In vitro fertilization, interpregnancy interval, and risk of adverse perinatal outcomes

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Objective: To compare associations between interpregnancy intervals (IPIs) and adverse perinatal outcomes in deliveries following IVF with deliveries following spontaneous conception or other (non-IVF) fertility treatments.
Design: Cohort using linked birth certificate and assisted reproductive technology surveillance data from Massachusetts and Michigan.
Setting: Not applicable.
Patient(s): 1,225,718 deliveries.
Intervention(s): None.
Main Outcomes Measure(s): We assessed associations between IPI and preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) according to live birth or nonlive pregnancy outcome in the previous pregnancy.
Result(s): In IVF deliveries following previous live birth, risk of PTB was 22.2% for IPI 12 to <24 months (reference); risk of PTB was higher for IPI <12 months (adjusted relative risk [aRR] 1.24, 95% confidence interval [CI] 1.09–1.41) and IPI ≥60 months (aRR 1.12, 95% CI 1.00–1.26). In non-IVF deliveries following live birth, risk of PTB was 6.4% for IPI 12 to <24 months (reference); risk of PTB was higher for IPI <12 and ≥60 months (aRR 1.19, 95% CI 1.16–1.21, for both). In both populations, U-shaped or approximately U-shaped associations were observed for SGA and LBW, although the association of IPI <12 months and SGA was not significant in IVF deliveries. In IVF and non-IVF deliveries following nonlive pregnancy outcome, IPI <12 months was not associated with increased risk of PTB, LBW, or SGA, but IPI ≥60 months was associated with significant increased risk of those outcomes in non-IVF deliveries.
Conclusion(s): Following live births, IPIs <12 or ≥60 months were associated with higher risks of most adverse perinatal outcomes in both IVF and non-IVF deliveries. (Fertil Steril® 2018;109:840–8. ©2018 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology (ART), birth intervals, interpregnancy interval, in vitro fertilization (IVF), preterm birth

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Interpregnancy interval (IPI) describes the interval from completion of one pregnancy to conception of the next pregnancy. Shorter (<12 months) and longer (≥60 months) IPIs after a live birth are associated with increased risk for adverse obstetrical and perinatal outcomes, including preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) (1–4). Adverse perinatal outcomes may be associated with short IPI because of insufficient maternal physiologic recovery from

the previous pregnancy (5–7) and with long IPI because of comorbidities associated with increasing maternal age (1, 3). Although fewer in number, most studies following nonlive pregnancy outcomes suggest no increased risk for adverse perinatal outcomes after short IPIs (4,8–11). The most recent recommendation regarding pregnancy spacing is from 2005, when the World Health Organization (WHO) recommended IPIs >24 months after a live birth and >6 months after a spontaneous or induced abortion (12).

Assisted reproductive technologies (ART)—fertility treatments in which either eggs or embryos are handled, primarily in vitro fertilization (IVF)—also are associated with increased risk for the same adverse perinatal outcomes as IPI (13, 14). It is unclear how IVF is associated with IPI and whether IPI contributes differentially to the risk of adverse outcomes in IVF versus non-IVF deliveries, i.e., deliveries resulting from spontaneous conceptions or fertility treatments other than IVF. Delineating these risks would inform recommendations regarding pregnancy spacing for infertility patients undergoing IVF. Aside from the WHO recommendation, there are no specific recommendations regarding pregnancy spacing among women undergoing IVF.

We aimed to compare the associations between IPI and PTB, LBW, and SGA according to live birth status of the most recent previous pregnancy in IVF and non-IVF populations. We hypothesized that short IPI would be associated with an increased risk of adverse perinatal outcomes and that the association would be stronger in IVF deliveries, given the high risk of adverse perinatal outcomes following IVF. Furthermore, we hypothesized that long IPI would not be associated with adverse perinatal outcomes after adjusting for potential confounders associated with subfertility.

MATERIALS AND METHODS

Data Source

We used linked birth certificate and National Assisted Reproductive Technology Surveillance System (NASS) records from the States Monitoring Assisted Reproductive Technology (SMART) Collaborative to conduct this study (15). SMART is a project between participating state health departments and the Centers for Disease Control and Prevention (CDC)'s Division of Reproductive Health to promote state-based ART surveillance and research on ART-related outcomes. This study was approved by the CDC and the Massachusetts Department of Public Health Institutional Review Boards; it was declared to be exempt from review by the Michigan Department of Health and Human Services and the University of California, San Diego, Institutional Review Boards.

Interpregnancy Interval

IPI was defined as the interval between the date when the most recent previous pregnancy ended (either in live birth or nonlive pregnancy outcome, i.e., spontaneous abortion, induced abortion, or stillbirth) and the date of the first day of the last menstrual period from the index delivery as recorded in the birth certificate. If month of delivery or last menses was provided, but day was missing, the day was set to the 15th (4). IPIs were set to missing when the most recent previous pregnancy outcome could not be determined. In the primary analysis, IPI was classified as <12 months, 12 to <24 months (reference), 24 to <60 months, and ≥60 months.

Adverse Perinatal Outcomes

PTB was defined as gestational age at delivery <37 weeks. Gestational age at delivery was determined from NASS data for IVF deliveries or by clinical estimate from birth certificate data otherwise. LBW was defined as a birth weight <2,500 g. SGA was defined as a sex-specific birth weight for gestational age <10th percentile with the use of a reference from 2009–2010 U.S. live birth files (16). Twin and higher-order multiple deliveries were classified as LBW or SGA if at least one of the infants was affected.

Inclusion and Exclusion Criteria

All live-birth deliveries in Massachusetts and Michigan from 2000 to 2010 to women with at least one previous pregnancy were eligible for the study (n = 1,404,809). Women could have more than one delivery included. We excluded deliveries conceived with zygote or gamete intrafallopian transfer and deliveries carried by a gestational surrogate (n = 288), as well as deliveries missing information on IPI (n = 176,744) and deliveries missing gestational age at delivery or birth weight (n = 2,059; Supplemental Fig. 1, available online at www.fertstert.org). All deliveries with IPI available had earlier pregnancy outcome status (live birth vs. other nonlive pregnancy outcome) available, with 82.6% of previous pregnancies resulting in live births. In comparison, 55.2% of deliveries missing IPI were missing outcome status in the previous pregnancy, and only 5.2% of deliveries missing IPI had a live birth in the previous pregnancy. Furthermore, IVF was more common among deliveries with IPI missing compared with deliveries with IPI available (1.7% vs. 1.0%), as was having maternal age younger than 25 years (28.2% vs. 21.4%), Black, non-Hispanic maternal race and ethnicity (24% vs. 14%), <12 grade education (18.5% vs. 14.2%) and maternal smoking (17.3% vs. 12.9%).

Analysis

We stratified all analyses by whether the most recent prior pregnancy was a live or nonlive pregnancy outcome. We used generalized estimating equations to estimate relative risks (RR) and 95% confidence intervals (CI) with robust variances to account for correlations among women with more than one delivery (17). Specifically, we used modified Poisson regression to compare the risks for adverse perinatal outcomes by IPI. We evaluated the association between IPI and adverse perinatal outcomes in IVF deliveries separately from non-IVF deliveries because tests for multiplicative effect modification of IPI by IVF revealed statistically significant interaction ($P<.05$) for PTB, LBW, and SGA in deliveries following a live birth and for PTB in deliveries following a nonlive pregnancy outcome. Also, we used multinomial regression to assess the association between IVF status and IPI categories for the index delivery (IVF used versus no IVF