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Association of Short Interpregnancy Interval With Pregnancy Outcomes According to Maternal Age

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Article Information

Risks of maternal mortality or severe morbidity (eg, mechanical ventilation, blood transfusion >3 U, intensive care unit admission, organ failure, death), small-for-gestational age (<10th birthweight percentile for gestational age and sex), fetal and infant composite outcome (stillbirth, infant death, <third birthweight percentile for gestational age and sex, delivery <28 weeks), and spontaneous and indicated preterm delivery. Risks of each outcome for 3- to 24-month interpregnancy intervals were estimated, according to maternal age at index birth (20-34 and ≥35 years). Adjusted risk ratios (aRRs) comparing predicted risks at 3-, 6-, 9-, and 12-month intervals with risks at 18-month intervals for each age group were calculated. The potential role of other factors explaining any differences (unmeasured confounding) was examined in several sensitivity analyses.

Results

Among 148 544 pregnancies, maternal mortality or severe morbidity risks were increased at 6-month compared with 18-month interpregnancy intervals for women aged 35 years or older (0.62% at 6 months vs 0.26% at 18 months; aRR, 2.39; 95% CI, 2.03-2.80), but not for women aged 20 to 34 years (0.23% at 6 months vs 0.25% at 18 months; aRR, 0.92; 95% CI, 0.83-1.02). Increased adverse fetal and infant outcome risks were more pronounced for women aged 20 to 34 years (2.0% at 6 months vs 1.4% at 18 months; aRR, 1.42; 95% CI, 1.36-1.47) than women 35 years or older (2.1% at 6 months vs 1.8% at 18 months; aRR, 1.15; 95% CI, 1.01-1.31). Risks of spontaneous preterm delivery at 6-month interpregnancy intervals were increased for women 20 to 34 years old (5.3% at 6 months vs 3.2% at 18 months; aRR, 1.65; 95% CI, 1.62-1.68) and to a lesser extent for women 35 years or older (5.0% at 6 months vs 3.6% at 18 months; aRR, 1.40; 95% CI, 1.31-1.49). Modest increases in risks of small-for-gestational age and indicated preterm delivery at short intervals did not vary meaningfully by maternal age. Sensitivity analyses suggested that observed associations were not fully explained by unmeasured confounding.

Conclusions and Relevance

The findings of this study suggest that short interpregnancy intervals are associated with increased risks for adverse pregnancy outcomes for women of all ages.

Introduction

Interpregnancy intervals (intervals between delivery and conception of the subsequent pregnancy) shorter than 18 months appear to be associated with increased risks of adverse outcomes, including preterm delivery, small-for-gestational-age (SGA) birth, and infant mortality.[1,2,3,4,5,6] Based on these associations, clinical postpartum practice[7,8] and public health[9,10] guidelines recommend interpregnancy intervals of at least 18 to 24 months.

However, it is currently unknown whether short intervals are associated with increased risks among older women to the same extent as among younger women. In the United States, women with a first birth at age 30 years or older have shorter interpregnancy intervals compared with women who began childbearing at younger ages.[11,12] Older maternal age is associated with increased reproductive birth risks, including infertility, chromosomal anomalies, and adverse birth outcomes.[13] Women who have delayed childbearing must balance the risks associated with a shorter interpregnancy interval against the risks of older maternal age at conception if they delay subsequent pregnancies to achieve the recommended interpregnancy interval.

Pregnancy and maternal characteristics associated with short interpregnancy interval may vary by maternal age (eg, unintended pregnancy, lower socioeconomic position, perinatal loss in the first pregnancy).[14,15] Therefore, the association between short interpregnancy interval and adverse outcomes may vary by maternal age such that short intervals might not be associated with increased risks in older women. With limited previous work on this question,[16] the extent to which the associations between short interpregnancy interval and adverse pregnancy outcomes vary by maternal age is poorly understood. The objective of this study was to evaluate whether the associations between short interpregnancy interval and pregnancy outcomes vary by maternal age.

Methods

Study Population

This population-based cohort was drawn from all women with at least 2 consecutive singleton pregnancies in British Columbia, Canada, from April 1, 2004, to March 31, 2014, using population-based health databases. Data analysis was performed from January 1 to July 20, 2018. Our primary database was the British Columbia Perinatal Data Registry,[17] maintained by Perinatal Services British Columbia, which contains demographic and clinical data abstracted from obstetrical and newborn medical records for nearly 100% of live or stillbirth births in British Columbia of 20 or more completed weeks' gestation or birthweight of 500 g or more, including maternal postpartum readmissions up to 42 days after delivery and baby transfers and readmissions up to 28 days post birth. Population Data BC, a multi-university data platform that provides researchers with deidentified linkages of British Columbia's administrative data, linked the British Columbia Perinatal Data Registry with additional population-level databases, including physician billing,[18] outpatient prescription,[19] and hospital discharge records,[20] census and community size data,[21,22] and vital statistics records.[23] The University of British Columbia/Children's and Women's Health Centre of British Columbia Research Ethics Board approved this study with waiver of informed consent.

Live births and stillbirths of 20 or more completed weeks' gestation were identified using the British Columbia Perinatal Data Registry. Pregnancies ending before 20 weeks' gestation were identified using physician billing, hospital discharge, or outpatient prescription codes for spontaneous or induced abortion (codes in eTable 1 in the Supplement). We excluded postinterval (subsequent) pregnancies if the preinterval pregnancy ended in a spontaneous or induced abortion at less than 20 weeks' gestation, stillbirth, or neonatal death, because the association between interpregnancy interval and outcomes in the subsequent pregnancy may be different following a live birth than following a perinatal or neonatal loss,[24] and guidelines differ for pregnancy spacing following a loss.[10] Women with more than 2 eligible interpregnancy intervals in the study period could contribute more than 1 observation for the analyses.

Exposure and Outcome Definitions

We defined interpregnancy interval as the time in months between the first eligible birth in the study period (the index birth) and the conception of the subsequent pregnancy. To calculate this interval, we subtracted the index birth date from the subsequent birth date minus the gestational age at birth of the subsequent pregnancy (using an algorithm-based estimate of gestational age based on last menstrual period, first ultrasonography [<20 weeks], clinical estimate from newborn examination, and documentation from maternal record). For subsequent pregnancies that ended in spontaneous or induced abortion at less than 20 weeks, we assumed the diagnosis, treatment, or hospital admission date to be the pregnancy loss date, and imputed gestational age at 12 weeks (97% were missing a gestational age estimate).

Outcomes included (1) maternal mortality or severe morbidity (mechanical ventilation, intensive care unit admission, organ failure, blood transfusion >3 U, unanticipated postpartum surgical procedure, or death) through pregnancy up to 42 days postpartum,[25] (2) SGA birth (<10th percentile for sex and gestational age),[26] (3) fetal and infant composite (stillbirth, infant death within 1 year after birth, extreme SGA birth [<3rd percentile], delivery <28 weeks), (4) spontaneous preterm delivery at less than 37 weeks, and (5) indicated preterm delivery at less than 37 weeks. Outcomes were defined using *International Classification of Disease, Ninth Edition* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, Canadian Classification of Interventions, Version 9, and British Columbia Medical Service Plan billing codes. Detailed variable definitions are provided in eTable 1 in the Supplement.

Statistical Analysis

We examined the association between interpregnancy interval and each outcome in the overall population and stratified by categories of maternal age at index birth: younger than 20 years, 20 to 34 years, and 35 years or older. First treating interpregnancy interval as a categorical variable, we tabulated the incidence of each outcome by interpregnancy interval in 6-month categories (<6, 6-11, 12-17, 18-23, and ≥24 months). Next, we used logistic regression and postestimation calculations[27] to estimate predicted odds of each

outcome in 1-month increments of interpregnancy interval from 3 to 24 months, which we then transformed to predicted absolute risks. To allow for curvilinear shapes, we modeled interpregnancy interval as a continuous variable using restricted cubic splines, with 4 knots at the 5th, 35th, 65th, and 95th percentiles of interpregnancy interval in the study population (5.7, 15.3, 24.8, and 55.3 months).[28] For each outcome, we fit unadjusted models including only interpregnancy interval spline terms and adjusted models also including baseline (ie, measured at or before the index birth) covariates identified as potential confounders of the association between short interpregnancy interval and adverse maternal and infant outcomes: nulliparity, smoking before or during index pregnancy, low neighborhood income, inadequate prenatal care, and outcome of index pregnancy (eg, preterm delivery in index pregnancy in model for preterm delivery). In unstratified models using the overall population, we also adjusted for maternal age. Adjusted risks were standardized to population average covariate values based on interpregnancy intervals of 18 months. We examined variance inflation factors to assess multicollinearity between variables included in adjusted models and considered values of 3 or higher as potentially concerning.

We plotted absolute predicted risks with 95% CIs in the overall population and separately for each age category to display the associations visually. We then used predicted absolute risks to calculate risk ratios (RRs) with 95% CIs comparing predicted risks at 3-, 6-, 9-, and 12-month interpregnancy intervals with predicted risks at the 18-month interval reference length, at population mean covariate values based on interpregnancy intervals of 18 months. In age-stratified analyses, we estimated RRs separately for each category of maternal age and performed a test for interaction for each outcome at each interval length.[29] Findings were considered significant at $P < .05$ (2-sided).

We used robust variance estimation to account for nonindependence of 2 or more interpregnancy intervals in the same woman. Analyses for all outcomes other than maternal mortality or severe morbidity were restricted to births at 20 weeks' or more gestation, as pregnancies ending earlier than 20 weeks were not at risk of birth outcomes. Analyses for SGA birth were restricted to those 22 to 43 weeks, owing to availability of reference charts. We excluded 616 records of pregnancies of 20 weeks or more owing to missing gestational age. We imputed missing values for number of antenatal visits (10 382 [7.0%]), using multiple imputation with 30 imputations based on all covariates and outcomes combined according to the Rubin formula.[30] For individuals with missing neighborhood income values for the index birth year (7857 [5.3%]), we assigned values from proximal years if available (7654 [5.2%]) and imputed missing values for the remaining 203 (0.1%). All analyses were conducted using Stata, version 14.2 (StataCorp).[31]

Sensitivity Analyses

To assess whether our results were sensitive to age categorization thresholds, we repeated analyses for women younger than 30 years and 30 years or older and for women younger than 40 years and 40 years or older. We conducted several analyses to examine the potential role of unmeasured and residual confounding. We (1) adjusted for additional measured baseline clinical and sociodemographic covariates that could be potential confounding variables (eg, rural residence, obesity, infertility treatment); (2) assessed potential confounding by pregnancy intention by restricting to pregnancies following an infertility diagnosis on the assumption that these pregnancies were more likely to be intended, (3) calculated E values, which represent the minimum strength of association that unmeasured confounding variables (eg, pregnancy intention,[32] intimate partner violence[33,34]) would need to have with both interpregnancy interval and each outcome to fully explain the observed association[35]; and (4) used the outcome of the index pregnancy as a negative control, on the assumption that no association between the outcome of the index pregnancy and interpregnancy interval could provide evidence against unmeasured confounding.[36] These approaches are detailed further in eAppendix 1 in the Supplement. To ensure that our findings were not sensitive to our methodologic approach of imputing missing data, we compared estimates using multiple imputation with those applying simple imputation (mean or missing indicator) and a complete case approach.

Results

Our study population included 123 122 women and 148 544 pregnancies subsequent to a live index birth (some women contributed more than 1 interpregnancy interval). Of these, 121 242 pregnancies (81.6%) continued to 20 weeks' or more gestation and the remaining 27 302 (18.4%) ended in spontaneous or induced abortion at less than 20 weeks. The majority of pregnancies (123 821 [83.4%]) were in women between ages 20 and 34 years at the index (preinterval) birth, while 7184 (4.8%) were in women younger than 20 years and 17 539 (11.8%) were in women 35 years or older at the index birth.

The distribution of interpregnancy interval differed somewhat by maternal age at index birth (eFigure 1 in the Supplement). Interpregnancy intervals shorter than 6 months were less common among women 35 years or older at the index birth than women aged 20 to 34 years (4.4% vs 5.5%). Women 35 years or older more often had interpregnancy intervals 6 to 11 and 12 to 17 months long than women aged 20 to 34 years (6-11 months, 17.7% vs 16.6% and 12-17 months, 25.2% vs 22.5%) but had fewer intervals 24 months or longer (32.8% vs 37.6%).

Sociodemographic and clinical characteristics of the study population at the time of index birth according to interpregnancy interval categories are reported in Table 1. Low neighborhood income, inadequate prenatal care, and smoking in pregnancy were most common among women with interpregnancy intervals shorter than 6 months. Women with interpregnancy intervals shorter than 6 months were also more likely to have a history of stillbirth, neonatal death, preterm delivery, or spontaneous abortion. In addition, pregnancies following intervals shorter than 6 months were much more likely to end in spontaneous or indicated abortion at less than 20 weeks. As reported in eTable 2 in the Supplement, maternal age younger than 20 years, smoking, inadequate prenatal care, and low neighborhood income also were associated with spontaneous or indicated abortion at less than 20 weeks.

The incidence of each outcome according to 6-month categories of interpregnancy interval for all women, and separately for those younger than 20 years, 20 to 34 years, and 35 years or older at index birth, is reported in Table 2. Figure 1 displays the unadjusted and adjusted predicted risk curves for each outcome according to 1-month increments of interpregnancy interval from 3 to 24 months. Risk curves were U- or L-shaped for all outcomes, with nadirs near 18 months, and similarly low risks for most outcomes from 12- to 24-month intervals. Adjusted RRs (aRRs) comparing predicted risks at 3-, 6-, 9-, and 12-month intervals with predicted risks at the referent 18-month interval length are tabulated in Table 3.

In the overall population, interpregnancy intervals of less than 12 months were associated with modest increases in risk of maternal mortality or severe morbidity (predicted risk, 0.30% at 6 months and 0.25% at 18 months; aRR comparing 6-month with 18-month intervals: 1.18; 95% CI, 1.09-1.27) and larger increases in risk of adverse fetal and infant outcomes (predicted risk, 2.0% at 6 months compared with 1.5% at 18 months: aRR, 1.36; 95% CI, 1.31-1.40), and spontaneous preterm delivery (predicted risk, 5.3% at 6 months compared with 3.3% at 18 months: aRR, 1.59; 95% CI, 1.56-1.2). Risk of SGA birth and indicated preterm delivery were only slightly higher at 6-month intervals (aRRs, 1.11; 95% CI, 1.08-1.14 and 1.08; 95% CI, 1.04-1.13, respectively).

Figure 2 presents adjusted risk curves after stratification by maternal age category (20-34 years and 35 years or older at index birth). Due to the small number of index pregnancies in women younger than 20 years, predicted risks for this group were unstable and are not presented. Risks for maternal mortality or severe morbidity differed meaningfully by age group. We found increased risks of maternal mortality or severe morbidity at 6-month compared with 18-month interpregnancy intervals for women 35 years or older (predicted risk of 0.62% at 6 months compared with 0.26% at 18 months: aRR, 2.39; 95% CI, 2.03-2.80), but not for women aged 20 to 34 years (predicted risk of 0.23% at 6 months compared with 0.25% at 18 months: aRR, 0.92; 95% CI, 0.83-1.02). Conversely, the increased risk of spontaneous preterm delivery at short interpregnancy intervals was more pronounced for younger women (predicted risk of 5.3% at 6 months compared with 3.2% at 18 months: aRR, 1.65; 95% CI, 1.62-1.68 for women 20-34 years at index birth) than older women (predicted risk of 5.0% at 6 months compared with 3.6% at 18 months: aRR, 1.40; 95% CI, 1.31-1.49 for women 35 years or older at index birth). Similarly, increased risk of adverse fetal and infant outcomes was more pronounced for women 20 to 34 years of age (predicted risk of 2.0% at 6 months vs 1.4% at 18 months: aRR, 1.42; 95% CI, 1.36-1.47) than women 35 years or older (predicted risk of 2.1% at 6 months vs 1.8% at 18 months: aRR, 1.15; 95% CI, 1.01-1.31, respectively). The shapes of the curves were similar across age groups for the other outcomes, generally

with the lowest risk at 18-month intervals, although not substantially higher at 12- or 24-month intervals. Women younger than 20 years at index birth had the highest risks of spontaneous preterm delivery across the interpregnancy interval spectrum and similar risks of other outcomes. Incidences and curves for component outcomes of the fetal and infant composite were similar to those of the composite and are presented in eTable 3, eFigures 2 and 3 in the Supplement.

Adjustment did not meaningfully change estimates for maternal mortality or severe morbidity. Increases in adverse fetal and infant composite, SGA birth, and spontaneous preterm delivery risks at short intervals were attenuated after adjustment. Aside from expected multicollinearity between cubic spline terms,[28] no variance inflation factors exceeded 2, indicating no problematic multicollinearity.

Sensitivity Analyses

Curves were similar when older maternal age was defined as 30 years or older (eFigure 4 in the Supplement). Because of the small number of women 40 years or older at index birth (n = 896), findings using this threshold were challenging to interpret owing to wide 95% CIs and are not presented. Sensitivity analyses examining the role of unmeasured or residual confounding indicated that confounding was unlikely to entirely explain our observed results (eAppendix 2 in the Supplement). Curves were similar after restricting to pregnancies following an infertility diagnosis (eFigures 5 and 6 in the Supplement), substantial confounding would be required to fully explain the observed association (eTable 4 in the Supplement), and negative control analyses produced different curve shapes, with no relationship or attenuated relationships with short interpregnancy interval (eFigures 7 and 8 in the Supplement).

Discussion

Our study found that increased risks of maternal mortality or severe morbidity, adverse fetal and infant outcomes, and spontaneous preterm delivery following short (<12-month) interpregnancy intervals persisted after stratifying by maternal age. Women 35 years or older at index birth had increased risks of maternal mortality or severe morbidity at short interpregnancy intervals, while women aged 20 to 34 years did not. Although short intervals were associated with elevated risks of spontaneous preterm delivery and adverse fetal and infant outcomes for women of all ages, these risks were highest among younger women. For other outcomes, elevation in risks at short interpregnancy intervals did not vary by maternal age categories. Overall, contrary to our hypothesis, risks following short interpregnancy intervals were not attenuated for older women.

Our results support a large body of literature examining increased risks of some fetal and infant outcomes, including preterm delivery, following short interpregnancy intervals.[1,2,3,4,5,6] While increased preterm delivery risk following short interpregnancy intervals has been studied extensively,[1,5,11] to our knowledge, few previous studies[4] have examined both spontaneous and indicated preterm delivery separately. We demonstrated that spontaneous preterm delivery was more strongly associated with short interpregnancy interval than was indicated preterm delivery. Furthermore, although the association between short interpregnancy interval and specific maternal outcomes have been studied in high-resource settings (eg, uterine rupture or blood transfusion,[37] abnormal placentation[38]), previous studies of maternal mortality or severe morbidity were restricted to low-resource settings.[39] Because previous findings may not be generalizable to high-resource settings owing to differences in maternal age, parity, pregnancy intention, or nutritional status, our findings regarding maternal mortality or severe morbidity add new insight to the literature. The small number of maternal mortality events in our study population (n = 5; 3.4 per 100 000) precluded examination of maternal mortality as a separate outcome, although this may be of interest for future research.

Current clinical and public health recommendations suggest a minimum interpregnancy interval of 18 months,[7,9] and some suggest a range from 18 to 60 months.[10] However, our findings suggest that the optimal interpregnancy interval is closer to 18 months, with a range of 12 to 24 months having risks that generally are comparable to the nadir at 18 months. In fact, for some outcomes (adverse fetal and infant outcomes for women ≥35 years old, SGA birth for all women), risks are similar to the nadir even at 9-month intervals.

More than 20% of interpregnancy intervals among women 35 years or older were shorter than 12 months, when risks of some outcomes remain elevated for older women, and nearly half were shorter than 18 months. Because pregnancies following short interpregnancy intervals among women 35 years or older at index birth are usually planned,[11,12] clinical counseling toward intervals closer to 12 or 18 months may be effective in reducing the risks that we have shown are still associated with short intervals among older women. While we believe these findings will be useful to women and clinicians, women's decisions regarding the optimal timing and spacing of pregnancy are multifactorial, and modest increases in risk associated with short intervals may not outweigh other factors, including those unrelated to health outcomes, that women and families consider in spacing their pregnancies.

Limitations

Our findings must be interpreted in the context of several limitations. Because our analyses examined differences in risks according to interpregnancy interval based on comparing outcomes of different women, they may be biased due to confounding by unmeasured factors that differ within and between women, including pregnancy intention[11,12] and intimate partner violence.[33,34] Previous studies found substantially attenuated associations between interpregnancy interval and adverse pregnancy outcomes using matched designs to examine successive interpregnancy intervals within the same women[40,41,42] compared with between-woman analyses. However, within-woman analyses cannot adequately account for the role of parity[2] and may not be generalizable to the overall population owing to restriction to women with at least 3 births and women with discordant health outcomes. While we cannot rule out unmeasured confounding, our sensitivity analyses examining the potential role of unmeasured or residual confounding provide reassurance that our findings are unlikely to be entirely explained by confounding.

Conclusions

We present what we believe to be new, robust evidence to guide clinicians counseling women considering short interpregnancy intervals. Our study used a large, population-based cohort with clinical detail based on validated[43] medical record abstraction, supplemented through linkages to additional health care and demographic information. This database enabled us to overcome many methodologic limitations of previous studies in this area, including controlling for both stillbirth and neonatal loss in the index birth and accurately measuring intervals between pregnancies by including the 18.4% of subsequent pregnancies that ended in spontaneous or induced abortions at less than 20 weeks in our definition.[44,45]

Short interpregnancy intervals (<12 months) are associated with increased maternal and fetal and infant risks for women aged 20 to 34 years and for women 35 years or older at index birth. Our findings indicate a shorter optimal interval than previously thought (12-24 months) for women of all ages. This finding may be reassuring particularly for older women who must weigh the competing risks of increasing maternal age with longer interpregnancy intervals (including infertility and chromosomal anomalies) against the risks of short interpregnancy intervals. We found evidence that confounding does not seem to fully explain the observed association between short interpregnancy interval and increased risks of several outcomes.

Notes

Supplement.

eTable 1. Detailed Variable Definitions

eAppendix 1. Methods for Sensitivity Analyses for Unmeasured or Residual Confounding

eFigure 1. Distribution of Interpregnancy Interval Length by Categories of Maternal Age at Index Birth

eTable 2. Sociodemographic and Clinical Characteristics of the Study Population According to Post-interval Pregnancy Resolution Type

eTable 3. Incidence of Component Outcomes of the Adverse Fetal-Infant Composite Outcome According to Categories of Interpregnancy Interval, Stratified by Maternal Age and Index Birth