes couples to conceive.[1,2] As most pregnancy planners take up to 3 months to conceive and approximately 15% of couples take ≥12 months to conceive,[3] a couple's actual IPI may be longer than their desired IPI.[1]

Short IPIs have been associated with several adverse perinatal outcomes, including small for gestational age, preterm birth, and infant mortality.[4,5] In 2006, the World Health Organization issued recommendations that women delay pregnancy for at least 24 months following a livebirth to achieve optimal birth outcomes in the subsequent pregnancy. Further, a 2018 systematic review concluded that IPIs shorter than 6 months (typically compared with 18- to 23-month intervals) were associated with increased risks of preterm birth and infant mortality.[5]

Short IPIs could affect perinatal outcomes by preventing sufficient time for mothers to recover from their preceding pregnancy, resulting in (i) suboptimal maternal nutritional status to support the needs of the mother and foetus; and (ii) inadequate physiologic restoration (including an abnormal process of remodelling endometrial blood vessels and, in the case of caesarean deliveries, incomplete uterine scar healing). While a 2012 meta-analysis[6] found evidence to support the hypothesis that incomplete healing of the uterine scar may be a plausible mechanism for adverse perinatal outcomes following short IPIs, they found little support for the maternal nutritional depletion hypothesis.

A prolonged IPI leads to an older age at subsequent pregnancy attempt, and older age may lead to a longer IPI, which in turn may increase the risk of subfertility and other adverse reproductive outcomes.[7,8] Additionally, a long IPI may increase the risk for adverse reproductive outcomes, independent of maternal age. A systematic review conducted in 2006 reported that long IPIs (typically ≥60 months), compared with intervals 18-23 months, were associated with increased risks of adverse perinatal outcomes.[4]

Long IPIs could increase the risk of adverse perinatal outcomes through a physiologic regression mechanism, wherein after giving birth, the hypothesized adaptive benefits of pregnancy decline over time as the body slowly reverts to a nulligravid state.[8] While there is limited evidence evaluating this hypothesis, prior studies among women with long IPIs and primigravid women have found similar risks of certain pregnancy-related conditions, such as preeclampsia and preterm birth.[9-11]

To our knowledge, no previous study has examined the association between the interval between giving birth and start of the next pregnancy attempt—herein defined as the "post-partum interval"—and fecundability, the per-cycle probability of conception among non-contracepting couples (Figure 1). IPI, unlike the post-partum interval, conflates the desired waiting time and the waiting time from unsuccessful pregnancy attempts and pregnancy losses for women planning to space their births.[1,12-14] We examined the association between length of the post-partum interval and subsequent fecundability within a prospective cohort of pregnancy planners in North America.

Synopsis

Study question

Is the post-partum interval, the time period between a livebirth and the initiation of the current pregnancy attempt, associated with fecundability?

What's already known

While short interpregnancy intervals have been associated with adverse reproductive outcomes, little is known about the influence of the post-partum interval on subsequent fecundability.

What this study adds

Among North American pregnancy planners, short post-partum intervals (<12 months) were weakly associated with reduced fecundability among some subgroups, including women with a history of a caesarean delivery and women with a planned pregnancy; long post-partum intervals (≥48 months) were more strongly associated with reduced fecundability.

2 | METHODS

2.1 | Study population

Pregnancy Study Online (PRESTO) is an ongoing North American internet-based prospective cohort study of pregnancy planners (2013 to present), described in detail elsewhere.[15] Briefly, women aged 21-45 years, living in the United States or Canada, not currently pregnant, attempting to conceive, and not using contraception or fertility treatment were eligible to participate. At baseline, female participants completed an online questionnaire on demographics and life style factors. Female participants completed follow-up questionnaires every two months to update pregnancy status until conception or 12 months, whichever occurred first.

2.2 | Exclusions

From June 2013 through April 2019, 10,518 eligible women completed the baseline questionnaire. We excluded women whose baseline date of last menstrual period (LMP) was greater than 6 months before study entry and women with insufficient LMP data (Figure S1). We also excluded women attempting pregnancy for >6 cycles at study entry because they may have less accurately reported attempt times. We restricted the analysis to women whose most recent pregnancy was a singleton livebirth, and women who had not changed partners since their prior birth (to control for

confounding by male factors). To reduce residual confounding by age, we excluded women <20 and >37 years old at the most recent pregnancy to confine the study population to the age range common to all compared. After exclusions, the final analytic sample comprised 1489 women (Figure S1).

2.3 | Assessment of time to pregnancy and time to viable pregnancy

We estimated time to pregnancy (TTP) using data from baseline and follow-up questionnaires. At baseline, women reported their LMP start date, menstrual cycle length (if regular), and the number of menstrual cycles they attempted pregnancy at study entry. For women who reported irregular cycles, we estimated cycle length based on their LMP start date at baseline and the consecutive menstruation dates reported at follow-up. On subsequent follow-up questionnaires, participants reported their LMP and current pregnancy status. TTP was estimated based on the total discrete cycles at risk, calculated as: cycles of attempt at study entry + [(LMP date from most recent follow-up questionnaire - date of baseline questionnaire completion)/usual cycle length] + 1. Females contributed observed cycles from baseline until reported conception, initiation of fertility treatment, cessation of pregnancy attempts, withdrawal, loss to follow-up, or 12 cycles, whichever came first. We additionally evaluated the association between post-partum interval and time to *viable* pregnancy, defined as

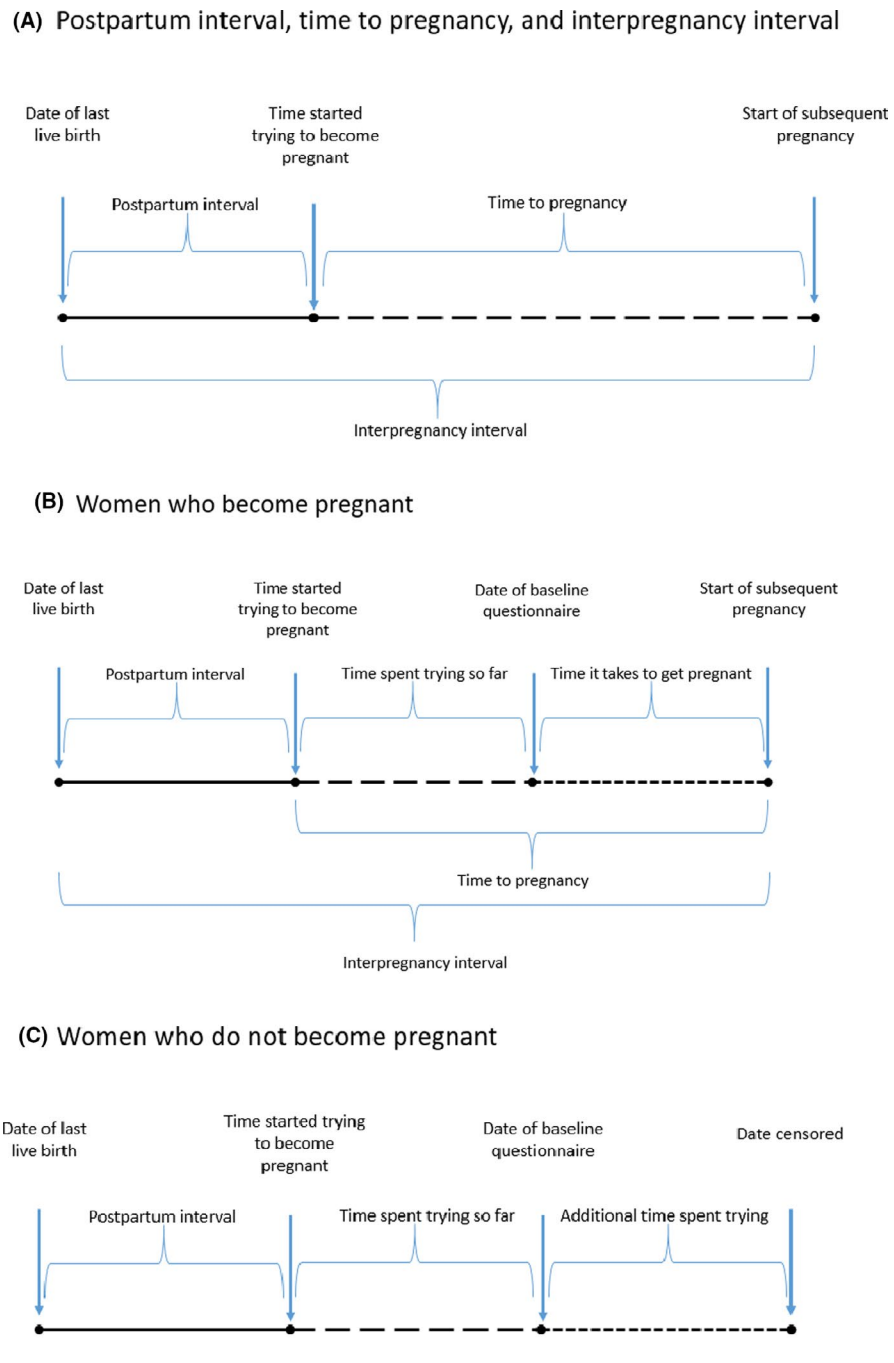

FIGURE 1 Diagram of post-partum interval [Colour figure can be viewed at wileyonlinelibrary.com]

a pregnancy lasting at least 20 weeks. In this analysis, women who reported a spontaneous abortion, induced abortion, or ectopic pregnancy were censored at their reported date of conception.

2.4 | Assessment of post-partum interval

On the baseline questionnaire, participants reported their LMP and the number of months they had been attempting pregnancy. We used this information to estimate the date the participant initiated the current pregnancy attempt. Additionally, participants were asked "How many times have you been pregnant? Please include live births, stillbirths, miscarriages (including chemical pregnancies), induced abortions, and tubal and other ectopic pregnancies." For each pregnancy, participants reported the pregnancy outcome and the date the pregnancy ended. We defined post-partum interval as the time between the date of the most recent singleton livebirth and the estimated date participants initiated the current pregnancy attempt (Figure 1). We categorized post-partum interval as <12, 12-23 (reference category), 24-47, and ≥48 months.[4,14,16]

2.5 | Assessment of covariates

At baseline, we collected extensive covariate data, including demographic, socio-economic, and behavioural variables, as well as medical and reproductive history. We assessed characteristics of the previous pregnancy. Body mass index (BMI) was calculated as self-reported weight (kilograms) divided by height (metres) squared.

2.6 | Statistical analysis

We used proportional probabilities regression models to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs) for the association between post-partum interval and fecundability. The FR is the ratio of the average per-cycle probability of conception within each exposure category relative to the reference category. The Andersen-Gill data structure outputs a single observation for each menstrual cycle at risk and accounts for left truncation by counting the number of pregnancy attempt cycles observed after enrolment.[17,18] We additionally examined the association between post-partum interval as a continuous variable and fecundability using restricted cubic splines.[19,20]

Potential confounders were determined a priori, based on prior literature and a directed acyclic graph (Figure S2). In the first model, we adjusted for variables ascertained at the time of recruitment that met the definition of a confounder[21]; these were variables assumed to influence the post-partum interval and subsequent fecundability. Variables included age at last birth (<25, 25-29, 30-34, ≥35 years), partner's age at last birth (<25, 25-29, 30-34, ≥35 years), race/ethnicity (non-Hispanic white vs other race/ethnicity), educational attainment (≤12, 13-15, 16, ≥17 years), household income (<$50 000, $50 000-$149 000, ≥$150 000 US dollars per year), number of prior pregnancies, smoking during the prior pregnancy, weight gain during the prior pregnancy (in 2 kg increments, plus ≥ 27.2 kg), whether the prior pregnancy was planned, season of last birth (spring, summer, fall, winter), and mode of prior delivery (vaginal vs caesarean). In addition to covariates adjusted for in the first model, the second model adjusted for characteristics assessed after the post-partum interval at the time of recruitment, which were considered proxies for factors that preceded the interval, including multivitamin use, BMI (<25, 25-29, 30-34, ≥35 kg/m^2), hormonal last method of contraception (ie oral contraceptives and intrauterine devices), caffeine intake (100 mg/day increments), alcohol intake (0, 1-6, 7-13, ≥14 drinks/week), and intercourse frequency (<1, 1-3, ≥4 times per week).

2.7 | Sensitivity analyses

We conducted a sensitivity analysis restricted to women without a history of subfertility (women who reported any prior pregnancy attempt time of ≥6 months),[22] as we hypothesized that women with such a history may be more likely to shorten their post-partum interval out of concern about future delays in conception.

We stratified our analyses by age at prior birth (<25, 25-29, and ≥30 years) to evaluate whether the association between post-partum interval and fecundability varied by age. We hypothesized that long post-partum intervals may have a stronger deleterious effect on fecundability among older women. Although it is difficult to disentangle the effects of current age from the post-partum interval, we conducted a sensitivity analysis stratified by current age (<30 and ≥30 years). Additionally, we assessed the extent to which the association between post-partum interval and fecundability varied by (1) mode of last delivery (vaginal vs caesarean), as women with caesarean delivery may have had underlying maternal conditions or pregnancy complications that may affect post-partum interval and fecundability[23]; (2) pregnancy intention of the previous pregnancy, which may influence the desired post-partum interval; (3) gestational weight gain (<13.6 vs ≥13.6 kg)[24] because among women with shorter post-partum intervals, those with sufficient weight gain may have better nutritional status and therefore more favourable perinatal outcomes[6]; and (4) attempt time at study entry as individuals with shorter attempt times at study entry are less likely to have misclassification of exposure and covariates and are less likely to change their behaviour in response to concerns about subfertility.

We conducted a sensitivity analysis controlling for breast feeding (any vs. none) and breast-feeding duration. While we believe it is more likely that the post-partum interval would influence breast feeding than breast feeding influencing the post-partum interval, this likely depends on the individual. Thus, we conducted two additional analyses: (1) adjusting for breast feeding (yes vs no) and (2) adjusting for breast-feeding duration. We additionally conducted an analysis excluding women who reported they were still breast feeding at baseline or stopped breast feeding the month they initiated their current pregnancy attempt.

2.8 | Missing data

We used multiple imputation to impute missing data on exposure, covariates, and pregnancy status.[25] We generated five imputed data sets with over 200 covariates to predict missing values. Each imputed data set was analysed separately and pooled to account for between- and within-imputation variation.[26] To reduce potential for selection bias from differential loss to follow-up, we assigned one cycle of follow-up for women with no follow-up data (N = 211) and then imputed their pregnancy status (pregnant vs not pregnant).[26] Missingness for post-partum interval was <1%. Missingness for covariates ranged from <0.1% (multivitamin use, intercourse frequency, and alcohol intake) to 4% for income. There were no missing values for age. All statistical analyses were performed using SAS version 9.4.[27]

2.9 | Ethics approval

This study was approved by the Institutional Review Board of the Boston University Medical Campus; online informed consent was obtained from all participants.

TABLE 1 Demographic, life style, and reproductive factors among 1489 female participants by post-partum interval as ascertained on the baseline questionnaire[a]

	Post-partum interval, months			
	<12	12-23	24-47	≥48
Number of women (n, %)	397 (27)	561 (38)	401 (27)	130 (9)
Age at current pregnancy attempt, years (mean)	29.4	30.4	31.0	32.5
Age at most recent pregnancy, years (mean)	28.6	28.8	28.0	26.7
Partner age at most recent pregnancy, years (mean)	31.8	30.4	29.4	28.2
Years in steady relationship with partner, years (mean)	6.5	7.9	8.4	10.0
White, non-Hispanic (%)	87.2	87.7	85.2	80.7
Household income <$50 k (%)	25.0	19.1	20.6	27.2
Less than college degree (%)	30.7	23.9	30.3	54.0
Body mass index, kg/m^2 (mean)	28.3	27.3	28.5	29.8
Physical activity, MET h/wk (mean)	27.7	29.5	29.8	29.6
Alcohol, drinks/week (mean)	2.1	2.7	2.8	2.5
Caffeine, mg/day (mean)	127.9	116.6	143.4	116.7
Ever smoker (%)	25.4	19.0	25.7	36.7
Daily multivitamin use (%)	79.3	79.5	76.4	64.7
Perceived stress scale score (mean)	15.6	15.3	16.3	16.7
Doing anything to improve chances (%)	64.0	75.5	76.1	74.5
Intercourse frequency (%)				
<1 time/week	29.6	31.8	27.2	18.2
≥4 times/week	10.3	11.1	7.3	17.7
History of subfertility (%)	34.5	20.9	15.6	15.9
History of unplanned pregnancy (%)	41.1	38.6	51.1	72.9
Maternal difficulty conceiving (%)	19.9	18.2	18.7	14.7
Number of prior pregnancies (mean)	2.3	1.8	1.7	1.9
Prior pregnancy information				
Planned (%)	81.5	76.4	67.5	45.7
Time to pregnancy, months (mean)	5.0	3.8	3.0	2.4
Smoke (%)	3.9	2.5	4.3	8.3
Weight gain, kg (mean)	13.2	14.6	14.7	14.3
Caesarean section (%)	24.1	29.7	29.1	35.6
Breast fed (%)	89.4	93.4	89.8	73.6
Fertility treatment (%)	8.5	3.5	2.4	0.8

[a]All characteristics, except age, are age-adjusted to the cohort at baseline.

3 | RESULTS

During June 2013-April 2019, 1489 female participants contributed 959 (65%) pregnancies and 5,003 cycles, accounting for lost to follow-up; 4% stopped trying to conceive; 5% started fertility treatment, 18% were lost to follow-up; 3% were still participating; and 9% were censored at 12 cycles. The median post-partum interval was 18 months (interquartile range: 11-29 months).

We examined the participants' characteristics ascertained on the baseline questionnaire by post-partum interval (Table 1). Women with a shorter post-partum interval were more likely to be non-Hispanic White, have planned their prior pregnancy, and have a history of subfertility. They were also less likely to be doing something to improve their chances of pregnancy (eg timing intercourse to the most fertile period) and to have had a caesarean delivery for the last birth. Women with a longer post-partum interval were younger at their prior birth and older at the current pregnancy attempt (due to a longer post-partum interval), had lower education, and were more likely to have smoked during their prior pregnancy.

Short and long post-partum intervals were associated with slightly reduced fecundability (Table 2). Relative to a 12- to 23-month post-partum interval, adjusted FRs for post-partum intervals of <12, 24-47, and ≥48 months were 0.89 (95% CI 0.77, 1.04), 1.06 (95% CI 0.91, 1.23), and 0.81 (95% CI 0.62, 1.05), respectively. Findings were similar when adjusting for variables considered to be true confounders (model A) and variables considered to be proxy confounders (model B). When modelled using restricted cubic splines, we observed reduced fecundability for women with the shortest and longest post-partum intervals (Figure 2). In a sub-analysis examining time to viable pregnancy, long (≥48 months) post-partum intervals were still associated with reduced fecundability, compared with 12-23 months (Table 2). Among women without a history of subfertility, we observed a similar association, although results were attenuated for post-partum intervals <12 months (Table 2). When modelled using restricted cubic splines, the association was consistent with the main results.

Among younger women at their prior birth (<25 and 25-29 years), fecundability was reduced for both the shortest and longest post-partum intervals, relative to the 12- to 23-month post-partum interval (Figure 3 and Table S1), although results were imprecise. For women <25 years at their prior birth, relative to the 12- to 23-month interval, adjusted FRs for post-partum intervals of <12 and ≥48 months were 0.86 (95% CI 0.50, 1.46) and 0.61 (95% CI 0.31, 1.24), respectively. Results were similar among women aged 25-29 years. Among older women (≥30 years), we observed a slightly weaker and less precise association for the longest post-partum interval category. Among women aged <30 years at cohort entry (Table S2), those with the shortest and longest post-partum intervals had reduced fecundability, relative to the 12- to 23-month post-partum interval. Among women ≥30 years at cohort entry, fecundability was reduced only for the longest post-partum interval relative to the 12- to 23-month post-partum interval. When modelled using restricted cubic splines, fecundability was reduced for both the shortest and longest post-partum intervals across all age groups (Figure 3).

When we stratified by mode of delivery of the previous birth (Table 3), we observed slightly reduced fecundability for the shortest post-partum interval among women with a caesarean delivery only, whereas results for long post-partum interval were consistent across strata. Likewise, we observed an association between short post-partum intervals and lower fecundability among those whose

TABLE 2 Association between post-partum interval and fecundability among female participants

	Fecundability					Time to viable pregnancy		
	Num Preg	Num Cycle	Unadjusted FR (95% CI)	Adjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)	Num Preg	Num Cycle	Adjusted[b] FR (95% CI)
Post-partum interval (months)								
<12	245	1386	0.90 (0.78, 1.05)	0.92 (0.80, 1.07)	0.89 (0.77, 1.04)	196	1386	0.88 (0.74, 1.04)
12-23	379	1860	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	313	1860	1.00 (Reference)
24-47	266	1252	1.06 (0.91, 1.23)	1.05 (0.91, 1.22)	1.06 (0.91, 1.23)	220	1252	1.05 (0.88, 1.25)
≥48	69	505	0.76 (0.58, 0.98)	0.77 (0.59, 1.00)	0.81 (0.62, 1.05)	55	505	0.75 (0.55, 1.02)
Restricted to those without a history of subfertility								
Post-partum interval (months)								
<12	175	885	0.96 (0.82, 1.14)	0.98 (0.82, 1.16)	0.96 (0.81, 1.13)	138	885	0.93 (0.76, 1.13)
12-23	312	1457	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	256	1457	1.00 (Reference)
24-47	235	1010	1.09 (0.93, 1.28)	1.08 (0.92, 1.26)	1.09 (0.93, 1.28)	195	1010	1.09 (0.91, 1.31)
≥48	57	427	0.73 (0.56, 0.96)	0.76 (0.58, 1.00)	0.81 (0.62, 1.07)	46	427	0.76 (0.56, 1.04)

[a]Age at prior pregnancy, partner's age at prior pregnancy, race, education, income, number of prior pregnancies, smoker during prior pregnancy, weight gain during prior pregnancy, prior pregnancy planned, season of prior birth, last pregnancy mode.

[b]Model a & multivitamin use, body mass index, use of hormonal contraceptives as last method of contraception, barrier method as last form of birth control, caffeine intake, alcohol intake, intercourse frequency.

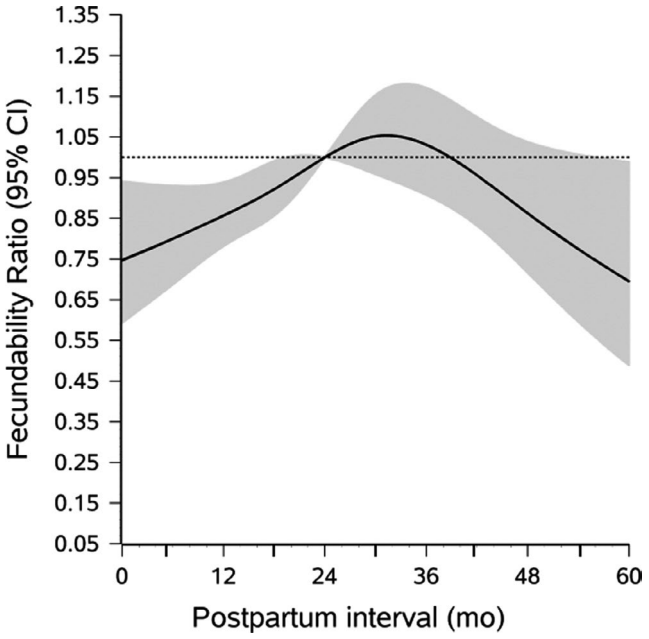

FIGURE 2 Restricted cubic spline of the association between post-partum interval and fecundability among 1489 female participants, 2013-2019. Reference value for spline is a 24-month post-partum interval. The splines are trimmed at the 95th percentile with four knot points at 11, 18, 29, and 48 mo. Adjusted for age at prior pregnancy, partner's age at prior pregnancy, race, education, income, number of prior pregnancies, smoker during prior pregnancy, weight gain during prior pregnancy, prior pregnancy planned, season of prior birth, last pregnancy mode, multivitamin use, body mass index, use of hormonal contraceptives as last method of contraception, barrier method as last form of birth control, caffeine intake, alcohol intake, intercourse frequency

previous pregnancy was planned, but not unplanned; results for long post-partum intervals were similar across strata (Table 3). Short and long post-partum intervals were associated with reduced fecundability only among women with gestational weight gains of <13.6 kg in their previous pregnancy; no appreciable associations were observed among those with gestational weight gains of ≥13.6 kg (Table 3). Reduced fecundability was observed for both the shortest and longest post-partum intervals in women with <3 cycles, but not 3-6 cycles, of attempt time at study entry.

When we additionally controlled for breast feeding (yes vs no) (Table S3), results for short post-partum interval were slightly attenuated; results were more strongly attenuated when adjusting for breast-feeding duration. When we excluded women who reported current breast feeding (n = 453) or recent breast-feeding cessation (n = 48), results were consistent with the primary analysis.

4 | COMMENT

4.1 | Principal findings

In this prospective cohort of North American pregnancy planners, long post-partum intervals (≥48 months) were associated with slightly reduced fecundability, independent of age at previous delivery (or age at cohort entry). We observed similar results when stratifying on characteristics of the previous birth, including mode of delivery and pregnancy intention. Additionally, although results were attenuated among those without a history of subfertility, short post-partum intervals (<12 months) were associated with longer TTP among all ages, and among women attempting to conceive <3 cycles at study entry, a subgroup for whom selection bias is less likely. A short post-partum interval was associated with reduced fecundability among women who, at the time of their previous delivery, had planned their pregnancy and had a caesarean delivery.

4.2 | Strengths of the study

The present study builds on prior research characterizing the influence of birth spacing and TTP on adverse perinatal outcomes by introducing the post-partum interval, an alternative to the IPI that has dominated previous research. In 2019, a working group released recommendations for future birth spacing research that illustrated a number of methodologic issues in attempting to characterize birth spacing.[14] The present study addressed several methodologic concerns previously raised. First, we ascertained data on maternal characteristics in the last pregnancy (eg maternal smoking) prior to ascertainment of pregnancy outcome for the current attempt. Second, we adjusted for characteristics reported during the current pregnancy attempt that may be proxies for characteristics prior to or during the last pregnancy (eg BMI, alcohol intake). Thus, our study is likely to have less unmeasured confounding than previous IPI studies, the majority of which were based on registry data.[1] Third, we restricted the analyses to women with the same partner in both pregnancies, limiting confounding by male partner characteristics. Fourth, we obtained information on intervening pregnancy losses and restricted analyses to women whose last pregnancy resulted in a livebirth. As the post-partum interval start date is defined as the end date of the last pregnancy among individuals whose last pregnancy was a livebirth, we hypothesize that women are likely to accurately recall their infant's birth date.[28-30] Additionally, the majority of women (71%) were recruited <3 months from the time when they ceased all contraception to when they were attempting to conceive again (ie the end of the post-partum interval). Thus, misclassification of the post-partum interval is likely to be small, specifically among this group due to more accurate reporting of pregnancy attempt time at study entry.

4.3 | Limitations of the data

There is potential for differential misclassification of variables identified as proxy confounders adjusted for in the second multivariable model. For life style characteristics measured at the end of the post-partum interval, we assumed that they represented the life

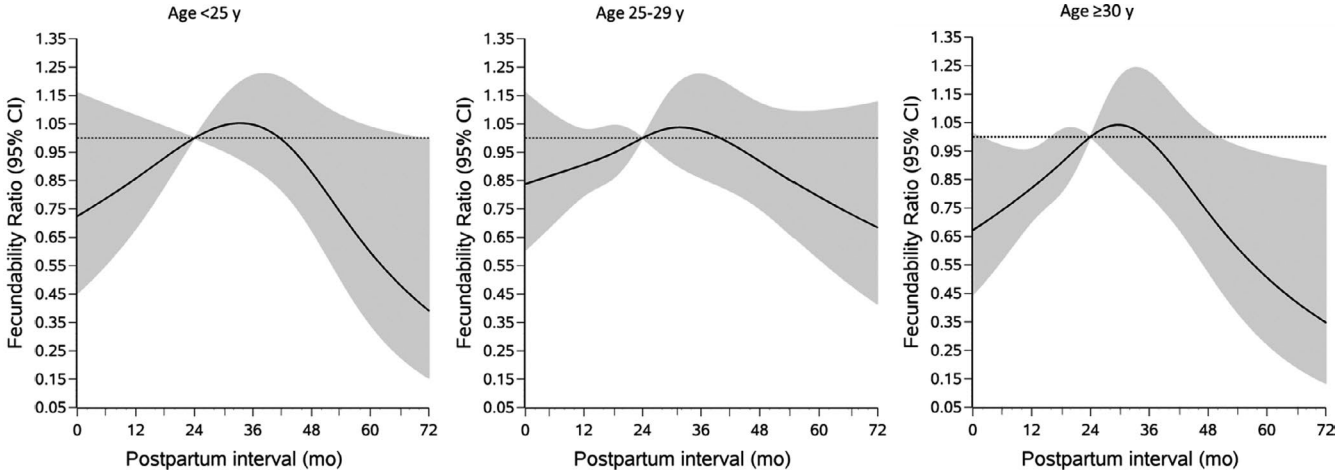

FIGURE 3 Restricted cubic splines of the association between post-partum interval and fecundability among 1489 female participants, 2013-2019 stratified by age at prior pregnancy. Reference value for spline is a 24-month post-partum interval. The splines have knot points at the 25th, 50th, 75th, and 90th percentiles corresponding to 13, 24, 44, and 60 mo for ages <25 y; 11, 18, 29, and 51 mo for ages 25-29 y; and 11, 18, 29, and 51 mo for ages ≥30 y. Adjusted for age at prior pregnancy, partner's age at prior pregnancy, race, education, income, number of prior pregnancies, smoker during prior pregnancy, weight gain during prior pregnancy, prior pregnancy planned, season of prior birth, last pregnancy mode, multivitamin use, body mass index, use of hormonal contraceptives as last method of contraception, barrier method as last form of birth control, caffeine intake, alcohol intake, intercourse frequency

style characteristic at the start of the post-partum interval (eg BMI). These variables were more likely to be misclassified among women with longer than shorter post-partum intervals: BMI at enrolment was more likely to reflect BMI at the end of the prior pregnancy for women with a post-partum interval <12 months than women with a post-partum interval of ≥48 months.

The time when ovulation returns after giving birth may vary throughout the post-partum period as women change their method of contraception, use contraceptive methods with varying efficacies, or are breast feeding. While our primary objective is to identify when a couple officially starts trying to conceive, we were unable to identify the first cycle at risk of conception.

4.4 | Interpretation

There is biologic plausibility for an adverse effect of longer spacing on reproductive outcomes, including reduced fecundability. In addition to the risks of advanced maternal age, it has been hypothesized that long waiting intervals after birth may result in a loss of the adaptive physiologic and anatomical benefits that the mother gained during gestation, reverting the mother's physiology to a nulligravid state.[6] Lending evidence to this theory, numerous studies, including a prior analysis conducted in PRESTO, have found that the age-related decline of fertility is steeper among nulliparous women compared with multiparae.[7,31,32] This suggests that pregnancy may offset the adverse effects of reproductive ageing due to the adaptive benefits the mother obtains during pregnancy. We observed a similar reduction in fecundability among women with a post-partum interval of ≥48 months across all age groups.

We also observed reduced fecundability for the shortest post-partum intervals (<12 months) among younger women and women with a caesarean delivery in their last birth. While not directly comparable, in a cohort of Canadian women,[33] short IPIs were associated with adverse infant and foetal outcomes overall, but associations were more pronounced among younger women (ages 20-34 years) compared with older women (ages ≥ 35 years).

Our finding of an inverse association between short post-partum interval and fecundability among women with a caesarean delivery as the mode of last delivery agrees with a 2013 meta-analysis that observed a slight increase in subfertility among women following a caesarean delivery compared with vaginal delivery (OR: 0.90, 95% CI: 0.86, 0.93).[23] Uterine restoration may be an important factor in successful implantation and pregnancy maintenance. A study that examined the time to complete uterine anatomy restoration through magnetic resonance imaging concluded that the complete restoration of uterine anatomy required ~6 to 9 months,[33] indicating that short birth spacing may not provide sufficient time for uterine recovery.

Results for short post-partum interval were attenuated among couples without a history of subfertility, supporting the hypothesis that couples with such a history may start trying to conceive following a birth sooner than couples without a history of subfertility. Additionally, we observed an association between short post-partum interval and fecundability among pregnancy planners, a group that may be less fecund than individuals with a history of unplanned pregnancies. Thus, results indicating an inverse association between short post-partum interval and fecundability may be overestimated.

5 | CONCLUSIONS

Long post-partum intervals (≥48 months) were associated with reduced fecundability among North American pregnancy planners.

TABLE 3 Association between post-partum interval and fecundability among female participants, stratified by characteristics of last pregnancy

	Num Preg	Num Cycle	Adjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)	Num Preg	Num Cycle	Adjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)
Post-partum interval (months)								
	Vaginal delivery				Caesarean delivery			
Livebirth								
<12	197	1036	0.96 (0.81, 1.14)	0.95 (0.80, 1.12)	48	350	0.82 (0.60, 1.14)	0.77 (0.55, 1.09)
12-23	270	1258	1.00 (Reference)	1.00 (Reference)	109	602	1.00 (Reference)	1.00 (Reference)
24-47	195	831	1.07 (0.90, 1.27)	1.09 (0.92, 1.30)	71	421	1.05 (0.79, 1.40)	1.13 (0.84, 1.52)
≥48	51	354	0.73 (0.53, 1.00)	0.83 (0.60, 1.14)	18	151	0.88 (0.53, 1.48)	0.75 (0.45, 1.26)
	Planned pregnancy				Unplanned pregnancy			
Livebirth								
<12	199	1134	0.88 (0.74, 1.05)	0.84 (0.71, 1.00)	46	252	1.11 (0.79, 1.55)	1.12 (0.80, 1.57)
12-23	307	1435	1.00 (Reference)	1.00 (Reference)	72	425	1.00 (Reference)	1.00 (Reference)
24-47	195	860	1.08 (0.92, 1.29)	1.07 (0.91, 1.26)	71	392	0.99 (0.71, 1.38)	0.98 (0.71, 1.35)
≥48	41	247	0.71 (0.50, 0.99)	0.86 (0.61, 1.21)	28	258	0.83 (0.55, 1.26)	0.82 (0.54, 1.24)
	Gestational weight gain < 13.6 kg (30 pds)				Gestational weight gain ≥ 13.6 kg (30 pds)			
Livebirth								
<12	114	663	0.95 (0.74, 1.21)	0.88 (0.68, 1.13)	131	723	0.91 (0.74, 1.10)	0.92 (0.75, 1.12)
12-23	154	776	1.00 (Reference)	1.00 (Reference)	225	1,084	1.00 (Reference)	1.00 (Reference)
24-47	99	543	0.96 (0.74, 1.25)	0.94 (0.72, 1.23)	167	709	1.11 (0.92, 1.33)	1.11 (0.93, 1.34)
≥48	24	238	0.60 (0.37, 0.97)	0.65 (0.40, 1.06)	45	267	0.92 (0.67, 1.28)	0.96 (0.69, 1.33)
	Attempt time at study entry: <3 cycles				Attempt time at study entry: 3-6 cycles			
Livebirth								
<12	179	1030	0.86 (0.73, 1.02)	0.84 (0.71, 0.99)	66	356	1.25 (0.90, 1.74)	1.19 (0.85, 1.67)
12-23	304	1434	1.00 (Reference)	1.00 (Reference)	75	426	1.00 (Reference)	1.00 (Reference)
24-47	210	854	1.08 (0.92, 1.27)	1.10 (0.93, 1.29)	56	398	0.99 (0.70, 1.40)	1.06 (0.74, 1.52)
≥48	44	311	0.73 (0.53, 1.01)	0.80 (0.57, 1.11)	25	194	0.93 (0.59, 1.46)	0.97 (0.61, 1.54)

[a]Age at prior pregnancy, partner's age at prior pregnancy, race, education, income, number of prior pregnancies, smoker during prior pregnancy, weight gain during prior pregnancy, prior pregnancy planned, season of prior birth, last pregnancy mode.

[b]Model a & multivitamin use, body mass index, use of hormonal contraceptives as last method of contraception, barrier method as last form of birth control, caffeine intake, alcohol intake, intercourse frequency.

Post-partum intervals shorter than average (<12 months) were also associated with reduced fecundability, but primarily among women with caesarean delivery in their prior pregnancy, women with a history of subfertility, and women who planned their previous pregnancies.

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CONFLICTS OF INTEREST

None of the authors have conflicts of interest to report.

ORCID

Sydney K. Willis https://orcid.org/0000-0002-6858-5450
Katherine A. Ahrens https://orcid.org/0000-0001-5139-9208

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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