OBSTETRICS

The effect of a very short interpregnancy interval and pregnancy outcomes following a previous pregnancy loss

Luchin F. Wong, MD; Karen C. Schliep, PhD; Robert M. Silver, MD; Sunni L. Mumford, PhD; Neil J. Perkins, PhD; Aijun Ye, PhD; Noya Galai, PhD; Jean Wactawski-Wende, PhD; Anne M. Lynch, MD; Janet M. Townsend, MD; David Faraggi, PhD; Enrique F. Schisterman, PhD

OBJECTIVE: We sought to assess the relationship between a short interpregnancy interval (IPI) following a pregnancy loss and subsequent live birth and pregnancy outcomes.

STUDY DESIGN: A secondary analysis of women enrolled in the Effects of Aspirin in Gestation and Reproduction trial with a human chorionic gonadotropin–positive pregnancy test and whose last reproductive outcome was a loss were included in this analysis (n = 677). IPI was defined as the time between last pregnancy loss and last menstrual period of the current pregnancy and categorized by 3-month intervals. Pregnancy outcomes include live birth, pregnancy loss, and any pregnancy complications. These were compared between IPI groups using multivariate relative risk estimation by Poisson regression.

RESULTS: Demographic characteristics were similar between IPI groups. The mean gestational age of prior pregnancy loss was 8.6 ± 2.8 weeks. The overall live birth rate was 76.5%, with similar live birth rates between those with IPI ≤3 months as compared to IPI >3 months (adjusted relative risk [aRR], 1.07; 95% confidence interval [CI], 0.98–1.16). Rates were also similar for periimplantation loss (aRR, 0.95; 95% CI, 0.51–1.80), clinically confirmed loss (aRR, 0.75; 95% CI, 0.51–1.10), and any pregnancy complication (aRR, 0.88; 95% CI, 0.71–1.09) for those with IPI ≤3 months as compared to IPI >3 months.

CONCLUSION: Live birth rates and adverse pregnancy outcomes, including pregnancy loss, were not associated with a very short IPI after a prior pregnancy loss. The traditional recommendation to wait at least 3 months after a pregnancy loss before attempting a new pregnancy may not be warranted.

Key words: interpregnancy interval, miscarriage, pregnancy loss, pregnancy outcomes, spontaneous abortion

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Pregnancy loss is the most frequent complication of early pregnancy (most commonly occurring <10 weeks' gestation) and affects approximately 12-15% of clinically recognized pregnancies.[1,2] After a pregnancy loss, couples often seek counseling on how long they should wait before attempting to conceive. The length of delay is of particular concern for women who may be subfertile or who are >35 years of age.

Most studies addressing interpregnancy interval (IPI) concentrate on the interval between live births and subsequent pregnancies. There is considerable evidence that an IPI <18 months after a term or preterm delivery is associated with an increased risk for poor maternal and perinatal outcome.[3-6] However, there is significant controversy as to what the optimal timing is for the

From the Department of Obstetrics and Gynecology, University of Utah School of Medicine, and Department of Maternal-Fetal Medicine, Intermountain Healthcare (both Drs Wong and Silver), Salt Lake City, UT; Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (Drs Schliep, Mumford, Perkins, Ye, and Schisterman); Department of Epidemiology and Environmental Health, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY (Dr Wactawski-Wende); Department of Obstetrics and Gynecology, School of Medicine, University of Colorado, Denver, CO (Dr Lynch); Department of Family, Community, and Rural Health, Commonwealth Medical College, Scranton, PA (Dr Townsend); and Department of Statistics, University of Haifa, Haifa, Israel (Drs Galai and Faraggi).

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Corresponding author: Luchin F. Wong, MD. luchin.wong@hsc.utah.edu

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next pregnancy following a pregnancy loss.

It is common practice for obstetricians to recommend waiting at least 3 months before attempting a new pregnancy after an early pregnancy loss,[7] while the World Health Organization (WHO) recommends a minimum IPI of at least 6 months after a spontaneous or elective abortion.[8,9] However, there are few data to support these recommendations and contemporary studies demonstrate an inverse relationship between the rate of live birth and increasing IPI.[10-13] Furthermore, published studies consist mostly of retrospective studies without uniformity in documentation of gestational age and outcomes, and the majority do not address very short IPI (<3 months).[9-12] Thus, our primary objective was to assess the relationship between the interval between pregnancy loss and subsequent live birth in a large cohort of women, recruited from multiple clinical centers in the United States, who were actively trying to conceive following a pregnancy loss. Our secondary objective was to explore the relationship between IPI and subsequent pregnancy complications including periimplantation and clinical loss, preterm birth, preeclampsia, and gestational diabetes.

Materials and Methods

This study is a secondary data analysis of women enrolled in the Effects of Aspirin in Gestation and Reproduction (EAGeR) trial. The EAGeR trial, a block-randomized, multicenter, double-blinded, placebo-controlled trial of preconception low-dose aspirin or placebo, enrolled 1228 women, aged 18-40 years, with a history of 1-2 pregnancy losses. Details of the study design and protocol have been published previously.[14] Women were stratified by eligibility criteria. The original eligibility stratum included women actively trying to conceive with a history of only 1 prior pregnancy loss at <20 weeks' gestation during the past year, up to 1 prior live birth, up to 1 elective termination/ectopic pregnancy, regular menstrual cycles of 21-42 days in length during the preceding 12 months, no history of diagnosed or treated infertility, and aged 18-40 years. Women in the expanded stratum included women who had 1 or 2 pregnancy losses, including those at >20 weeks' gestation, with pregnancy losses occurring >1 year prior to enrollment, and with up to 2 prior live births. All other criteria were identical between the 2 strata. Of note, 14 women withdrew immediately following randomization and were excluded from further analysis because they contributed no observed follow-up time.

The trial was conducted at 4 clinical sites in the United States with recruitment from 2007 through 2011. Women were followed for up to 6 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 prior to randomization.

Medical records were obtained documenting at least 1 of the up to 2 prior pregnancy losses with hCG, ultrasound, and/or histology. Each woman underwent an extensive questionnaire at baseline regarding her medical and obstetric history. Medical records were abstracted by trained study personnel. The majority of women (n = 653, 96.5%) had a medically documented date of last loss. For the remaining 24 women (3.5%), we relied on their self-reported date of last loss. Similarly, the majority of women (n = 589, 87.0%) had a medically documented gestational age of last loss, with an additional 86 women having a self-reported gestational age of loss.

Data for this study assessing IPI and pregnancy outcomes were limited to women whose last reproductive outcome was a pregnancy loss (n = 1074/1214, 88.5%) and subsequently became pregnant (n = 677/1214, 55.8%). Pregnancy was ascertained by a urine pregnancy test (clinic and/or home with the majority [89%] having both) and confirmed by a 6- to 7-week ultrasound. IPI was defined as the time between previous loss and the last menstrual period of the confirmed pregnancy. IPI was categorized by 3-month intervals (0-3, >3-6, >6-9, >9-12, and >12 months).

The primary outcome was live birth. Secondary outcomes included pregnancy loss, types of pregnancy loss,[15] and obstetric complications (preeclampsia, gestational diabetes, and preterm birth <37 weeks). Periimplantation loss was defined as a pregnancy loss <5 weeks with no gestational sac visible on ultrasound. Preembryonic loss was defined as a pregnancy loss at 5 0/7 to 5 6/7 weeks with visible gestational sac and/or yolk sac, but no visible embryo on ultrasound. Embryonic loss was defined as a pregnancy loss at 6 0/7 to 9 6/7 weeks of an embryo with crown-rump length (CRL) <10 mm and no visible cardiac activity on ultrasound. Fetal loss was defined as a pregnancy loss at 10 0/7- 19 6/7 weeks with documented fetal cardiac activity ≥10 weeks (CRL ≥30 mm) or passage of conceptus with CRL measuring at least 30 mm. Stillbirth was defined as a pregnancy loss of a fetus at ≥20 weeks' gestation without signs of life at the time of delivery. Clinically confirmed loss was defined as any stillbirth, preembryonic, embryonic, fetal loss, or other (including ectopic pregnancy). Preeclampsia was defined as having a systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg that did not antedate the pregnancy and presented >20 weeks' gestation on ≥2 occasions at least 4 hours apart and proteinuria ≥0.3 g in a 24-hour urine specimen or 1+ on dipstick.[16] Preterm birth was defined as any delivery <37 weeks (including spontaneous and medically indicated preterm births).

Participant demographic, lifestyle, and reproductive history characteristics between IPI were compared using χ^2 or where appropriate Fisher exact test for categorical variables, and analysis of variance for continuous variables. Multivariable Poisson regression with robust error variance (to correctly estimate SE) was used to assess the relative risk (RR) of live birth, periimplantation loss, clinical loss, or pregnancy complication by IPI category (0-3, >6-9, >9-12, and >12 vs reference of >3-6