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Title

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Permalink

https://escholarship.org/uc/item/6kf4n2c6

Journal

Fertility and Sterility, 109(5)

ISSN

0015-0282

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Publication Date

2018-05-01

DOI

10.1016/j.fertnstert.2018.01.019

Peer reviewed

In Vitro Fertilization, Interpregnancy Interval, and Risk for Adverse Perinatal Outcomes

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Abstract

Objective—To compare associations between interpregnancy intervals (IPI) and adverse perinatal outcomes in deliveries following IVF with deliveries following spontaneous conception or other fertility treatments (non-IVF).

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Design—Cohort using linked birth certificate and assisted reproductive technology surveillance data from Massachusetts and Michigan.

Setting—Not applicable.

Patients—1,225,718 deliveries.

Interventions—None.

Main Outcomes Measures—We assessed associations between IPI and preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA), according to live birth or non-live pregnancy outcome in the previous pregnancy.

Results—In IVF deliveries following prior 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, 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, 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 IPI <12 months and SGA association was not significant in IVF deliveries. In IVF and non-IVF deliveries following non-live 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.

Conclusions—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.

Keywords

assisted reproductive technology (ART); birth intervals; interpregnancy interval; in vitro fertilization (IVF); preterm birth

Introduction

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 following a prior live birth are associated with increased risk for adverse obstetric 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 due to insufficient maternal physiologic recovery from the previous pregnancy (5–7) and with long IPI due to comorbidities associated with increasing maternal age (1,3). Although fewer in number, most studies following non-live 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 following a live birth and >6 months following 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.

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's Division of Reproductive Health to promote state-based assisted reproductive technology (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 exempt by the Michigan Department of Health and Human Services and the University of California, San Diego Institutional Review Boards.

IPI

IPI was defined as the interval between the date when the most recent previous pregnancy ended (either in live birth or non-live 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, 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 onths.

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 <2,500g. SGA was defined as a sex-specific birth weight for gestational age less than the 10th percentile with the use of a

reference from 2009–2010 US 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 Figure 1). All deliveries with IPI available had prior pregnancy outcome status (live birth vs other non-live pregnancy outcome) available, with 82.6% of prior 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 non-live 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 ($p<0.05$) for PTB, LBW, and SGA in deliveries following a live birth and for PTB in deliveries following a non-live 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 used). Covariates were treated as categorical variables. The cut points for covariates included in regression models differed between IVF and non-IVF analyses because of the smaller number of deliveries in the IVF population and are listed in Supplemental Table 1. We adjusted all models for birth year (2000–2003, 2004–2007, 2008–2010). Fully adjusted models additionally controlled for state, maternal age (12–29, 30–34, 35–39, 40–44, 45 for IVF; 12–24, 25–29, 30–34, 35–39, 40–44, 45 for non-IVF), maternal race and ethnicity (non- Hispanic white, other for IVF; non-Hispanic white, non-Hispanic black, non-Hispanic Asian/Pacific Islander, Hispanic, other for non-IVF), maternal education (<4 years of college, 4 years of college for IVF; <12th grade, completed 12th grade, <4 years of college, 4 years of college for IVF), gravidity (2 pregnancies, 3 pregnancies for IVF; 2 pregnancies, 3 pregnancies, 4 pregnancies for non-IVF), diabetes or gestational diabetes, pre-pregnancy hypertension, and maternal smoking (yes, no) as recorded in the birth certificates. In analyses of IVF deliveries, we additionally adjusted for number of previous ART cycles (0, 1, 2, 3), indication for IVF (Supplementary Table 1), oocyte source, and number of embryos

transferred (1 or 2, 3, 4) as recorded in NASS data. Information was missing in <1% for any covariate, and observations missing covariate information were excluded from adjusted analyses.

Multiple gestation is a downstream consequence of multiple embryo transfer in IVF and does not affect interval length. Assuming unmeasured confounding between multiples and preterm birth we avoided stratifying on plurality in the primary analysis to avoid potential selection bias (18) and restricted IVF deliveries to singletons as a sensitivity analysis. Furthermore, because of small numbers, we conducted a sensitivity analysis to examine the association between IPI <6 months and adverse perinatal outcomes in IVF deliveries.

Cell counts <20 were suppressed, as were any values allowing for the calculation of a count <20. We used SAS version 9.3 (SAS Institute) and SUDAAN version 11.0 (RTI International) to conduct the analyses.

Results

Study population characteristics

We studied 12,633 IVF deliveries and 1,213,085 non-IVF deliveries from 2000 to 2010. A larger proportion of IVF deliveries occurred in white non-Hispanic women and in women ages 30 and older (Table 1) compared to non-IVF deliveries (Table 2). The prevalence of diabetes or gestational diabetes, pre-pregnancy hypertension, and multiple births was higher in IVF deliveries than in non-IVF deliveries.

IPI and risk for adverse perinatal outcomes-IVF population

Following a live birth in the IVF population, the risk of PTB was 22.2%, LBW 14.1%, and SGA 9.7% for IPI 12 to <24 months (Table 3). The association between IPI and PTB was U-shaped (IPI <12 vs 12 to <24 months: adjusted RR=1.24, CI=1.09–1.41; IPI 60 vs 12 to <24 months: adjusted RR=1.12, CI=1.00–1.26). The adjusted RRs for LBW and SGA followed a similar U-shaped pattern, although the increased risk of SGA for IPI <12 months was not statistically significant. When restricting to singleton deliveries after a live birth in the IVF population, the risk of PTB was 11.2%, LBW 4.8%, and SGA 5.5% for IPI 12 to <24 months (Supplemental Table 2). Short, but not long IPI, was associated with PTB (IPI <12 vs 12 to <24 months: adjusted RR=1.35, CI=1.09–1.68; IPI 60 vs 12 to <24 months: adjusted RR=0.99, CI=0.80–1.23). The associations between IPI and LBW (IPI <12 vs 12 to <24 months: adjusted RR=1.55, CI=1.09–2.19; IPI 60 vs 12 to <24 months: adjusted RR=1.44, CI=1.05–1.98) and IPI and SGA (IPI <12 vs 12 to <24 months: adjusted RR=1.27, CI=0.90–1.78; IPI 60 vs 12 to <24 months: adjusted RR=1.39, CI=1.06–1.84) showed a U-shaped pattern, although not all associations were statistically significant.

In IVF deliveries after a non-live pregnancy outcome, the risk of PTB was 24.3%, LBW 18.3%, and SGA 14.0% for IPI 12 to <24 months (Table 3). There was no statistically significant increased risk of PTB, LBW, and SGA for IPI <12 months or IPI 60 months. For singleton IVF deliveries, the risk of PTB was 11.1%, LBW 6.3%, and SGA 9.3% for IPI 12 to <24 months, but again, there was no significant increased risk of PTB, LBW, and SGA for IPI <12 months or IPI 60 months (Supplemental Table 2).

Regardless of most recent pregnancy outcome, IPI <6 months was not associated with a significantly increased risk for the adverse perinatal outcomes in IVF deliveries (Supplemental Table 3). The adjusted RRs were 1.12 (CI=0.85–1.49) for PTB, 0.99 (CI=0.65–1.52) for LBW, and 1.22 (CI=0.75–1.97) for SGA for IPI <6 compared with IPI 12 to <24 months following a live birth.

IPI and risk for adverse perinatal outcomes – non-IVF population

Following a live birth in the non-IVF population, the risk of PTB was 6.4%, LBW 4.4%, and SGA 6.5% for IPI 12 to <24 months (Table 3). The association between IPI and PTB was U-shaped, with increased risk for both short and long IPI (IPI <12 vs 12 to <24 months: adjusted RR=1.19, CI=1.16–1.21; IPI 60 vs 12 to <24 months: adjusted RR=1.19, CI=1.16–1.21), as was the association between IPI and LBW (IPI <12 vs 12 to <24 months: adjusted RR=1.16, CI=1.13–1.19; IPI 60 vs 12 to <24 months: adjusted RR=1.38, CI=1.34–1.41). However, the U-shaped pattern was less apparent for SGA (IPI <12 vs 12 to <24 months: adjusted RR=1.04, CI=1.02–1.06; IPI 60 vs 12 to <24 months: adjusted RR=1.31, CI=1.28–1.34). The RRs for the IPI 60 vs 12–24 month comparisons were attenuated by >10% in the adjusted models compared with the birth-year adjusted models. The attenuations were driven primarily by maternal race/ethnicity, maternal education, pre-pregnancy hypertension, and smoking.

Following a non-live pregnancy outcome in non-IVF deliveries, the risk of PTB was 9.6%, LBW 7.9%, and SGA 10.6% for IPI 12 to <24 months. For PTB, short IPI <12 vs 12 to <24 months was associated with decreased risk (adjusted RR=0.94, CI=0.91–0.97) whereas long IPI 60 vs 12 to <24 months was associated with increased risk (adjusted RR=1.10, CI=1.04–1.16). The pattern was similar for LBW and SGA.

IVF and IPI

Women with IVF deliveries had lower risks of having an IPI <12 months compared with women without IVF deliveries, regardless of whether the most recent pregnancy outcome was a live birth (adjusted RR=0.70, CI=0.66–0.75) or not (adjusted RR=0.89, CI=0.86–0.92) (Table 4). Women with IVF deliveries were more likely to have an IPI of 24 months following a live birth and an IPI of 12 to <60 months following a non-live pregnancy outcome compared with non-IVF deliveries.

Discussion

In IVF deliveries after a prior live birth, offspring of women with short IPIs of less than one year had significantly higher risks of PTB and LBW, and offspring of women with long IPIs of five or more years (60 months) had higher risks of PTB, LBW and SGA, compared with offspring of women with IPIs of 12 to <24 months. Non-IVF deliveries also had increased risks for adverse perinatal outcomes after short or long IPIs following a prior live birth. The absolute risks of PTB, LBW and SGA overall were higher in IVF versus non-IVF deliveries. However, the general shape and magnitudes of the relative associations between IPI and adverse perinatal outcomes were similar in the IVF and non-IVF populations, despite a statistical difference between IVF and non-IVF deliveries in the association between IPI and

some outcomes in this highly powered study. Although the relative increases in these outcomes were modest, the observation that short or long IPI following a live birth may increase adverse perinatal outcome risks offers an opportunity for optimizing pregnancy timing, including the IVF population where the risk of adverse perinatal outcomes is already elevated owing in part due to the frequency of multifetal gestation. However, long IPIs may not be modifiable if long IPI is due to subfertility.

For both IVF and non-IVF deliveries following a non-live pregnancy outcome, short IPI was not associated with increased risk for adverse perinatal outcomes. These findings are consistent with some (4,8,9), but not all (10,11), studies. California birth certificate data showed slightly protective associations between short IPIs following a non-live pregnancy (4) outcome and PTB, similar to our findings for the non-IVF population. In contrast, Finnish population-based data showed that PTB risk was higher with short IPI following pregnancy terminations (11). For those planning an IVF pregnancy after a pregnancy loss, the data from the current study did not suggest a significant increase in risk for the adverse outcomes when pregnancies are less than a year apart. Long IPI following a non-live pregnancy outcome was associated with modestly increased risks for PTB, LBW and SGA. These results reached statistical significance in non-IVF deliveries, but not in the smaller IVF population.

Following a prior live birth, the magnitude of the association between short IPI and adverse outcomes in IVF pregnancies was similar to results from earlier population-based studies (1,19,20). One proposed mechanism to explain the finding of increased risk of adverse outcomes for a short IPI after a live birth, but not after a non-live pregnancy outcome, is insufficient maternal recovery from the nutritional burden and physiologic stress of the previous pregnancy and/or feeding and caring for an infant while pregnant (5,6,21). In addition, short IPIs may not allow for adequate recovery from post-delivery changes in vaginal microbiota before the next pregnancy (7), and vaginal community characteristics are associated with the development of preterm birth (22,23). The increased risk for adverse outcomes after a long IPI may reflect residual confounding by maternal chronic conditions associated with subfertility (including, e.g., cancer, obesity, and diabetes (3,24–26)). Notably, the proportion of women ages 40 years and older was greatest among women with IPI 60 months regardless of IVF and previous pregnancy outcomes status, and a greater prevalence of chronic conditions would be expected among women in this age group. The similar pattern of results between IVF and non-IVF deliveries suggests similar mechanism(s) underlying IPI and adverse outcomes.

IVF deliveries were less likely to have short IPIs, regardless of prior pregnancy outcome. This observation may be explained by longer time to pregnancy in subfertile couples, the need to recover financially before initiating a new cycle, and more opportunities for counseling on pregnancy spacing. IVF providers need to be aware of potential risks of short IPI following a live birth to avoid iatrogenically increasing outcomes.

The major limitation of the present study was incomplete information on IPI, especially for pregnancies following a non-live pregnancy outcome. Because only women with IPI available were eligible, factors related to missing IPI, e.g., previous pregnancy outcome, and

the study's outcomes could cause selection bias (27). We sought to mitigate this by adjusting for measured factors related to missing IPI, i.e., maternal age, race/ethnicity, education, and smoking. Some prior deliveries in the live birth group may be misclassified as live births due to missing non-live pregnancy outcomes, which may have overestimated IPIs; this may bias RRs for longer IPI towards the null. Furthermore, the association between IPI and adverse perinatal outcomes may reflect residual confounding by unmeasured factors. Previous studies using within-woman or within-family comparisons to account, at least in part, for unmeasured factors have reported the attenuation or elimination of associations between IPI and adverse birth outcomes compared with conventional analysis (4,28–30). Other limitations include: the inclusion of live birth deliveries only for the index pregnancy; inability to stratify previous non-live pregnancy outcomes (i.e. pregnancy loss, induced abortion, or stillbirth); inability to account for characteristics of the previous pregnancy such as spontaneous or ART conception and gestational age at pregnancy outcome; and possible limited generalizability due to the inclusion of only two U.S. states.

In IVF and non-IVF populations, short (<12 months) and long (60 months) IPI following a live birth was associated with significantly higher risks of adverse perinatal outcomes, supporting the need for awareness of pregnancy spacing in all women. Although patients with infertility and/or subfertility may desire to have subsequent pregnancies with minimal spacing, given high risks of adverse perinatal outcomes associated with IVF, the data presented here support waiting a year before attempting pregnancy again for those planning an IVF pregnancy following a live birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. JAMA : the journal of the American Medical Association. 2006; 295(15):1809–1823. [PubMed: 16622143]

2. Grisaru-Granovsky S, Gordon ES, Haklai Z, Samueloff A, Schimmel MM. Effect of interpregnancy interval on adverse perinatal outcomes--a national study. Contraception. 2009; 80(6):512–518. [PubMed: 19913144]

3. Shachar BZ, Lyell DJ. Interpregnancy interval and obstetrical complications. Obstetrical & gynecological survey. 2012; 67(9):584–596. [PubMed: 22990461]

4. Shachar BZ, Mayo JA, Lyell DJ, Baer RJ, Jeliffe-Pawlowski LL, Stevenson DK, Shaw GM, et al. Interpregnancy interval after live birth or pregnancy termination and estimated risk of preterm birth: a retrospective cohort study. BJOG. 2016; 123(12):2009–2017. [PubMed: 27405702]

5. Miller JE. Birth intervals and perinatal health: an investigation of three hypotheses. Fam Plann Perspect. 1991; 23(2):62–70. [PubMed: 2060613]

6. Smits LJ, Essed GG. Short interpregnancy intervals and unfavourable pregnancy outcome: role of folate depletion. Lancet. 2001; 358(9298):2074–2077. [PubMed: 11755634]

7. DiGiulio DB, Callahan BJ, McMurdie PJ, Costello EK, Lyell DJ, Robaczewska A, Sun CL, et al. Temporal and spatial variation of the human microbiota during pregnancy. Proc Natl Acad Sci U S A. 2015; 112(35):11060–11065. [PubMed: 26283357]

8. Love ER, Bhattacharya S, Smith NC. Effect of interpregnancy interval on outcomes of pregnancy after miscarriage: retrospective analysis of hospital episode statistics in Scotland. BMJ. 2010; 341:c3967. [PubMed: 20688842]

9. Wong LF, Schliep KC, Silver RM, Mumford SL, Perkins NJ, Ye A, Galai N, et al. The effect of a very short interpregnancy interval and pregnancy outcomes following a previous pregnancy loss. Am J Obstet Gynecol. 2015; 212(3):375e371–311. [PubMed: 25246378]

10. 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]

11. Mannisto J, Bloigu A, Mentula M, Gissler M, Heikinheimo O, Niinimaki M. Interpregnancy Interval After Termination of Pregnancy and the Risks of Adverse Outcomes in Subsequent Birth. Obstet Gynecol. 2017; 129(2):347–354. [PubMed: 28079768]

12. Report of a WHO Technical Consultation on Birth SpacingGenenva, Switzerland: WHO; 2007Available at: http://apps.who.int/iris/bitstream/10665/69855/1/WHO_RHR_07.1_eng.pdf [Accessed December 11, 2017]

13. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. Human reproduction update. 2012; 18(5):485–503. [PubMed: 22611174]

14. Dhalwani NN, Boulet SL, Kissin DM, Zhang Y, McKane P, Bailey MA, et al. Assisted reproductive technology and perinatal outcomes: conventional versus discordant-sibling design. Fertil Steril. 2016; 106(3):710–716. e712. [PubMed: 27187051]

15. Mneimneh AS, Boulet SL, Sunderam S, Zhang Y, Jamieson DJ, Crawford S, et al. States Monitoring Assisted Reproductive Technology (SMART) Collaborative: data collection, linkage, dissemination, and use. J Womens Health (Larchmt). 2013; 22(7):571–577. [PubMed: 23829183]

16. Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. Pediatrics. 2014; 133(5):844–853. [PubMed: 24777216]

17. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. Statistical methods in medical research. 2013; 22(6):661–670. [PubMed: 22072596]

18. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol. 2002; 155(2):176–184. [PubMed: 11790682]

19. Zhu BP, Rolfs RT, Nangle BE, Horan JM. Effect of the interval between pregnancies on perinatal outcomes. The New England journal of medicine. 1999; 340(8):589–594. [PubMed: 10029642]

20. Khoshnood B, Lee KS, Wall S, Hsieh HL, Mittendorf R. Short interpregnancy intervals and the risk of adverse birth outcomes among five racial/ethnic groups in the United States. Am J Epidemiol. 1998; 148(8):798–805. [PubMed: 9786235]

21. Scholl TO, Reilly T. Anemia, iron and pregnancy outcome. J Nutr. 2000; 130(2S Suppl):443S–447S. [PubMed: 10721924]

22. Callahan BJ, DiGiulio DB, Goltsman DSA, Sun CL, Costello EK, Jeganathan P, et al. Replication and refinement of a vaginal microbial signature of preterm birth in two racially distinct cohorts of US women. Proc Natl Acad Sci U S A. 2017; 114(37):9966–9971. [PubMed: 28847941]

23. Stout MJ, Zhou Y, Wylie KM, Tarr PI, Macones GA, Tuuli MG. Early pregnancy vaginal microbiome trends and preterm birth. Am J Obstet Gynecol. 2017; 217(3):356e351–356 e318. [PubMed: 28549981]

24. Levine JM, Kelvin JF, Quinn GP, Gracia CR. Infertility in reproductive-age female cancer survivors. Cancer. 2015; 121(10):1532–1539. [PubMed: 25649243]

25. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril. 2017; 107(4):840–847. [PubMed: 28292619]

26. Eisenberg ML, Sundaram R, Maisog J, Buck Louis GM. Diabetes, medical comorbidities and couple fecundity. Hum Reprod. 2016; 31(10):2369–2376. [PubMed: 27591240]

27. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004; 15(5):615–625. [PubMed: 15308962]

28. Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. BMJ. 2014; 349:g4333. [PubMed: 25056260]

29. Hanley GE, Hutcheon JA, Kinniburgh BA, Lee L. Interpregnancy Interval and Adverse Pregnancy Outcomes: An Analysis of Successive Pregnancies. Obstet Gynecol. 2017; 129(3):408–415. [PubMed: 28178044]

30. Klebanoff MA. Interpregnancy Interval and Pregnancy Outcomes: Causal or Not? Obstet Gynecol. 2017; 129(3):405–407. [PubMed: 28178065]

Table 1

Characteristics of vitro fertilization (IVF) deliveries, by interpregnancy interval (IPI) and most recent pregnancy outcome

Characteristics	Most Recent Pregnancy: Live Birth, n (%)				Most Recent Pregnancy: Non-Live Pregnancy Outcome*, n (%)			
	IPI <12 months	IPI 12 to <24 months	IPI 24 to <60 months	IPI 60 months	IPI <12 months	IPI 12 to <24 months	IPI 24 to <60 months	IPI 60 months
	N=853	N=2600	N=3676	N=1955	N=1736	N=781	N=621	N=411
Maternal age, years								
<30	86 (10.1)	159 (6.1)	213 (5.8)	116 (5.9)	186 (10.7)	73 (9.3)	52 (8.4)	29 (7.1)
30–34	261 (30.6)	853 (32.8)	1058 (28.8)	497 (25.4)	575 (33.1)	251 (32.1)	202 (32.5)	119 (29.0)
35–39	324 (38.0)	1113 (42.8)	1689 (45.9)	802 (41.0)	656 (37.8)	278 (35.6)	218 (35.1)	157 (38.2)
40–44	153 (17.9)	405 (15.6)	621 (16.9)	416 (21.3)	278 (16.0)	145 (18.6)	120 (19.3)	77 (18.7)
45	29 (3.4)	70 (2.7)	95 (2.6)	124 (6.3)	41 (2.4)	34 (4.4)	29 (4.7)	29 (7.1)
Maternal Race/ethnicity Non-Hispanic White†	780 (91.4)	2395 (92.1)	3308 (90.0)	1588 (81.2)	1591 (91.6)	683 (87.5)	525 (84.5)	344 (83.7)
Gravidity 3 pregnancies	338 (39.6)	801 (30.8)	1093 (29.7)	873 (44.7)	1102 (63.5)	455 (58.3)	332 (53.5)	128 (31.1)
Diabetes or gestational diabetes†	50 (5.9)	136 (5.2)	216 (5.9)	148 (7.6)	130 (7.5)	50 (6.4)	40 (6.4)	23 (5.6)
Pre-pregnancy hypertension†	21 (2.5)	45 (1.7)	70 (1.9)	56 (2.9)	53 (3.1)	20 (2.6)	--	--
Maternal smoking†	--	25 (1.0)	36 (1.0)	77 (3.9)	40 (2.3)	--	--	--
IVF indications‡								
Male factor	329 (38.6)	1003 (38.6)	1293 (35.2)	613 (31.4)	565 (32.5)	236 (30.2)	166 (26.7)	173 (42.1)
Tubal factor	128 (15.0)	398 (15.3)	551 (15.0)	678 (34.7)	358 (20.6)	172 (22.0)	149 (24.0)	99 (24.1)
Other factor	159 (18.6)	459 (17.7)	700 (19.0)	275 (14.1)	279 (16.1)	138 (17.7)	92 (14.8)	47 (11.4)
Unexplained infertility	123 (14.4)	447 (17.2)	658 (17.9)	236 (12.1)	290 (16.7)	106 (13.6)	93 (15.0)	53 (12.9)
Ovulatory disorder	125 (14.7)	372 (14.3)	506 (13.8)	172 (8.8)	287 (16.5)	114 (14.6)	86 (13.8)	43 (10.5)
History of endometriosis	98 (11.5)	309 (11.9)	385 (10.5)	141 (7.2)	186 (10.7)	84 (10.8)	80 (12.9)	39 (9.5)
Decreased ovarian reserve	93 (10.9)	239 (9.2)	385 (10.5)	296 (15.1)	214 (12.3)	121 (15.5)	110 (17.7)	75 (18.2)
Uterine factor	26 (3.0)	88 (3.4)	89 (2.4)	47 (2.4)	66 (3.8)	31 (4.0)	30 (4.8)	--
Oocyte source								
Fresh non-donor	548 (64.2)	1823 (70.1)	2750 (74.8)	1524 (78.0)	1291 (74.4)	587 (75.2)	432 (69.6)	311 (75.7)
Fresh donor	26 (3.0)	105 (4.0)	250 (6.8)	221 (11.3)	108 (6.2)	101 (12.9)	96 (15.5)	55 (13.4)
Frozen non-donor	215 (25.2)	576 (22.2)	583 (15.9)	165 (8.4)	279 (16.1)	72 (9.2)	68 (11.0)	33 (8.0)

Characteristics	Most Recent Pregnancy: Live Birth, n (%)				Most Recent Pregnancy: Non-Live Pregnancy Outcome*, n (%)			
	IPI <12 months	IPI 12 to <24 months	IPI 24 to <60 months	IPI 60 months	IPI <12 months	IPI 12 to <24 months	IPI 24 to <60 months	IPI 60 months
	N=853	N=2600	N=3676	N=1955	N=1736	N=781	N=621	N=411
Frozen donor	64 (7.5)	96 (3.7)	93 (2.5)	45 (2.3)	58 (3.3)	21 (2.7)	25 (4.0)	--
Multiple births	225 (26.4)	693 (26.7)	999 (27.2)	564 (28.8)	436 (25.1)	212 (27.1)	193 (31.1)	106 (25.8)

--Indicates <20 deliveries

*
Spontaneous abortion, induced abortion, stillbirth

†
Unknown in <1%

‡
Indications are not mutually exclusive

Table 2

Characteristics of non-IVF deliveries, by interpregnancy interval (IPI) and most recent pregnancy outcome

Characteristics	Most Recent Pregnancy: Live Birth, n (%)				Most Recent Pregnancy: Non-Live Pregnancy Outcome,* n (%)			
	IPI <12 months	IPI 12 to <24 months	IPI 24 to <60 months	IPI ≥60 months	IPI <12 months	IPI 12 to <24 months	IPI 24 to <60 months	IPI ≥60 months
	N=193906	N=289457	N=354405	N=165188	N=117503	N=37141	N=35264	N=20221
Maternal age, years								
<30	117979 (60.8)	139520 (48.2)	167081 (47.1)	52784 (32.0)	64537 (54.9)	22135 (59.6)	21696 (61.5)	8201 (40.6)
30–34	49599 (25.6)	98203 (33.9)	113793 (32.1)	56360 (34.1)	31211 (26.6)	8312 (22.4)	7806 (22.1)	7011 (34.7)
35–39	22853 (11.8)	45001 (15.5)	62441 (17.6)	42816 (25.9)	17546 (14.9)	5100 (13.7)	4325 (12.3)	3933 (19.5)
40–44	3409 (1.8)	6571 (2.3)	10687 (3.0)	12547 (7.6)	4088 (3.5)	1508 (4.1)	1331 (3.8)	998 (4.9)
≥45	66 (0.0)	162 (0.1)	403 (0.1)	681 (0.4)	121 (0.1)	86 (0.2)	106 (0.3)	78 (0.4)
Maternal race/ethnicity†								
Non-Hispanic White	137624 (71.0)	224196 (77.5)	251860 (71.1)	101235 (61.3)	86055 (73.2)	24228 (65.2)	22539 (63.9)	14642 (72.4)
Non-Hispanic Black	29312 (15.1)	29138 (10.1)	44534 (12.6)	31530 (19.1)	17958 (15.3)	7541 (20.3)	7603 (21.6)	3502 (17.3)
Hispanic	17639 (9.1)	21801 (7.5)	35627 (10.1)	21773 (13.2)	8003 (6.8)	3175 (8.6)	3036 (8.6)	1076 (5.3)
Non-Hispanic Asian/Pacific Islander	6707 (3.5)	11010 (3.8)	17596 (5.0)	7662 (4.6)	4020 (3.4)	1617 (4.4)	1504 (4.3)	743 (3.7)
Other	2194 (1.1)	2667 (0.9)	3983 (1.1)	2619 (1.6)	1166 (1.0)	517 (1.4)	511 (1.5)	231 (1.1)
Gravidity ≥3 pregnancies	106518 (54.9)	139291 (48.1)	177209 (50.0)	87051 (52.7)	84381 (71.8)	25496 (68.7)	21475 (60.9)	8298 (41.0)
Diabetes or gestational diabetes†	5535 (2.9)	8338 (2.9)	12600 (3.6)	8706 (5.3)	4409 (3.8)	1464 (3.9)	1426 (4.0)	931 (4.6)
Pre-pregnancy hypertension†	2436 (1.3)	3655 (1.3)	5502 (1.6)	4389 (2.7)	2336 (2.0)	758 (2.0)	777 (2.2)	554 (2.7)
Maternal smoking†	27167 (14.0)	27828 (9.6)	41999 (11.9)	26963 (16.3)	16819 (14.3)	6761 (18.2)	7131 (20.2)	3499 (17.3)
Multiple births	2728 (1.4)	4353 (1.5)	5658 (1.6)	2829 (1.7)	1981 (1.7)	590 (1.6)	488 (1.4)	335 (1.7)

*
Spontaneous abortion, induced abortion or stillbirth

†
Unknown in <1%

Table 3

Association between interpregnancy interval (IPI) and adverse perinatal outcomes, by IVF or non-IVF population and most recent pregnancy outcome

Interpregnancy Interval	Preterm Birth			Low Birth Weight			Small for Gestational Age		
	n (%)	Delivery Year Adjusted RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted RR & CI	Adjusted* RR & CI
IVF Deliveries Most Recent									
Pregnancy: Live Birth									
IPI <12 months	237 (27.8)	1.26 (1.10–1.43)	1.24 (1.09–1.41)	149 (17.5)	1.24 (1.04–1.47)	1.25 (1.05–1.49)	95 (11.1)	1.15 (0.93–1.44)	1.16 (0.93–1.45)
IPI 12 to <24 months (Reference)	576 (22.2)	-	-	367 (14.1)	-	-	251 (9.7)	-	-
IPI 24 to <60 months	869 (23.6)	1.06 (0.97–1.17)	1.05 (0.96–1.15)	577 (15.7)	1.11 (0.98–1.25)	1.10 (0.97–1.24)	356 (9.7)	1.00 (0.86–1.17)	0.98 (0.84–1.15)
IPI 60 months	546 (27.9)	1.25 (1.13–1.38)	1.12 (1.00–1.26)	419 (21.4)	1.50 (1.32–1.70)	1.37 (1.19–1.59)	248 (12.7)	1.31 (1.11–1.54)	1.23 (1.03–1.47)
IVF Deliveries Most Recent									
Pregnancy: Non-Live									
Pregnancy Outcome†									
IPI <12 months	450 (25.9)	1.07 (0.92–1.24)	1.07 (0.92–1.23)	329 (19.0)	1.04 (0.87–1.24)	1.02 (0.85–1.21)	220 (12.7)	0.91 (0.73–1.12)	0.94 (0.76–1.16)
IPI 12 to <24 months (Reference)	190 (24.3)	-	-	143 (18.3)	-	-	109 (14.0)	-	-
IPI 24 to <60 months	181 (29.2)	1.20 (1.01–1.43)	1.17 (0.98–1.39)	139 (22.4)	1.22 (0.99–1.51)	1.19 (0.97–1.47)	96 (15.5)	1.11 (0.86–1.43)	1.09 (0.84–1.40)
IPI 60 months	104 (25.3)	1.04 (0.85–1.28)	1.02 (0.82–1.26)	99 (24.1)	1.31 (1.05–1.64)	1.23 (0.97–1.56)	71 (17.3)	1.24 (0.94–1.63)	1.13 (0.85–1.49)
Non-IVF Deliveries									
Most Recent Pregnancy: Live Birth									
IPI <12 months	16100 (8.3)	1.28 (1.26–1.31)	1.19 (1.16–1.21)	11520 (5.9)	1.31 (1.27–1.34)	1.16 (1.13–1.19)	15156 (7.8)	1.17 (1.15–1.20)	1.04 (1.02–1.06)
IPI 12 to <24 months (Reference)	18443 (6.4)	-	-	12842 (4.4)	-	-	18906 (6.5)	-	-
IPI 24 to <60 months	24304 (6.9)	1.06 (1.05–1.08)	1.02 (1.00–1.04)	18302 (5.2)	1.15 (1.12–1.17)	1.07 (1.05–1.10)	27074 (7.6)	1.16 (1.14–1.18)	1.08 (1.06–1.10)
IPI 60 months	14818 (9.0)	1.38 (1.35–1.41)	1.19 (1.16–1.21)	12847 (7.8)	1.71 (1.67–1.75)	1.38 (1.34–1.41)	16991 (10.3)	1.55 (1.52–1.58)	1.31 (1.28–1.34)
Non-IVF Deliveries									
Most Recent Pregnancy: Non-Live									
Pregnancy Outcome†									
IPI <12 months	10252 (8.7)	0.91 (0.88–0.95)	0.94 (0.91–0.97)	8131 (6.9)	0.88 (0.84–0.91)	0.95 (0.91–0.99)	10795 (9.2)	0.87 (0.84–0.90)	0.94 (0.91–0.97)

Interpregnancy Interval	Preterm Birth			Low Birth Weight			Small for Gestational Age		
	n (%)	Delivery Year Adjusted RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted RR & CI	Adjusted* RR & CI
IPI 12 to <24 months (Reference)	3547 (9.6)	-	-	2940 (7.9)	-	-	3917 (10.6)	-	-
IPI 24 to <60 months	3271 (9.3)	0.97 (0.93–1.02)	0.97 (0.92–1.01)	2884 (8.2)	1.03 (0.98–1.09)	1.01 (0.96–1.06)	4089 (11.6)	1.10 (1.06–1.15)	0.97 (0.93–1.01)
IPI 60 months	2170 (10.7)	1.12 (1.07–1.18)	1.10 (1.04–1.16)	1865 (9.2)	1.17 (1.10–1.23)	1.16 (1.09–1.23)	2341 (11.6)	1.10 (1.05–1.16)	1.10 (1.04–1.16)

RR: Relative risk, CI: 95% confidence interval

*
Non-IVF deliveries adjusted for birth year, state, maternal age, maternal race/ethnicity, maternal education, gravidity, diabetes or gestational diabetes, pre-pregnancy hypertension, maternal smoking. IVF population deliveries adjusted for birth year, state, maternal age, maternal race/ethnicity, maternal education, gravidity, diabetes or gestational diabetes, pre-pregnancy hypertension, maternal smoking, indications for IVF, # of previous ART cycles, oocyte source, # of embryos transferred.

†
Spontaneous abortion, induced abortion, stillbirth

Table 4

Association between IVF use and interpregnancy interval (IPI), by most recent pregnancy outcome

IVF Status	IPI < 12 months			IPI 12 to 24 months			IPI 24 to < 60 months			IPI ≥ 60 months		
	n (%)	Delivery Year Adjusted* RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted* RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted* RR & CI	Adjusted* RR & CI	n (%)	Delivery Year Adjusted* RR & CI	Adjusted* RR & CI
Most Recent Pregnancy: Live Birth												
IVF	853 (9.4)	0.49 (0.46–0.52)	0.70 (0.66–0.75)	2600 (28.6)	0.99 (0.96–1.02)	0.99 (0.96–1.02)	3676 (40.5)	1.14 (1.11–1.17)	1.14 (1.11–1.17)	1955 (21.5)	1.30 (1.25–1.35)	1.07 (1.03–1.12)
Non-IVF (reference)	193906 (19.3)	-	-	289457 (28.9)	-	-	354405 (35.3)	-	-	165188 (16.5)	-	-
Most Recent Pregnancy: Non-Live Pregnancy Outcome†												
IVF	1736 (48.9)	0.87 (0.84–0.90)	0.89 (0.86–0.92)	781 (22.0)	1.25 (1.17–1.33)	1.36 (1.28–1.45)	621 (17.5)	1.04 (0.97–1.12)	1.14 (1.06–1.22)	411 (11.6)	1.21 (1.10–1.32)	0.71 (0.65–0.78)
Non-IVF (reference)	117503 (55.9)	-	-	37141 (17.7)	-	-	35264 (16.8)	-	-	20221 (9.6)	-	-

RR: Relative risk, CI: 95% confidence interval

*
Adjusted for birth year, state, maternal age, maternal race/ethnicity, maternal education, gravidity, diabetes or gestational diabetes, pre-pregnancy hypertension, maternal smoking.

†
Spontaneous abortion, induced abortion, stillbirth.