



# HHS Public Access

Author manuscript

*Obstet Gynecol.* Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

*Obstet Gynecol.* 2016 February ; 127(2): 204–212. doi:10.1097/AOG.0000000000001159.

## Trying to Conceive After an Early Pregnancy Loss: An Assessment on How Long Couples Should Wait

Karen C. Schliep, PhD<sup>1,2</sup>, Emily M. Mitchell, PhD<sup>1</sup>, Sunni L. Mumford, PhD<sup>1</sup>, Rose G. Radin, PhD<sup>1</sup>, Shvetha M. Zarek, MD<sup>1,3</sup>, Lindsey Sjaarda, PhD<sup>1</sup>, and Enrique F. Schisterman, PhD<sup>1</sup>

<sup>1</sup>Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD, United States

<sup>2</sup>Division of Public Health, Department of Family & Preventive Medicine, University of Utah, Salt Lake City, UT, United States

<sup>3</sup>Program of Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health & Human Development, Bethesda, MD, United States

### Abstract

**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 1–2 prior early losses and whose last pregnancy outcome was a non-ectopic or non-molar 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 (OR) adjusting for age, race, BMI, education, and subfertility. While 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 (n=765 [76.7%]) versus >3 month (n=233 [23.4%]) interval were more likely to achieve a live birth (53.2% versus 36.1%) with a significantly shorter time to pregnancy leading to live birth (median (IQR) 5 cycles (3, 8), adjusted fecundability OR: 1.71 [95% CI: 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 physiological evidence for delaying pregnancy attempt after an early loss.

---

**Corresponding author:** Enrique F. Schisterman, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development 6100 Executive Blvd., 7B03; Rockville, MD 20852; Phone (301) 435-6893; schistee@mail.nih.gov..

**Financial Disclosure:** The authors did not report any potential conflicts of interest.

Presented in part at the annual meeting of the Society for Epidemiologic Research, Denver CO, June 17, 2015.

## INTRODUCTION

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 following an early loss (7).

Most studies addressing pregnancy spacing concentrate on the interval between live births and subsequent pregnancies (interpregnancy interval [IPI]), with the majority of findings indicating that an IPI 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 following a non-ectopic, non-molar, <20-week gestational age pregnancy loss. Studies to date have been limited in enrolling already pregnant women and then determining how their IPI affects pregnancy outcomes (6, 11-14). While these studies answer the question of “When should couples *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 intertrying 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 women who started trying to conceive within versus greater than 3 months of their pregnancy loss.

## MATERIALS AND METHODS

The Effects of Aspirin in Gestation and Reproduction (EAGeR) trial (2007–2011), a multicenter, block-randomized, double-blinded, 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 1228 women, aged 18–40, 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 a spontaneous abortion (n=1071, 98.9%) or a planned termination (n=12, 1.1%) were included in this analysis while women whose last outcome was a 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 of 19 weeks gestation, with 54.1% having had a last loss of 8 weeks).

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 (IRB) at each site, with each site serving as the IRB designated by the National

Institutes of Health under a reliance agreement. All participants gave written informed consent prior to 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 time from last pregnancy loss to time attempting a subsequent conception (Figure 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 via a standardized form. Additionally, each participant completed an extensive health and reproductive history questionnaire at baseline. The majority of women (n=1041, 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 1074 (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?" with answers completed in number of months (1006 [92.9%] completed the question). When the reported date of initiation of trying to conceive was reported as occurring prior to the date of last loss, the intertrying interval was defined as zero months, i.e, assuming no interruption in attempting conception. From the 1074 women with a documented loss date and the 1006 women who responded to the specific intertrying interval question, we were able to successfully calculate the intertrying interval for 998 women (92.2%). As outlined below, multiple imputation was used to impute intertrying intervals for the remaining 85 women (17) (Figure 2).

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

For the primary statistical analyses, the intertrying interval was categorized dichotomously (0 to 3 months, > 3 months), based on prior recommendations on intertrying interval and pregnancy loss (3, 12). We additionally assessed intertrying interval based on 3-month intervals (0–3, >3–6, >6–9, >9–12, and >12 months). Participant demographic, lifestyle, and reproductive history characteristics between intertrying intervals (0 to 3 months, > 3 months) were compared using chi-squared or where appropriate Fisher's exact test for categorical variables, and Student's *t* test for continuous variables.

Among women who achieved pregnancy, time to pregnancy was defined as conception cycle (via 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 since this is the unit used for relevant recommendations (5). Women who did not achieve pregnancy were censored at end of follow-up or withdrawal date. Discrete Cox proportional hazards regression models were used to estimate the fecundability odds ratio (FOR) and 95%

confidence intervals (CI) corresponding to the cycle-specific probability of conception. In order to account for left truncation (21), time trying to achieve pregnancy as indicated by number of menstrual cycles prior to 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 odds ratios, where women achieving pregnancy that ended in a loss were censored at the time of positive pregnancy test (22).

Based on a review of the prior literature, we considered the potential confounders of age (continuous), partner's age (continuous), BMI (continuous), race (white vs. non-white), education (> versus high school), income ( \$19K, \$20–39K, \$40–74K, \$75–99K, \$ 100K), smoking (never, sometimes, daily), alcohol (never, sometimes, daily), physical activity (low, moderate, high), marital status (married vs. other), subfertility (yes vs. no with yes being a report of ever trying for more than 12 months to achieve a pregnancy), parity (0, 1, 2), prior number of losses (1 or 2), gestational age of prior loss (continuous), and whether a dilation and curettage (D & C) was performed for last loss (yes vs. no). While we did not consider treatment as a confounder given that our exposure (intertrying interval) was assessed prior to 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 impute missing exposure and covariate data (17), thus all 1083 women were included in all analyses performed. Analyses were conducted using SAS software (version 9.4; SAS Institute, Inc) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

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 prior to 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. While this is an improvement compared to dropping these women from the analyses altogether, this strategy may still result in misclassification of intertrying 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 FOR 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 impute plausible values for delayed entry times were applied based on potential predictors of this value. Additionally, as an alternate strategy, we applied Monte Carlo sampling techniques to randomly assign a feasible time at risk for those couples reporting implausible intertrying interval values. This procedure was performed 500 times, and average FORs and 95% CIs were calculated using Rubin's combining rules (25).

## RESULTS

The majority of women (76.6%) had an intertrying interval of 0–3 months while 23.4% had an intertrying interval of >3 months (9.0% >3–6 months, 2.3% >6–9 months, 1.7% >9–12 months, and 10.3% >12 months). Women with a 0–3 month versus >3 month intertrying interval were slightly younger (mean 28.6 years versus 29.4 years), had a partner slightly younger (mean 29.8 years versus 31.0 years), lower BMI (mean 26.0 kg/m<sup>2</sup> versus 27.2 kg/m<sup>2</sup>), more likely to be white (96.9% versus 91.9%), have above a high school education (89.4% versus 80.7%), never smokers (96.5% versus 91.9%), and more likely to be married (93.1% versus 87.9%) (Table 1). In terms of reproductive history, women with a 0–3 month versus >3 month intertrying interval had less frequently reported subfertility (6.6% versus 10.3%), a slightly younger age of menarche (12.5 years versus 12.8 years), younger gestational age of last loss, and an older age of first intercourse (mean age 19.8 years versus 18.6 years).

Women with a 0–3 month versus >3 month intertrying interval were more likely to achieve a pregnancy (68.6% versus 51.1%) and achieve a pregnancy leading to a live birth (53.2% versus 36.1%) (Table 2). Median (IQR) for time to pregnancy among women with 0–3 month versus >3 month was 5 cycles (3, 8) versus 6 cycles (3, 9) and time to pregnancy leading to live birth, 5 cycles (3, 8) versus 6 cycles (4, 9). After adjusting for age, race, BMI, education, and subfertility, women with a 0–3 month versus >3 month intertrying interval had a shorter time to pregnancy (FOR: 1.58 [95% CI: 1.25, 2.00]) and shorter time to pregnancy leading to a live birth (FOR: 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 intertrying interval 0–3 months versus >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 D & C performed for last loss did not alter FOR (1.52 [95% CI: 1.20, 1.92]) or FOR leading to a live birth (1.65 [95% CI: 1.26, 2.16]), nor did further adjustment for low-dose aspirin (Table 4).

In regards to alternative cut points for intertrying intervals, compared to an intertrying interval of >3–6 months, women with an intertrying interval 0–3 months had shorter time to pregnancy with a FOR of 1.24 (0.90, 1.72), while women with longer intertrying intervals had longer time to pregnancies: intertrying interval >6–9 months (FOR: 0.90, 95% CI: 0.44, 1.83); intertrying interval >9–12 months (FOR: 0.83, 95% CI: 0.38, 1.81); >12 months (FOR 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 intertrying intervals (data not shown).

In the sensitivity analysis using multiply imputed values for the misspecified intertrying intervals, women with a 0–3 month versus a >3 month intertrying interval had an attenuated but still significantly shorter time to pregnancy (FOR: 1.31 [95% CI: 1.03, 1.67]) and time to pregnancy leading to live birth (FOR: 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 prior to their loss when reporting how long they had been trying to conceive, average FOR for pregnancy, 1.35 (95% CI: 1.07, 1.73) and pregnancy leading to a live birth, 1.56 (95% CI: 1.18, 2.06).

## DISCUSSION

In a preconception cohort of women with a history of 1–2 spontaneous pregnancy losses, women who waited 3 months or less, versus longer, from their most recent pregnancy loss to start trying again had higher live birth rates. Notably, women with the longest intertrying interval of >12 months had reduced fecundability compared to women with an intertrying interval of 0–3 or >3–6 months. Our findings also demonstrated no increased risk for pregnancy complications, including peri-implantation losses, among women with a short interval. Our results indicate that there is no physiologic basis for delaying pregnancy attempt after a non-ectopic, non-molar, <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.

While 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 inter-pregnancy intervals. As most pregnancy losses occur prior to 20 weeks of gestation, as in our study where >99% occurred prior to 20 weeks, 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).

While our study supports the hypothesis that there is no physiological reason for delaying pregnancy attempt after a loss, whether a couple needs time to heal emotionally following a loss may be dependent on many factors. While emotional versus 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 pre-conceptionally, obtained detailed demographic, lifestyle, and reproductive history information prior to conception, and closely followed participants through delivery with details of pregnancy outcomes carefully and objectively determined. While 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. While information on prior loss was obtained via medical records, our assessment of starting to try to conceive after the last loss was obtained via self-report and thus subject to recall error. However, there is no other source of this data than self-report. Additionally, there may be differences between women with equivalent intertrying intervals in regards to time at risk of pregnancy due to such factors as fertility tracking or intercourse frequency. Future studies that enroll women pre-conceptionally immediately after a loss, and follow them prospectively through pregnancy outcome are needed to corroborate our findings. Finally, while low-dose aspirin was shown to neither confound nor modify the relationship between intertrying 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 EAGeR trial who achieved pregnancy within 3 versus > 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 women 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 women who wait until after 3 months to start trying. Additionally, we found that women with a long intertrying interval, >12 months versus 0–3 or >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.

## Acknowledgments

Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland (Contract Nos. HHSN267200603423, HHSN267200603424, HHSN267200603426).

## REFERENCES

1. Rai R, Regan L. Recurrent miscarriage. *Lancet*. 2006; 12(368):601–11. [PubMed: 16905025]
2. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. *N Engl J Med*. 1988; 28(319):189–94. [PubMed: 3393170]
3. Katz, VL. Spontaneous and recurrent abortion: etiology, diagnosis, treatment. *Comprehensive gynecology*. In: Katz, VL.; Lentz, GM.; Lobo, RA.; Gershenson, DM., editors. *Comprehensive Gynecology*. 5th. Mosby Elsevier; Philadelphia (PA): 2007. p. 381
4. After a Miscarriage: Getting Pregnant Again Pregnancy Loss. Available at: <http://americanpregnancy.org/pregnancy-loss/after-miscarriage-getting-pregnant-again/>. Retrieved June 13, 2015
5. World Health Organization. Report of a WHO technical consultation on birth spacing, Geneva Switzerland 13-15 June 2005. Available at: [http://www.who.int/maternal\\_child\\_adolescent/documents/birth\\_spacing.pdf](http://www.who.int/maternal_child_adolescent/documents/birth_spacing.pdf). Accessed June 13, 2015
6. Conde-Agudelo A, Belizan JM, Breman R, Brockman SC, Rosas-Bermudez A. Effect of the interpregnancy interval after an abortion on maternal and perinatal health in Latin America. *Int J Gynaecol Obstet*. 2005; 89(Suppl 1):S34–40. [PubMed: 15820366]
7. Zhu BP, Rolfs RT, Nangle BE, Horan JM. Effect of the interval between pregnancies on perinatal outcomes. *N Engl J Med*. 1999; 340:589–94. [PubMed: 10029642]

8. Fuentes-Afflick E, Hessol NA. Interpregnancy interval and the risk of premature infants. *Obstet Gynecol.* 2000; 95:383–90. [PubMed: 10711549]
9. Zhu BP, Haines KM, Le T, McGrath-Miller K, Boulton ML. Effect of the interval between pregnancies on perinatal outcomes among white and black women. *Am J Obstet Gynecol.* 2001; 185:1403–10. [PubMed: 11744916]
10. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA.* 2006; 295:1809–23. [PubMed: 16622143]
11. Love ER, Bhattacharya S, Smith NC, Bhattacharya S. Effect of interpregnancy interval on outcomes of pregnancy after miscarriage: retrospective analysis of hospital episode statistics in Scotland. *BMJ.* 2010; 341:c3967. [PubMed: 20688842]
12. Bentolila Y, Ratzon R, Shoham-Vardi I, Serjienko R, Mazor M, Bashiri A. Effect of interpregnancy interval on outcomes of pregnancy after recurrent pregnancy loss. *J Matern Fetal Neonatal Med.* 2013; 26:1459–64. [PubMed: 23488821]
13. Davanzo J, Hale L, Rahman M. How long after a miscarriage should women wait before becoming pregnant again? Multivariate analysis of cohort data from Matlab, Bangladesh. *BMJ Open.* 2012; 2:e001591.
14. El Behery MM, Siam S, Seksaka MA, Ibrahim ZM. Reproductive performance in the next pregnancy for nulliparous women with history of first trimester spontaneous abortion. *Arch Gynecol Obstet.* 2013; 288:939–44. [PubMed: 23564054]
15. Schisterman EF, Silver RM, Leshner LL, Faraggi D, Wactawski-Wende J, Townsend JM. Preconception lowdose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet.* 2014; 384:29–36. [PubMed: 24702835]
16. Schisterman EF, Silver RM, Perkins NJ, Mumford SL, Whitcomb BW, Stanford JB, et al. A Randomised Trial to Evaluate the Effects of Low-dose Aspirin in Gestation and Reproduction: Design and Baseline Characteristics. *Paediatr Perinat Epidemiol.* 2013; 27:598–609. [PubMed: 24118062]
17. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med.* 2010; 29:2920–31. [PubMed: 20842622]
18. Wong LF, Schliep KC, Silver RM, Mumford SL, Perkins NJ, Ye A, et al. The effect of a very short interpregnancy interval and pregnancy outcomes following a previous pregnancy loss. *Am J Obstet Gynecol.* 2015; 212:375.e1–11. [PubMed: 25246378]
19. Silver RM, Branch DW, Goldenberg R, Iams JD, Klebanoff MA. Nomenclature for pregnancy outcomes: time for a change. *Obstet Gynecol.* 2011; 118:1402–8. [PubMed: 22105271]
20. Weinberg, C.; Wilcox, A.; Rothman, KJ.; Greenland, S.; Lash, TL. *Modern Epidemiology*. 3rd. Lippencott Williams & Wilkins; Philadelphia (PA): 2008. Methodologic Issues in Reproductive Epidemiology; p. 585-608.
21. Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy loss due to selection bias in cohort studies with left truncation. *Paediatr Perinat Epidemiol.* 2013; 27:491–502. [PubMed: 23930785]
22. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol.* 2009; 170:244–56. [PubMed: 19494242]
23. Schisterman EF, Mumford SL, Schliep KC, Sjaarda LA, Stanford JB, Leshner LL, et al. Preconception low dose aspirin and time to pregnancy: findings from the effects of aspirin in gestation and reproduction randomized trial. *J Clin Endocrinol Metab.* 2015; 100:1785–91. [PubMed: 25710565]
24. Hauck WW, Anderson S, Marcus SM. Should we adjust for covariates in nonlinear regression analyses of randomized trials? *Control Clin Trials.* 1998; 19:249–56. [PubMed: 9620808]
25. Rubin, DB. *Multiple Imputation for Nonresponse in Surveys*. J. Wiley & Sons; New York: 1987.
26. Daugirdaite V, van den Akker O, Purewal S. Posttraumatic stress and posttraumatic stress disorder after termination of pregnancy and reproductive loss: a systematic review. *J Pregnancy.* 2015:646345. [PubMed: 25734016]
27. Goldstein RR, Croughan MS, Robertson PA. Neonatal outcomes in immediate versus delayed conceptions after spontaneous abortion: a retrospective case series. *Am J Obstet Gynecol.* 2002; 186:1230–34. [PubMed: 12066103]



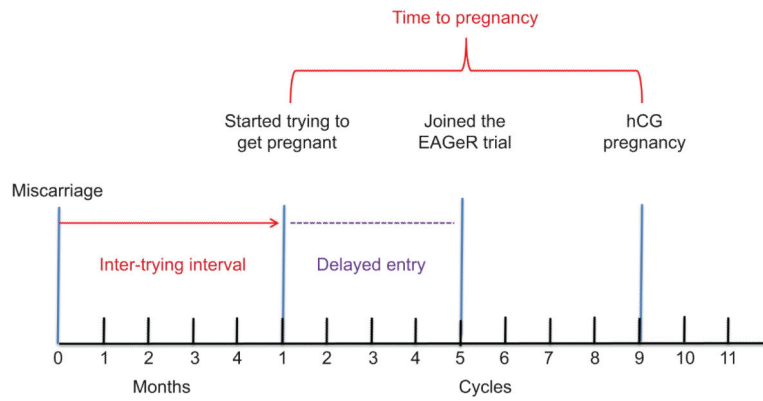
28. Smits LJ, Essed GG. Short interpregnancy intervals and unfavourable pregnancy outcome: role of folate depletion. *Lancet*. 2001; 358:2074–77. [PubMed: 11755634]
29. Cuisinier M, Janssen H, de Graauw C, Bakker S, Hoogduin C. Pregnancy following miscarriage: course of grief and some determining factors. *J Psychosom Obstet Gynaecol*. 1996; 17:168–74. [PubMed: 8892163]

Author Manuscript

Author Manuscript

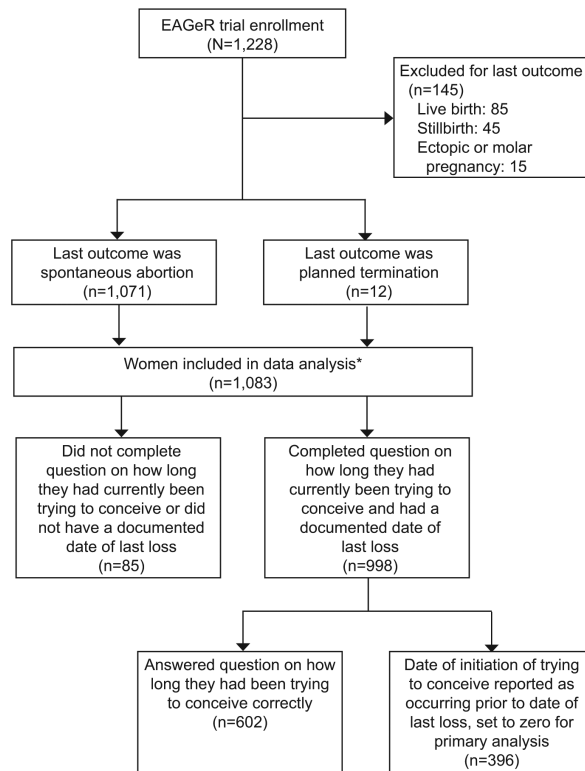
Author Manuscript

Author Manuscript



**Figure 1.**

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



**Figure 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 due to missing information.

**Table 1**

Demographic, lifestyle, and reproductive history of Effects of Aspirin in Gestation and Reproduction study population by inter-trying interval (ITI)\*

Characteristics	Total n=998	Inter-trying interval		P-value <sup>1</sup>
		0-3mo n=765 (76.7)	>3mo n=233 (23.4)	
Age, years (mean ± SD)	28.8 ± 4.8	28.6 ± 4.8	29.4 ± 4.8	0.02
Partner age, years (mean ± SD)	30.1 ± 5.4	29.8 ± 5.3	31.0 ± 5.7	0.01
BMI, kg/m <sup>2</sup> (mean ± SD)	26.2 ± 6.5	26.0 ± 6.4	27.2 ± 7.0	0.01
Race				0.001
White	955 (95.7)	741 (96.9)	214 (91.9)	
Non-White	43 (4.3)	24 (3.1)	19 (8.2)	
Education				<0.001
> High School	871 (87.2)	683 (89.2)	188 (80.7)	
High School	126 (12.6)	81 (10.6)	45 (19.3)	
Low-dose aspirin Treatment	499 (50.0)	388 (50.7)	111 (47.6)	0.42
Smoking in past year				0.003
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				0.05
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)	0.20
Physical Activity				0.91
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				0.77
\$100 000	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	75 (7.5)	58 (7.6)	17 (7.3)	
Marital Status				0.03
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)	0.05
Age of Menarche (years)	12.7 ± 1.5	12.5 ± 1.5	12.8 ± 1.5	0.01
Ever Hormonal Prescriptions	796 (79.8)	602 (78.7)	194 (83.4)	0.12
Previous Number of Live Births				0.59

Characteristics	Inter-trying interval			P-value <sup>1</sup>
	Total n=998	0-3mo n=765 (76.7)	>3mo n=233 (23.4)	
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)	
Previous Number of Losses				0.10
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)	0.79
Gestational age of prior loss (weeks)				0.01
7.99	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 (years)	19.5 ± 4.2	19.8 ± 4.3	18.6 ± 3.8	<0.001
Past month's intercourse frequency				0.88
3-6 per week	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)	
<1 per month	54 (5.4)	42 (5.5)	12 (5.2)	

\* Analyses performed via chi-square or Fisher's exact test as appropriate for categorical variables and Student's *t* test for continuous variables. Values reported are n (%) unless otherwise noted. All variables are complete except for missing n=85 for ITI (i.e., 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, n=2 for age of first intercourse, and

**Table 2**

Pregnancy outcome of Effects of Aspirin in Gestation and Reproduction study population by intertryping interval

Characteristics	Intertryping Interval			P-value*
	Total n=998	0-3mo n=765 (76.7%)	>3mo n=233 (23.4%)	
Pregnancy (n [%])	644 (64.5)	525 (68.9)	119 (51.1)	<0.001
Live birth (n [%])	491 (49.2)	407 (53.2)	84 (36.1)	<0.001
Preterm birth <sup>†</sup>	22 (8.8)	19 (9.2)	3 (6.8)	0.62
Peri-implantation Loss (n [%])	49 (4.9)	38 (5.0)	11 (4.7)	0.88
Clinical Loss (n [%])	113 (11.2)	88 (11.5)	25 (10.7)	0.74
Gestational Age of Loss <sup>‡</sup>	9.6 ± 5.2	9.7 ± 4.3	9.9 ± 3.5	0.77
Pre-eclampsia <sup>§</sup>	52 (8.2)	42 (8.5)	10 (7.2)	0.63
Gestational Diabetes <sup>§</sup>	20 (3.3)	19 (3.6)	1 (0.9)	0.11

\* Analyses performed via chi-square or Fisher's exact test as appropriate for categorical variables and Student's *t* test for continuous variables.

<sup>†</sup> Among the live births (n=491)

<sup>‡</sup> Among those with a clinical loss (n=113)

<sup>§</sup> Among women achieving pregnancy (n=644)

Fecundability odds ratio for pregnancy and pregnancy leading to a live birth (95% CI) by intertrying interval (0–3 months versus >

**Table 3**

Time to pregnancy		FOR (95% CI)				
Intertrying interval	Pregnancy n (%)	Unadjusted	Adjusted Model 1*	Adjusted Model 2†	Sensitivity Analysis 1‡	Sensitivity Analysis 2§
0–3 months	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)
>3 months	119 (51.1)	1.0	1.0	1.0	1.0	1.0
Time to pregnancy leading to live birth		FOR (95% CI)				
0–3 months	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)
>3 months	84 (36.1)	1.0	1.0	1.0	1.0	1.0

**3 months)**

\* Adjusted for age, race, BMI, 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 D & C performed for last loss

‡ Sensitivity analysis using multiple imputation to impute 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 FOR [95% CI] reported for 500 simulations. Model 1 adjustment.

**Table 4**

Fecundability odds ratio (FOR) for pregnancy and pregnancy leading to a live birth (95% CI) by inter-trying interval (0–3 months versus > 3 months) stratified by LDA treatment

LDA Treatment		FOR (95% CI)	
Time to Pregnancy			
Inter-trying interval	Pregnancy n (%)	Unadjusted	Adjusted Model 1* Adjusted Model 2†
0–3 months	278 (71.7)	1.65 (1.21, 2.26)	1.50 (1.09, 2.06) 1.46 (1.06, 2.02)
>3 months	61 (55.0)	1.0	1.0
Time to Pregnancy Leading to a Live Birth		FOR (95% CI)	
Inter-trying interval	Pregnancy n (%)	Unadjusted	Adjusted Model 1* Adjusted Model 2†
0–3 months	216 (55.7)	1.69 (1.18, 2.41)	1.52 (1.06, 2.18) 1.50 (1.04, 2.16)
>3 months	46 (41.4)	1.0	1.0
Placebo		FOR (95% CI)	
Time to Pregnancy			
Inter-trying interval	Pregnancy n (%)	Unadjusted	Adjusted Model 1* Adjusted Model 2†
0–3 months	247 (65.5)	1.70 (1.22, 2.35)	1.60 (1.14, 2.24) 1.54 (1.10, 2.16)
>3 months	58 (47.5)	1.0	1.0
Time to Pregnancy Leading to a Live Birth		FOR (95% CI)	
Inter-trying interval	Pregnancy n (%)	Unadjusted	Adjusted Model 1* Adjusted Model 2†
0–3 months	191 (50.7)	1.98 (1.34, 2.93)	1.86 (1.24, 2.78) 1.83 (1.21, 2.77)
>3 months	38 (31.2)	1.0	1.0

\* Adjusted for age, race, BMI, education, and subfertility.



<sup>†</sup> 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 D & C performed for last loss.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript