Original Research

Trying to Conceive After an Early Pregnancy Loss

An Assessment on How Long Couples Should Wait

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OBJECTIVE: To compare time to pregnancy and live birth among couples with varying intervals of pregnancy loss date to subsequent trying to conceive date.

METHODS: In this secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial, 1,083 women aged 18–40 years with one to two prior early losses and whose last pregnancy outcome was a nonectopic or nonmolar loss were included. Participants were actively followed for up to six menstrual cycles and, for women achieving pregnancy, until pregnancy outcome. We calculated intervals as start of trying to conceive date minus pregnancy loss date. Time to pregnancy was defined as start of trying to conceive until subsequent conception. Discrete Cox models, accounting for left truncation and right censoring, estimated fecundability odds ratios (ORs) adjusting for age, race, body mass index, education, and subfertility. Although intervals were assessed prior to randomization and thus reasoned to have no relation with treatment assignment, additional adjustment for treatment was evaluated given that low-dose aspirin was previously shown to be predictive of time to pregnancy.

RESULTS: Couples with a 0–3-month interval (n=765 [76.7%]) compared with a greater than 3-month (n=233 [23.4%]) interval were more likely to achieve live birth (53.2% compared with 36.1%) with a significantly shorter time to pregnancy leading to live birth (median [interquartile range] five cycles [three, eight], adjusted fecundability OR 1.71 [95% confidence interval 1.30–2.25]). Additionally adjusting for low-dose aspirin treatment did not appreciably alter estimates.

CONCLUSION: Our study supports the hypothesis that there is no physiologic evidence for delaying pregnancy attempt after an early loss.

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After an early pregnancy loss[1,2] couples often seek counseling on how long to wait before attempting conception again. Many clinicians recommend waiting at least 3 months,[3,4] with the World Health Organization recommending a minimum of 6 months.[5,6] However, there are no data to support these recommendations, and previous studies have shown that the uterus may be more receptive to a pregnancy directly after an early loss.[7]

Most studies addressing pregnancy spacing concentrate on the interval between live births and subsequent pregnancies (interpregnancy interval) with the majority of findings indicating that an interpregnancy interval of less than 18 months is associated with increased risk for poor maternal and perinatal outcomes.[7–10] What has not been well studied is the optimal timing after a nonectopic, nonmolar, less than 20-week gestational age pregnancy loss. Studies to date have been limited in enrolling already pregnant women and then determining how their interpregnancy

interval affects pregnancy outcomes.[6,11–14] Although these studies answer the question of when couples should achieve a pregnancy after a loss, the more relevant public health question is when should couples start trying to achieve pregnancy after a loss. We set out to assess the relationship between the related but distinct construct of inter-trying interval, time from last pregnancy loss to conception attempt, and fecundability. Our a priori hypothesis is that there would be no difference in reproductive success among couples who started trying to conceive within compared with greater than 3 months of their pregnancy loss.

MATERIALS AND METHODS

The Effects of Aspirin in Gestation and Reproduction trial (2007–2011), a multicenter, block-randomized, double-blind, placebo-controlled trial to evaluate the effect of preconception-initiated daily low-dose aspirin on reproductive outcomes in women with a history of pregnancy loss, enrolled 1,228 women, aged 18–40 years, with one to two prior losses. Trial results of primary outcomes indicate that preconception low-dose aspirin treatment increases the probability of becoming pregnant, but does not prevent pregnancy loss, among women with one pregnancy loss in the previous year.[15] Details of the study design and protocol have been published previously.[16] Briefly, women were included if they had regular menstrual cycles of 21–42 days in length, no known history of infertility, and were trying or stated intention to start trying to conceive. Women whose last outcome was either spontaneous abortion (n=1,071 [98.9%]) or planned termination (n=12 [1.1%]) were included in this analysis, and women whose last outcome was live birth (n=85 [7.0%]), stillbirth (n=45 [3.7%]), or ectopic or molar pregnancy (known to require longer follow-up care) (n=15 [1.2%]) were excluded, resulting in a study sample of 1,083 women for this analysis (99.8% of whom had a last loss at 19 weeks of gestation or less, with 54.1% having had a last loss at 8 weeks of gestation or less).

Women were followed for up to six menstrual cycles while trying to conceive and through delivery if they became pregnant. The study was approved by the institutional review board at each site with each site serving as the institutional review board designated by the National Institutes of Health under a reliance agreement. All participants gave written informed consent before randomization. A data coordinating center was responsible for developing a computerized remote data capture system, training study site personnel in data entry, and data management throughout the trial.[16]

Inter-trying interval, defined as the time from last pregnancy loss to time attempting a subsequent conception (Fig. 1), was our primary exposure. Date of loss and gestational age of last loss were obtained from the participant's previous physician who provided details regarding the prior loss through a standardized form. Additionally, each participant completed an extensive health and reproductive history questionnaire at baseline. The majority of women (n=1,041 [96.1%]) had a medically documented date of last loss. For women without a medically documented date of last loss, we relied on their self-report, resulting in 1,074 (99.2%) women having a date of last loss. Date of starting to try to conceive was obtained from the baseline health and reproductive history questionnaire. Specifically, each couple was asked the question "How long have you currently been trying to become pregnant?" Answers were provided in number of months (1,006 [92.9%] completed the question). When the reported date of initiation of trying to conceive was reported as occurring before the date of last loss, the inter-trying interval was defined as zero months, that is, assuming no interruption in attempting conception. From the 1,074 women with a documented loss date and the 1,006 women who responded to the specific inter-trying interval question, we were able to successfully calculate the inter-trying interval for 998 women (92.2%). As outlined subsequently, multiple imputation was used to discern inter-trying intervals for the remaining 85 women[17] (Fig. 2).

Primary outcomes of this study were human chorionic gonadotropin-detected pregnancy and live birth. Pregnancy during the trial was ascertained by a urine pregnancy test (clinic, home, or both, with the majority [89%] having both) and confirmed by a 6- to 7-weeks ultrasonogram. Live birth was defined as a live-delivered neonate as indicated from medical records. Secondary outcomes included pregnancy loss, types of pregnancy loss, and obstetric complications (preeclampsia, gestational diabetes, and preterm birth at less than 37 weeks of gestation) as previously described.[18,19]

For the primary statistical analyses, the inter-trying interval was categorized dichotomously (0–3 months, greater than 3 months) based on prior recommendations on inter-trying interval and pregnancy loss.[3,12] We additionally assessed inter-trying interval based on 3-month intervals (0–3, greater than 3–6, greater than 6–9, greater than 9–12, and greater than 12 months). Participant demographic, lifestyle, and reproductive history characteristics between inter-trying intervals (0–3 months, greater than 3 months) were compared using χ^2 or where appropriate Fisher exact test for categorical variables and Student's t test for continuous variables.

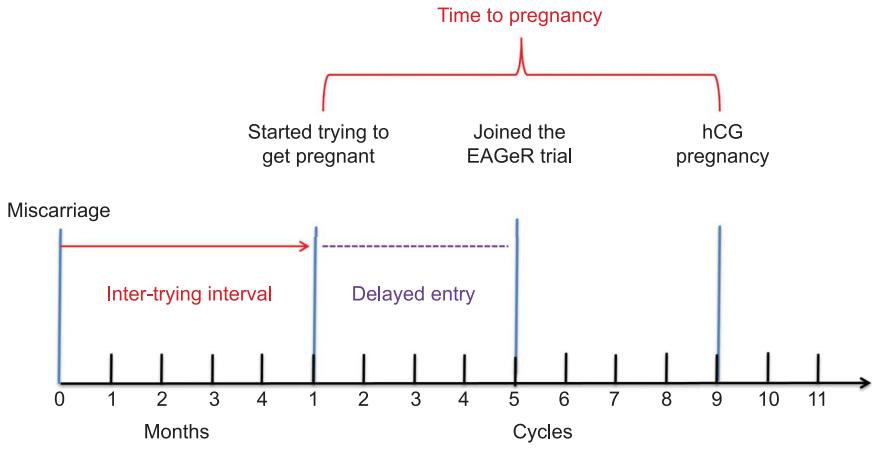

Fig. 1. An illustration of the relationship between the variables included in the survival model, in which inter-trying interval is the exposure of interest, time to pregnancy is the outcome of interest, and the *dotted line* represents the delayed entry time. EAGeR, Effects of Aspirin in Gestation and Reproduction; hCG, human chorionic gonadotropin.

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Among women who achieved pregnancy, time to pregnancy was defined as conception cycle (through a positive pregnancy test) minus number of menstrual cycles reported for trying to become pregnant. Given that time to pregnancy is inherently discrete,[20] we used cycles as our unit of time for assessing time to pregnancy but kept our exposure in months because this is the unit used for relevant recommendations.[5] Women who did not achieve pregnancy were censored at the end of follow-up or withdrawal date. Discrete Cox proportional hazards regression models were used to estimate the fecundability odds ratio (OR) and 95% confidence intervals (CIs) corresponding to the cycle-specific probability of conception. To account for left truncation,[21] time trying to achieve pregnancy as indicated by number of menstrual cycles before enrollment was incorporated into the model as the delayed entry time. For time to pregnancy leading to a live birth, a competing risks approach was applied to estimate cause-specific fecundability ORs, where women achieving pregnancy that ended in a loss were censored at the time of a positive pregnancy test.[22]

Based on a review of the prior literature, we considered the potential confounders of age (continuous), partner's age (continuous), body mass index (BMI) (continuous, calculated as weight (kg)/[height (m)]^2), race (white compared with nonwhite), education (greater than compared with high school or less), income ($19,000 or less, $20,000–39,000, $40,000–74,000, $75,000–99,000, $100,000 or greater), smoking (never, sometimes, daily), alcohol (never, sometimes, daily), physical activity (low, moderate, high), marital status (married compared with other), subfertility (yes compared with no with yes being a report of ever trying for more than 12 months to achieve a pregnancy), parity (zero, one, two, or greater), prior number of losses (one or two), gestational age of prior loss (continuous), and whether a dilation and curettage was performed for last loss (yes compared with no). Although we did not consider treatment as a confounder given that our exposure (inter-trying interval) was assessed before randomization and thus was reasoned to have no relation with treatment assignment, we did evaluate whether additionally adjusting for treatment appreciably altered estimates given that low-dose aspirin was previously shown to be predictive of time to pregnancy.[23,24] The choice of covariates to include in fully adjusted models was determined by directed acyclic graphs and statistical testing for confounding identification. Final models adjusted for age, race, BMI, education, and subfertility. Multiple imputation was performed to discern missing exposure and covariate data[17]; thus, all 1,083 women were included in all analyses performed. Analyses were conducted using SAS 9.4 and R 3.0.2.

Several sensitivity analyses were conducted to assess the robustness of our results. In our primary analyses, we corrected time at risk for those couples who had included time before their loss when reporting how long they had been trying to conceive by calculating the minimum number of months among the reported time trying and the number of months since the most recent loss. Although this is an improvement compared with dropping these women from the analyses altogether, this strategy may still result in misclassification of inter-trying intervals given our assumption that all couples reporting an implausible value started trying to conceive immediately after their loss. To determine the robustness of the fecundability OR estimates to this assumption, we performed two types of sensitivity analyses based on multiple imputation and Monte Carlo simulations. Specifically, standard multiple imputation techniques to discern plausible values for delayed entry times were applied based on potential predictors of this value. Additionally,

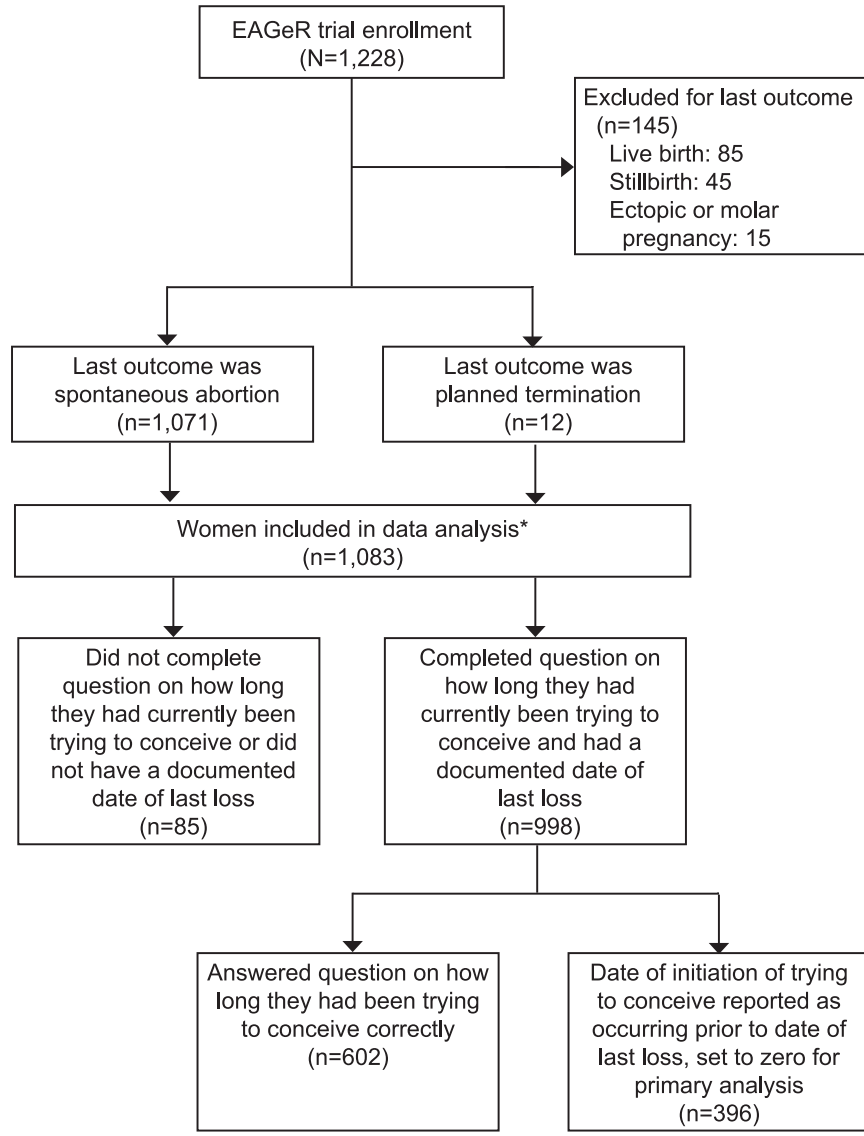

Fig. 2. Flow diagram outlining participants included and excluded in this analysis from the original Effects of Aspirin in Gestation and Reproduction (EAGeR) trial study population. *Multiple imputation used for 85 women to correct for bias resulting from missing information.

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as an alternate strategy, we applied Monte Carlo sampling techniques to randomly assign a feasible time at risk for those couples reporting implausible inter-trying interval values. This procedure was performed 500 times, and average fecundability ORs and 95% CIs were calculated using Rubin's combining rules.[25]

RESULTS

The majority of women (76.6%) had an inter-trying interval of 0–3 months; 23.4% had an inter-trying interval of greater than 3 months (9.0% greater than 3–6 months, 2.3% greater than 6–9 months, 1.7% greater than 9–12 months, and 10.3% greater than 12 months). Women with a 0- to 3-month compared with greater than 3-month inter-trying interval were slightly younger (mean 28.6 compared with 29.4 years), had a partner slightly younger (mean 29.8 compared with 31.0 years), lower BMI (mean 26.0 compared with 27.2), more likely to be white (96.9% compared with 91.9%), have above a high school education (89.4% compared with 80.7%), never smokers (96.5% compared with 91.9%), and more likely to be married (93.1% compared with 87.9%) (Table 1). In terms of reproductive history, women with a 0- to 3-month compared with greater than 3-month inter-trying interval had less frequently reported subfertility (6.6% compared with 10.3%), a slightly younger age of menarche (12.5 compared with 12.8 years), younger gestational age of last loss, and an older age of first intercourse (mean age 19.8 compared with 18.6 years).

Women with a 0- to 3-month compared with greater than 3-month inter-trying interval were more

Table 1. Demographic, Lifestyle, and Reproductive History of Effects of Aspirin in Gestation and Reproduction Study Population by Inter-trying Interval

Characteristic	Total (N=998)	Inter-trying Interval (Months)		*P**
		0–3 (n=765 [76.7])	Greater Than 3 (n=233 [23.4])	
Age (y)	28.8±4.8	28.6±4.8	29.4±4.8	.02
Partner age (y)	30.1±5.4	29.8±5.3	31.0±5.7	.01
BMI (kg/m^2)	26.2±6.5	26.0±6.4	27.2±7.0	.01
Race				.001
White	955 (95.7)	741 (96.9)	214 (91.9)	
Nonwhite	43 (4.3)	24 (3.1)	19 (8.2)	
Education				<.001
More than high school	871 (87.2)	683 (89.2)	188 (80.7)	
High school or less	126 (12.6)	81 (10.6)	45 (19.3)	
Low-dose aspirin treatment	499 (50.0)	388 (50.7)	111 (47.6)	.42
Smoking in past year				.003
No	952 (95.4)	738 (96.5)	214 (91.9)	
Yes	46 (4.6)	27 (3.5)	19 (8.2)	
Alcohol consumption in past year				.05
Never	656 (65.7)	516 (67.4)	140 (60.1)	
Sometimes	313 (31.3)	237 (31.0)	86 (36.9)	
Often	21 (2.1)	14 (1.8)	7 (3.0)	
Coffee consumer	272 (27.3)	201 (26.3)	71 (30.5)	.20
Physical activity				.91
Low	251 (25.2)	190 (24.8)	61 (26.2)	
Moderate	419 (42.0)	322 (42.1)	97 (41.6)	
High	328 (32.9)	253 (33.1)	75 (32.2)	
Income ($)				.77
100,000 or greater	393 (39.4)	293 (38.3)	100 (42.9)	
75,000–99,999	123 (12.3)	96 (12.6)	27 (11.6)	
40,000–74,999	152 (15.2)	117 (15.3)	35 (15.0)	
20,000–39,999	255 (25.6)	211 (26.3)	54 (23.2)	
19,999 or less	75 (7.5)	58 (7.6)	17 (7.3)	
Marital status				.03
Married	917 (91.9)	712 (93.1)	205 (87.9)	
Living with a partner	57 (5.7)	39 (5.1)	18 (7.7)	
Other	24 (2.4)	14 (1.8)	10 (4.3)	
Previous subfertility	74 (7.4)	50 (6.5)	24 (10.3)	.05
Age of menarche (y)	12.7±1.5	12.5±1.5	12.8±1.5	.01
Ever hormonal prescriptions	796 (79.8)	602 (78.7)	194 (83.4)	.12
No. of previous live births				.59
0	498 (49.9)	376 (49.2)	122 (52.4)	
1	345 (34.6)	266 (34.8)	79 (33.9)	
2	155 (15.5)	123 (16.1)	32 (13.7)	
No. of previous losses				.10
1	669 (67.0)	523 (68.4)	146 (62.7)	
2	329 (33.0)	242 (31.6)	87 (37.3)	
D&C performed on prior loss	324 (32.5)	250 (32.7)	74 (31.8)	.79
Gestational age of prior loss (wk)				.01
7.99 or less	439 (44.0)	336 (43.9)	101 (43.3)	
8–13.99	503 (50.4)	397 (51.9)	106 (45.5)	
14–19.99	52 (5.2)	30 (3.9)	22 (9.4)	
20–31.99	3 (0.003)	2 (0.3)	1 (0.004)	
Age of first intercourse (y)	19.5±4.2	19.8±4.3	18.6±3.8	<.001

(*continued*)

Table 1. Demographic, Lifestyle, and Reproductive History of Effects of Aspirin in Gestation and Reproduction Study Population by Inter-trying Interval (*continued*)

Characteristic	Total (N=998)	Inter-trying Interval (Months)		*P**
		0–3 (n=765 [76.7])	Greater Than 3 (n=233 [23.4])	
Past month's intercourse frequency				.88
3–6 per week or greater	315 (31.5)	242 (31.6)	72 (30.9)	
1–2 per week to 2–3 per month	579 (58.0)	439 (57.4)	140 (60.1)	
Less than 1 per month	54 (5.4)	42 (5.5)	12 (5.2)	

SD, standard deviation; BMI, body mass index; D&C, dilation and curettage.
Data are mean±SD or n (%) unless otherwise specified.
All variables are complete except for the following missing data: n=85 for inter-trying interval (ie, did not complete question on how long they had currently been trying to conceive or did not have a documented date of last loss), n=1 for partner age, n=1 for education, n=8 for past year's alcohol consumption, n=4 for previous subfertility report, n=11 for age of menarche, n=1 for gestational age of prior loss, and n=2 for age of first intercourse.
* Analyses performed by χ^2 or Fisher exact test as appropriate for categorical variables and Student's *t* test for continuous variables.

likely to achieve a pregnancy (68.6% compared with 51.1%) and achieve a pregnancy leading to a live birth (53.2% compared with 36.1%) (Table 2). Median (interquartile range) for time to pregnancy among women with 0–3 months compared with greater than 3 months was five cycles (three, eight) compared with six cycles (three, nine) and time to pregnancy leading to live birth, five cycles (three, eight) compared with six cycles (four, nine). After adjusting for age, race, BMI, education, and subfertility, women with a 0- to 3-month compared with greater than 3-month inter-trying interval had a shorter time to pregnancy (fecundability OR 1.58 [95% CI 1.25–2.00]) and shorter time to pregnancy leading to a live birth (fecundability OR 1.71 [95% CI 1.30–2.25]) (Table 3). There was no significant increased risk for any pregnancy complication (including pregnancy loss, preterm birth, preeclampsia, and gestational diabetes) among women with an inter-trying interval 0–3 months compared with greater than 3 months. Additional adjustment for other demographic and reproductive history potential confounders including partner's age, smoking, alcohol intake, parity, previous number of losses, recency of loss, gestational age of last loss, age of first intercourse, age of menarche, and dilation and curettage performed for last loss did not alter fecundability OR (1.52 [95% CI 1.20–1.92]) or fecundability OR leading to a live birth (1.65 [95% CI 1.26–2.16]) nor did further adjustment for low-dose aspirin (Table 4).

In regard to alternative cut points for inter-trying intervals, compared with an inter-trying interval of greater than 3–6 months, women with an inter-trying interval of 0–3 months had a shorter time to

Table 2. Pregnancy Outcome of Effects of Aspirin in Gestation and Reproduction Study Population by Inter-trying Interval

Characteristic	Total (N=998)	Inter-trying Interval (Months)		*P**
		0–3 (n=765 [76.7])	Greater Than 3 (n=233 [23.4])	
Pregnancy	644 (64.5)	525 (68.9)	119 (51.1)	<.001
Live birth	491 (49.2)	407 (53.2)	84 (36.1)	<.001
Preterm birth†	22 (8.8)	19 (9.2)	3 (6.8)	.62
Peri-implantation loss	49 (4.9)	38 (5.0)	11 (4.7)	.88
Clinical loss	113 (11.2)	88 (11.5)	25 (10.7)	.74
Gestational age of loss (wk)‡	9.6±5.2	9.7±4.3	9.9±3.5	.77
Preeclampsia§	52 (8.2)	42 (8.5)	10 (7.2)	.63
Gestational diabetes§	20 (3.3)	19 (3.6)	1 (0.9)	.11

Data are n (%) or mean±SD unless otherwise specified.
* Analyses performed by χ^2 or Fisher exact test as appropriate for categorical variables and Student's *t* test for continuous variables.
† Among live births (n=491).
‡ Among those with a clinical loss (n=113).
§ Among women achieving pregnancy (n=644).

Table 3. Fecundability Odds Ratio for Pregnancy and Pregnancy Leading to Live Birth by Inter-trying Interval (0–3 Months vs Greater Than 3 Months)

Inter-trying Interval	Pregnancy	Unadjusted	Adjusted Model 1*	Adjusted Model 2†	Sensitivity Analysis 1‡	Sensitivity Analysis 2§
Time to pregnancy (mo)						
0–3	525 (68.9)	1.69 (1.35–2.13)	1.58 (1.25–2.00)	1.52 (1.20–1.92)	1.31 (1.03–1.67)	1.35 (1.07–1.73)
Greater than 3	119 (51.1)	1.0	1.0	1.0	1.0	1.0
Time to pregnancy leading to live birth (mo)						
0–3	407 (53.2)	1.85 (1.42–2.41)	1.71 (1.30–2.25)	1.65 (1.26–2.16)	1.49 (1.13–1.99)	1.56 (1.18–2.06)
Greater than 3	84 (36.1)	1.0	1.0	1.0	1.0	1.0

Data are n (%) or fecundability odds ratio (95% confidence interval).
* Adjusted for age, race, body mass index, education, and subfertility.
† Adjusted for Model 1 covariates plus partner's age, smoking, alcohol intake, parity, previous number of losses, recency of loss, gestational age of last loss, age of first intercourse, age of menarche, and dilation and curettage performed for last loss.
‡ Sensitivity analysis using multiple imputation to discern the plausible values for delayed entry times. Model 1 adjustments.
§ Sensitivity analysis using Monte Carlo simulations to randomly assign time at risk for those couples with implausible values for time trying to conceive. Average fecundability odds ratio (95% confidence interval) reported for 500 simulations. Model 1 adjustment.

pregnancy, with a fecundability OR of 1.24 (0.90–1.72). Women with longer inter-trying intervals had longer times to pregnancy (inter-trying interval greater than 6–9 months: fecundability OR 0.90, 95% CI 0.44–1.83; inter-trying interval greater than 9–12 months: fecundability OR 0.83, 95% CI 0.38–1.81; inter-trying interval greater than 12 months: fecundability OR 0.60, 95% CI 0.38–0.95) after adjusting for age, race, BMI, education, and subfertility. Similar decreased success in achieving pregnancy leading to live birth was seen with increasing inter-trying intervals (data not shown).

In the sensitivity analysis using multiply imputed values for the misspecified inter-trying intervals, women with a 0- to 3-month compared with a greater than 3-month inter-trying interval had an attenuated but still significantly shorter time to pregnancy (fecundability OR 1.31 [95% CI 1.03–1.67]) and time to pregnancy leading to live birth (fecundability OR 1.49 [95% CI 1.13–1.99]). Similar shorter time to pregnancy was observed after applying Monte Carlo simulation techniques to randomly assign time at risk for those couples who had included time before their loss when reporting how long they had been trying to

Table 4. Fecundability Odds Ratios for Pregnancy and Pregnancy Leading to Live Birth by Inter-trying Interval (0–3 Months vs Greater Than 3 Months) Stratified by Low-Dose Aspirin Treatment

Inter-trying Interval	Pregnancy	Unadjusted	Adjusted Model 1*	Adjusted Model 2†
Low-dose aspirin treatment				
Time to Pregnancy (mo)				
0–3 mo	278 (71.7)	1.65 (1.21–2.26)	1.50 (1.09–2.06)	1.46 (1.06–2.02)
Greater than 3 mo	61 (55.0)	1.0	1.0	1.0
Time to pregnancy leading to a live birth (mo)				
0–3	216 (55.7)	1.69 (1.18–2.41)	1.52 (1.06–2.18)	1.50 (1.04–2.16)
Greater than 3	46 (41.4)	1.0	1.0	1.0
Placebo				
Time to pregnancy (mo)				
0–3	247 (65.5)	1.70 (1.22–2.35)	1.60 (1.14–2.24)	1.54 (1.10–2.16)
Greater than 3	58 (47.5)	1.0	1.0	1.0
Time to pregnancy leading to a live birth (mo)				
0–3 mo	191 (50.7)	1.98 (1.34–2.93)	1.86 (1.24–2.78)	1.83 (1.21–2.77)
Greater than 3 mo	38 (31.2)	1.0	1.0	1.0

Data are n (%) or fecundability odds ratio (95% confidence interval).
* Adjusted for age, race, body mass index, education, and subfertility.
† Adjusted for Model 1 covariates plus partner's age, smoking, alcohol intake, parity, previous number of losses, recency of loss, gestational age of last loss, age of first intercourse, age of menarche, and dilation and curettage performed for last loss.

conceive (average fecundability OR for pregnancy 1.35, 95% CI 1.07–1.73) and pregnancy leading to a live birth (fecundability OR 1.56, [95% CI 1.18–2.06]).

DISCUSSION

In a preconception cohort of women with a history of one to two spontaneous pregnancy losses, women who waited 3 months or less, compared with longer, from their most recent pregnancy loss to start trying again had higher live birth rates. Notably, women with the longest inter-trying interval of greater than 12 months had reduced fecundability compared with women with an inter-trying interval of 0–3 or greater than 3–6 months. Our findings also demonstrated no increased risk for pregnancy complications, including peri-implantation losses, among women with short intervals. Our results indicate that there is no physiologic basis for delaying pregnancy attempt after a nonectopic, nonmolar, less than 20-week gestational age pregnancy loss. Recommendations to delay pregnancy attempts for at least 3–6 months among couples who are psychologically ready to begin trying[4,26,27] may be unwarranted and should be revisited.

Although several professional women's health organizations concur on the recommended interval of at least 24 months after a live birth before attempting another pregnancy,[27] there are no consistent guidelines on how long a woman should wait after experiencing a pregnancy loss. The "depletion hypothesis" may partially explain potential detrimental effects for a short interval between a live birth, but not a pregnancy loss, and a subsequent pregnancy.[11,28] This hypothesis proposes that decreasing levels of folate in the mother from the fifth month of gestation, continuing into the postpartum period during breastfeeding, lead to poorer birth outcomes including neural tube defects, intrauterine growth restriction, and preterm birth among women with short interpregnancy intervals. Because most pregnancy losses occur before 20 weeks of gestation, like in our study in which greater than 99% occurred before 20 weeks of gestation, women conceiving after an early pregnancy loss are not at risk for depletion of vital nutrients and consequently not likely at risk for adverse outcomes. Hypothesized advantages to attempting pregnancy immediately after a pregnancy loss include enhanced growth-supporting capacities and increased uterine blood volume and flow.[7]

Although our study supports the hypothesis that there is no physiologic reason for delaying pregnancy attempt after a loss, whether a couple needs time to heal emotionally after a loss may be dependent on many factors. Although emotional compared with physical readiness may require individual couple assessment, previous research has found that a speedy new pregnancy and birth of a living child lessens grief among couples who are suffering from a pregnancy loss.[29]

Our study has many strengths and is an improvement over previous studies given that we enrolled women preconceptionally; obtained detailed demographic, lifestyle, and reproductive history information before conception; and closely followed participants through delivery with details of pregnancy outcomes carefully and objectively determined. Although these differences in demographic and reproductive history characteristics were statistically different, they are unlikely to be clinically meaningful. Nevertheless, our study is not without limitations. Although information on prior loss was obtained through medical records, our assessment of starting to try to conceive after the last loss was obtained by self-report and thus subject to recall error. However, there is no other source of these data than self-report. Additionally, there may be differences between women with equivalent inter-trying intervals in regard to time at risk of pregnancy as a result of such factors as fertility tracking or intercourse frequency. Future studies that enroll women preconceptionally immediately after a loss and follow them prospectively through pregnancy outcome are needed to corroborate our findings. Finally, although low-dose aspirin was shown to neither confound nor modify the relationship between inter-trying intervals and pregnancy outcomes, it is currently not part of routine care among women with an early pregnancy loss and thus additional studies are warranted to corroborate our findings.

In summary, we previously reported that women in the Effects of Aspirin in Gestation and Reproduction trial who achieved pregnancy within 3 compared with greater than 3 months of their last loss had no significant differences in live birth rates or adverse pregnancy outcomes.[18] In the present study we demonstrate that couples who begin trying to achieve pregnancy within 3 months have just as fast, if not faster, time to pregnancy leading to a live birth, with no risk of pregnancy complications, as those who wait until after 3 months to start trying. Additionally, we found that women with long inter-trying intervals, greater than 12 months compared with 0–3 or greater than 3–6 months, had significantly lower fecundability after taking into account many confounding factors including a history of subfertility. Taken together, our findings suggest that the traditional recommendation to wait at least 3 months after a pregnancy loss before attempting to conceive may be unwarranted.

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