Original Research

Interpregnancy Interval and Adverse Pregnancy Outcomes

An Analysis of Successive Pregnancies

Gillian E. Hanley, PhD, Jennifer A. Hutcheon, PhD, Brooke A. Kinniburgh, MPH, and Lily Lee, MPH

OBJECTIVE: To examine the association between interpregnancy interval and maternal–neonate health when matching women to their successive pregnancies to control for differences in maternal risk factors and compare these results with traditional unmatched designs.

METHODS: We conducted a retrospective cohort study of 38,178 women with three or more deliveries (two or greater interpregnancy intervals) between 2000 and 2015 in British Columbia, Canada. We examined interpregnancy interval (0–5, 6–11, 12–17, 18–23 [reference], 24–59, and 60 months or greater) in relation to neonatal outcomes (preterm birth [less than 37 weeks of gestation], small-for-gestational-age birth [less than the 10th centile], use of neonatal intensive care, low birth weight [less than 2,500 g]) and maternal outcomes (gestational diabetes, beginning the subsequent pregnancy obese [body mass index 30 or greater], and preeclampsia–eclampsia). We used conditional logistic regression to compare interpregnancy intervals within the same mother and unconditional (unmatched) logistic regression to enable comparison with prior research.

RESULTS: Analyses using the traditional unmatched design showed significantly increased risks associated with short interpregnancy intervals (eg, there were 232 preterm births [12.8%] in 0–5 months compared with 501 [8.2%] in the 18–23 months reference group; adjusted odds ratio [OR] for preterm birth 1.53, 95% confidence interval [CI] 1.35–1.73). However, these risks were eliminated in within-woman matched analyses (adjusted OR for preterm birth 0.85, 95% CI 0.71–1.02). Matched results indicated that short interpregnancy intervals were significantly associated with increased risk of gestational diabetes (adjusted OR 1.35, 95% CI 1.02–1.80 for 0–5 months) and beginning the subsequent pregnancy obese (adjusted OR 1.61, 95% CI 1.05–2.45 for 0–5 months and adjusted OR 1.43, 95% CI 1.10–1.87 for 6–11 months).

CONCLUSION: Previously reported associations between short interpregnancy intervals and adverse neonatal outcomes may not be causal. However, short interpregnancy interval is associated with increased risk of gestational diabetes and beginning a subsequent pregnancy obese.

(Obstet Gynecol 2017;129:408–15)
DOI: 10.1097/AOG.0000000000001891

See related editorial on page 405.

From the Perinatal Services BC, and the Department of Obstetrics & Gynaecology, University of British Columbia, Vancouver, British Columbia, Canada.

Gillian E. Hanley is funded by the Canadian Cancer Society Research Institute and a New Investigator Award from the Canadian Institutes of Health Research. Jennifer A. Hutcheon holds New Investigator Awards from the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research.

The funders played no role in this study.

Each author has indicated that he or she has met the journal's requirements for authorship.

Corresponding author: Gillian E. Hanley, PhD, Diamond Health Care Centre, 6207A 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada; email: Gillian.hanley@phsa.ca.

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

ISSN: 0029-7844/17

The World Health Organization currently recommends that the interval between a woman's previous delivery and her subsequent conception (the interpregnancy interval) should be a minimum of 2 years.[1] This recommendation is based on studies indicating that both short (less than 18 months) and long (greater than 59 months) interpregnancy intervals are associated with increased risks of preterm birth, low birth weight, small-for-gestational-age birth, and neonatal intensive care unit admission.[2–6] Longer interpregnancy intervals have also been associated with increased risk of preeclampsia.[7]

However, shorter interpregnancy intervals may simply reflect differences in socioeconomic status, lifestyle, and access to contraception–all conditions that also tend to correlate with differences in

reproductive risks.[8,9] Convincing evidence that these relationships may be heavily confounded has been published. Erickson and Bjerkdal[10] used Norwegian data to examine the association between interpregnancy interval and birth weight and reported that it was equally predictive of birth weight in the first and second births. Given that the length of the interpregnancy interval should not affect birth weight in the first birth, they concluded the relationship was unlikely to be causal. More recently, Ball et al[11] examined the relationship between interpregnancy interval and adverse neonatal outcomes matching interpregnancy intervals in the same mother among women who had three or more singleton live births in their study period. They reported that the matched design showed no statistically significant effects and questioned the causal effect of short interpregnancy interval on adverse birth outcomes. However, the relationship between interpregnancy interval and maternal adverse outcomes has received considerably less attention.

We build on these existing approaches by examining the association between interpregnancy interval and adverse pregnancy outcome using a within-woman matched analysis of successive pregnancies. Using a mother as her own control aims to reduce confounding by unmeasured, or difficult to measure, determinants of health that are more likely to remain constant within women over time but might otherwise result in apparent increased risks with short and long interpregnancy intervals.

MATERIALS AND METHODS

We conducted a retrospective cohort study and used data from the British Columbia Perinatal Data Registry, a database built from abstracted obstetric and neonatal medical charts for more than 99% of deliveries in British Columbia. To ensure completion and validity, abstractors were trained in how to locate and abstract data from the medical chart and provincially standardized forms were available and widely used across the province. Ongoing quality checks helped ensure completion and validity of database variables and the information in the Registry was recently found to be valid.[12] Women who delivered more than one neonate during our study period were identified through probabilistic linkage using a combination of Personal Health Number (a unique lifetime identifier given to each British Columbia resident), first and last names, and date of birth. Research ethics approval was obtained from the University of British Columbia's and Children's and Women's Clinical Research Ethics Board.

Our primary analyses included all women with at least three singleton deliveries (ie, two interpregnancy intervals) in British Columbia between April 1, 2000, and March 31, 2015, delivered at 20–44 weeks of gestation inclusive. We did not exclude stillbirths or terminations. Sensitivity analyses examined all women with at least two singleton deliveries (one interpregnancy interval) during the study period.

Interpregnancy interval was defined as the number of months between the delivery date of the first neonate and the conception date of the subsequent pregnancy, which was estimated using the delivery date of the second neonate minus its gestational age at birth. Interpregnancy interval was modeled as a categorical variable classified as: 0–5 months, 6–11 months, 12–17 months, 18–23 months (reference category), 24–59 months, and 60 months or greater.

Neonatal outcomes included preterm birth (delivery less than 37 completed weeks of gestation), low birth weight (birth weight less than 2,500 g), and small-for-gestational-age birth (SGA, less than the 10th centile for sex and gestational age). We also examined neonatal intensive care use; however, analyses were restricted to the years 2006–2015 as a result of changes in data collection for this variable. Maternal outcomes included gestational diabetes (International Classification of Diseases, 10th Revision codes O24.4, O24.8 or O24.9 or International Classification of Diseases, 9th Revision code 648.0), prepregnancy obesity (body mass index [BMI, calculated as weight (kg)/[height (m)]^2] 30 or greater), and preeclampsia or eclampsia (International Classification of Disease, 10th Revision codes O11.x or O13.x or O14.x or O15.x or International Classification of Diseases, 9th Revision codes 642.3x, 642.4x, 642.5x or 642.6x).

We controlled for possible confounders including maternal age at the time of each delivery, delivery year, diabetes (both pre-existing and gestational with the exception of models examining risk of gestational diabetes), hypertension (defined as any diagnosis of high blood pressure, which was not controlled for in models examining preeclampsia or eclampsia), smoking during pregnancy, and history of perinatal death. Prepregnancy BMI data is missing for approximately 25% of women in our cohort, so we conducted a sensitivity analysis examining whether inclusion of maternal BMI when entering the first pregnancy in our study period changed our point estimates. None of our point estimates changed by more than 10% when restricting to women with complete BMI information, so we present the results for the entire cohort unadjusted for BMI.

We first ran unconditional logistic regression to calculate the population-level association between interpregnancy interval and adverse outcome (ie, the conventional approach that examines differences

between women). Confidence intervals (CIs) were adjusted to account for nonindependence of successive deliveries to the same woman. Next we used conditional logistic regression to estimate the effect of interpregnancy interval on adverse pregnancy outcome within the same woman (ie, a successive pregnancy-matched design within the same woman). This approach matched a woman to her successive pregnancies, which controlled for characteristics that do not change or remain highly stable over time. We evaluated the potential for confounding in the conventional models by comparing the odds ratios (ORs) and 95% CIs obtained from the unconditional (between-women) model with those from the conditional (within-woman) models.

To examine whether meaningful differences existed in women with at least three deliveries from women who had only two births, we conducted a sensitivity analysis comparing our between-women estimates with those from a model including the larger cohort of women in British Columbia with two or more deliveries (ie, one or more interpregnancy interval). We expected that, if the relationship between interpregnancy interval and adverse pregnancy outcomes was significantly different in women with three or more deliveries compared with women with two or more deliveries, the sensitivity analysis using unconditional logistic regression to compare between women would result in significantly different effect estimates when examining women with three or more deliveries compared with women with two or more deliveries.

RESULTS

There were 411,699 deliveries in British Columbia during our study period, including 183,442 to women with two or more deliveries and 39,712 to women with three or more deliveries. Excluding women who delivered multiples and those with extreme gestational ages (less than 20 weeks or greater than 44 weeks of gestation) as well as those with missing outcome data left 178,709 women with at least two deliveries and 38,178 women with at least three deliveries. Of these 38,178 women, only 20,664 had available data for neonatal intensive care use (ie, neonates born 2006–2015) and 20,771 had complete data on BMI.

Approximately 4% of deliveries occurred after an interpregnancy interval of 0–5 months, 22% after an interpregnancy interval of 12–17 months, and 32% after an interpregnancy interval of 24–59 months (Table 1). Women with shorter interpregnancy intervals tended to be younger and were more likely to have had a previous perinatal death than women in other categories. Rates of diabetes and smoking during pregnancy were higher at the short and long extremes of the interpregnancy interval categories. Any diagnosis of hypertension was more likely among women with a long interpregnancy interval (Table 2).

Table 1. Characteristics of the Study Population by Interpregnancy Interval for Both Second and Third Births

	Interpregnancy Interval (mo)					
Characteristic	0–5	6–11	12–17	18–23	24–59	60 or More
Total (N=76,356)	3,242	14,607	16,772	12,069	24,541	5,125
2nd birth (n=38,178)	1,815	8,255	9,339	6,180	10,568	2,021
3rd birth (n=38,178)	1,427	6,352	7,433	5,889	13,973	3,104
Delivery year						
April 1, 2000–March 31, 2005	990 (30.5)	3,738 (25.6)	3,634 (21.7)	2,216 (18.4)	2,116 (8.6)	0 (0)
April 1, 2005–March 31, 2010	1,368 (42.2)	6,447 (44.1)	7,538 (44.9)	5,584 (46.3)	11,817 (48.2)	1,589 (31.0)
April 1, 2010–March 31, 2015	884 (27.3)	4,422 (30.3)	5,600 (33.4)	4,269 (35.4)	10,608 (43.2)	3,536 (69.0)
Maternal age (y)						
0–17	44 (1.4)	81 (0.6)	24 (0.1)	16 (0.1)	10 (0.04)	0 (0)
18–24	1,089 (33.6)	3,433 (23.5)	2,789 (16.6)	1,850 (15.3)	3,403 (13.9)	202 (3.9)
25–29	1,007 (31.1)	4,941 (33.8)	5,420 (32.3)	3,649 (30.2)	7,276 (29.7)	1,291 (25.2)
30–34	778 (24.0)	4,253 (29.1)	5,902 (35.2)	4,346 (36.0)	8,418 (34.3)	1,918 (37.4)
35–39	288 (8.9)	1,704 (11.7)	2,315 (13.8)	1,924 (15.9)	4,653 (19.0)	1,366 (26.7)
40 or older	36 (1.1)	195 (1.3)	322 (1.9)	284 (2.4)	781 (3.2)	348 (6.8)
Diabetes	260 (8.0)	869 (6.0)	1,069 (6.4)	830 (6.9)	2,188 (8.9)	629 (12.3)
Any hypertension	93 (2.9)	363 (2.5)	452 (2.7)	392 (3.3)	900 (3.7)	270 (5.3)
Smoked during pregnancy	544 (16.8)	1,458 (10.0)	1,217 (7.3)	996 (8.3)	2,965 (12.1)	935 (18.2)
Previous perinatal death	421 (13.0)	655 (4.5)	442 (2.6)	269 (2.2)	490 (2.0)	91 (1.8)

Data are n or n (%).

Table 2. Rates of Neonatal and Maternal Adverse Outcomes by Interpregnancy Interval and Birth Number

Neonatal and Maternal Adverse Outcome	Total	Interpregnancy Interval (mo)					
		0–5	6–11	12–17	18–23	24–59	60 or More
Preterm birth							
2nd birth	3,422 (9.0)	232 (12.8)	714 (8.7)	707 (7.6)	501 (8.1)	1,024 (9.7)	244 (12.1)
3rd birth	3,665 (9.6)	227 (15.9)	650 (10.2)	607 (8.2)	505 (8.6)	1,305 (9.3)	371 (12.0)
SGA birth							
2nd birth	1,946 (5.1)	108 (6.0)	411 (5.0)	420 (4.5)	291 (4.7)	593 (5.7)	123 (6.1)
3rd birth	1,659 (4.4)	82 (5.8)	258 (4.1)	287 (3.9)	237 (4.0)	624 (4.5)	171 (5.5)
Neonatal intensive care use (n=20,664)							
2nd birth	1,109 (5.4)	51 (6.7)	212 (5.4)	230 (4.8)	142 (4.5)	330 (5.4)	144 (7.6)
3rd birth	1,701 (5.3)	72 (7.1)	272 (5.8)	261 (4.6)	241 (5.0)	650 (5.1)	205 (6.6)
Low birth weight							
2nd birth	1,886 (4.9)	143 (7.9)	346 (4.2)	369 (4.0)	304 (4.9)	589 (5.6)	135 (6.7)
3rd birth	1,645 (4.3)	107 (7.5)	293 (4.6)	267 (3.6)	197 (3.4)	604 (4.3)	177 (5.7)
Gestational diabetes							
2nd birth	2,202 (5.8)	119 (6.6)	399 (4.8)	452 (4.8)	338 (5.5)	718 (6.8)	176 (8.7)
3rd birth	3,319 (8.7)	128 (9.0)	426 (6.7)	565 (7.6)	442 (7.5)	1,345 (9.6)	413 (13.3)
Entering pregnancy obese (n=18,407)							
2nd birth	3,501 (14.2)	184 (17.4)	717 (13.5)	720 (11.7)	529 (12.8)	1,104 (16.3)	247 (18.8)
3rd birth	4,256 (17.0)	173 (21.6)	701 (18.1)	721 (14.9)	607 (15.3)	1,613 (17.1)	441 (20.5)
Preeclampsia–eclampsia							
2nd birth	796 (2.1)	28 (1.5)	132 (1.6)	161 (1.7)	118 (1.9)	284 (2.7)	73 (3.6)
3rd birth	1,093 (2.9)	30 (2.1)	127 (2.0)	169 (2.3)	187 (3.2)	441 (3.2)	139 (4.5)

SGA, small for gestational age.
Data are n (%).

Rates of all adverse neonatal outcomes were higher among women with the shortest and longest interpregnancy intervals than those in the middle categories (Table 2). Gestational diabetes and prepregnancy obesity were more common among women with both shorter and longer intervals, whereas preeclampsia–eclampsia was more common among women with the longest intervals. Given that conditional logistic regression models primarily take advantage of discordance within the same mother, we present tables outlining the discordance between interpregnancy interval categories and the outcomes of interest across the two pregnancies in the same mother in Appendices 1 and 2, available online at http://links.lww.com/AOG/A921.

We report in detail on the between-women analyses to facilitate comparison with previous research that has used this statistical approach and to highlight how the associations change when using a within-woman approach. In unconditional (unmatched) logistic regression analyses, short interpregnancy interval was associated with increased risk of preterm birth, SGA birth, and low birth weight (Table 3). Women with an interpregnancy interval of 0–5 months were significantly more likely to have neonates born preterm (adjusted OR 1.53, 95% CI 1.35–1.73), to have a neonate born SGA (adjusted OR 1.26, 95% CI 1.06–1.50), and to have a low-birth-weight neonate (adjusted OR 1.64, 95% CI 1.39–1.94). Longer interpregnancy interval was also significantly associated with increased risk of preterm birth, SGA birth, a low-birth-weight neonate, and neonatal intensive care use with an adjusted OR of 1.44 (95% CI 1.23–1.67) for an interpregnancy intervals of 60 months or greater. Increased risks were reported for women with interpregnancy intervals of 24–59 months for preterm birth, SGA birth, and low birth weight (adjusted OR 1.11, 95% CI 1.02–1.20; adjusted OR 1.13, 95% CI 1.02–1.26; and adjusted OR 1.14, 95% CI 1.03–1.27, respectively).

In the matched design of conditional logistic regression, interpregnancy intervals shorter than the reference category were no longer associated with significantly increased risk of any of the adverse neonatal outcomes (Table 4). Rather, short interpregnancy intervals appeared protective for low birth weight for women in the two shortest interpregnancy interval categories (adjusted OR 0.57, 95% CI 0.46–0.72 for interpregnancy interval of 0–5 months and adjusted OR 0.79, 95% CI 0.66–0.95 for women with an interpregnancy interval of 6–11 months). Long

Table 3. Neonatal Outcomes and Interpregnancy Interval

Outcome	Unmatched But Restricted to Women With 3 Live Births (n=38,178)		Matched and Restricted to Women With 3 Live Births (n=38,178)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Preterm birth (mo)				
0–5	**1.81 (1.61–2.04)**	**1.53 (1.35–1.73)**	0.84 (0.71–1.01)	0.85 (0.71–1.02)
6–11	**1.13 (1.04–1.23)**	**1.10 (1.02–1.21)**	0.90 (0.78–1.03)	0.91 (0.79–1.04)
12–17	0.93 (0.85–1.01)	0.94 (0.87–1.03)	0.95 (0.83–1.09)	0.97 (0.84–1.11)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	**1.15 (1.07–1.25)**	**1.11 (1.02–1.20)**	1.05 (0.93–1.19)	0.99 (0.88–1.13)
60 or greater	**1.50 (1.35–1.67)**	**1.33 (1.19–1.49)**	**1.28 (1.08–1.52)**	1.09 (0.91–1.30)
SGA birth (mo)				
0–5	**1.36 (1.15–1.62)**	**1.26 (1.06–1.50)**	0.82 (0.63–1.06)	0.81 (0.62–1.06)
6–11	1.05 (0.93–1.18)	1.03 (0.92–1.16)	0.87 (0.72–1.04)	0.85 (0.71–1.03)
12–17	0.96 (0.86–1.08)	0.97 (0.86–1.09)	1.01 (0.84–1.21)	1.00 (0.84–1.21)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	**1.14 (1.03–1.27)**	**1.13 (1.02–1.26)**	0.97 (0.82–1.14)	1.06 (0.89–1.25)
60 or greater	**1.33 (1.15–1.55)**	**1.29 (1.10–1.50)**	0.98 (0.78–1.22)	1.21 (0.94–1.54)
Neonatal intensive care use (n=20,664) (mo)				
0–5	**1.46 (1.19–1.80)**	1.19 (0.96–1.48)	1.14 (0.80–1.62)	1.11 (0.78–1.60)
6–11	**1.17 (1.02–1.34)**	1.13 (0.99–1.30)	1.15 (0.90–1.45)	1.10 (0.87–1.41)
12–17	0.97 (0.84–1.11)	0.98 (0.85–1.12)	1.07 (0.85–1.36)	1.04 (0.82–1.32)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	1.08 (0.96–1.22)	1.05 (0.93–1.18)	0.91 (0.73–1.14)	0.94 (0.75–1.17)
60 or greater	**1.48 (1.27–1.72)**	**1.44 (1.23–1.67)**	**1.42 (1.05–1.92)**	**1.39 (1.02–1.90)**
Low birth weight (mo)				
0–5	**1.93 (1.65–2.26)**	**1.64 (1.39–1.94)**	**0.56 (0.45–0.70)**	**0.57 (0.46–0.72)**
6–11	1.06 (0.94–1.19)	1.03 (0.92–1.16)	**0.79 (0.66–0.94)**	**0.79 (0.66–0.95)**
12–17	0.91 (0.81–1.03)	0.92 (0.82–1.04)	0.96 (0.80–1.15)	0.96 (0.79–1.15)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	**1.18 (1.06–1.31)**	**1.14 (1.03–1.27)**	1.09 (0.92–1.28)	1.11 (0.94–1.31)
60 or greater	**1.50 (1.29–1.73)**	**1.35 (1.16–1.57)**	1.24 (0.98–1.57)	**1.31 (1.02–1.68)**

SGA, small for gestational age.
Bold indicates significance at the 95% confidence level.
* Adjusted for maternal age at the time of each delivery, delivery year, diabetes, hypertension, smoking during pregnancy, and history of perinatal death.

interpregnancy intervals of 60 months or greater remained significantly associated with increased risk of neonatal intensive care use (adjusted OR 1.39, 95% CI 1.02–1.90) and low birth weight (adjusted OR 1.31, 95% CI 1.02–1.68).

The unmatched analyses (Table 4) indicate that women were at increased risk of gestational diabetes and prepregnancy obesity if their interpregnancy intervals were 0–5 months (adjusted OR 1.47, 95% CI 1.26–1.72 and adjusted OR 1.29, 95% CI 1.06–1.50, respectively) or greater than 24 months. Only women with interpregnancy intervals 60 months or greater were at increased risk of preeclampsia–eclampsia (adjusted OR 1.31, 95% CI 1.09–1.58). Women with interpregnancy intervals less than 18–23 months all appeared to be at slightly lower risk of preeclampsia–eclampsia.

In conditional logistic regression models, only gestational diabetes and entering the pregnancy obese were significantly associated with a short interpregnancy interval. The highest adjusted OR was for entering a pregnancy obese among women with an interpregnancy interval of 0–5 months (adjusted OR 1.61, 95% CI 1.05–2.45). Entering a pregnancy obese was also significantly associated with an interpregnancy interval of 6–11 months (adjusted OR 1.43, 95% CI 1.10–1.87). The risk of gestational diabetes was also significantly increased among women with an interpregnancy interval of 0–5 months (adjusted OR 1.35, 95% CI 1.02–1.80). Women with an interpregnancy interval of 12–18 months had significantly lower odds of preeclampsia–eclampsia (adjusted OR 0.71, 95% CI 0.54–0.94).

Sensitivity analyses conducted using unconditional logistic regression models among all women who had at least two births are reported in Appendices 3 and 4, available online at http://links.lww.com/AOG/A921.

Table 4. Maternal Outcomes and Interpregnancy Interval

Outcome	Unmatched But Restricted to Women With 3 Live Births (n=38,178)		Matched and Restricted to Women With 3 Live Births (n=38,178)	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Gestational diabetes (mo)				
0–5	**1.19 (1.03–1.39)**	**1.47 (1.26–1.72)**	1.15 (0.87–1.51)	**1.35 (1.02–1.80)**
6–11	**0.87 (0.78–0.96)**	1.00 (0.90–1.11)	0.84 (0.69–1.01)	0.99 (0.81–1.20)
12–17	0.93 (0.85–1.03)	0.99 (0.90–1.09)	0.93 (0.78–1.11)	1.01 (0.84–1.23)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	**1.32 (1.22–1.45)**	**1.22 (1.12–1.33)**	**1.29 (1.10–1.52)**	0.97 (0.81–1.16)
60 or greater	**1.88 (1.68–2.10)**	**1.32 (1.18–1.48)**	**2.11 (1.71–2.62)**	1.02 (0.80–1.32)
Obese at beginning of pregnancy (n=18,407) (mo)				
0–5	**1.46 (1.28–1.66)**	**1.29 (1.13–1.48)**	1.35 (0.90–2.02)	**1.61 (1.05–2.45)**
6–11	**1.12 (1.03–1.22)**	1.09 (1.00–1.19)	1.26 (0.97–1.62)	**1.43 (1.10–1.87)**
12–17	0.92 (0.85–1.00)	0.92 (0.85–1.01)	1.01 (0.79–1.31)	1.10 (0.85–1.43)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	**1.23 (1.14–1.33)**	**1.17 (1.08–1.27)**	**1.26 (1.01–1.58)**	1.01 (0.80–1.29)
60 or greater	**1.51 (1.36–1.68)**	**1.34 (1.20–1.49)**	**1.72 (1.28–2.29)**	0.79 (0.56–1.11)
Preeclampsia (mo)				
0–5	**0.70 (0.53–0.93)**	**0.73 (0.55–0.97)**	0.77 (0.49–1.21)	0.83 (0.53–1.31)
6–11	**0.70 (0.59–0.83)**	**0.74 (0.62–0.87)**	**0.66 (0.50–0.86)**	**0.71 (0.54–0.94)**
12–17	**0.77 (0.66–0.90)**	**0.79 (0.68–0.93)**	0.92 (0.71–1.18)	0.96 (0.74–1.24)
18–23	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
24–59	**1.17 (1.02–1.35)**	1.09 (0.95–1.25)	1.31 (1.04–1.65)	1.09 (0.86–1.38)
60 or greater	**1.66 (1.39–2.00)**	**1.31 (1.09–1.58)**	**2.23 (1.60–3.10)**	1.39 (0.97–2.00)

Bold indicates significance at the 95% confidence level.

* Adjusted for maternal age at the time of each delivery, delivery year, diabetes (both pre-existing and gestational, with the exception of models examining risk of gestational diabetes), hypertension (defined as any diagnosis of high blood pressure, which was not controlled for in models examining preeclampsia or eclampsia), smoking during pregnancy, and history of perinatal death.

These results are very similar to those reported for the unmatched (between-women) analyses in our cohort of women with three or more births. The ORs suggest a strong effect of short and long interpregnancy interval on preterm birth, neonatal intensive care use, and low birth weight (Appendix 3, http://links.lww.com/AOG/A921). With respect to maternal adverse outcomes, Appendix 4, available online at (http://links.lww.com/AOG/A921), indicates that short interpregnancy intervals increase risk of gestational diabetes and entering a pregnancy obese. Long interpregnancy intervals were associated with an increased risk of gestational diabetes, entering a pregnancy obese, and preeclampsia–eclampsia.

DISCUSSION

Our study found that the majority of associations between interpregnancy interval and adverse neonatal outcomes (preterm birth, SGA birth, and low birth weight) observed using the conventional between-women analysis was no longer significant when women were used as their own controls. This suggests that factors that remain constant or relatively stable for a given woman over successive pregnancies (eg, socioeconomic status, lifestyle factors, and access to care) are important confounders in the relationship between interpregnancy interval and the adverse neonatal outcomes of preterm birth, SGA, low birth weight, and use of neonatal intensive care.

With respect to maternal outcomes, the findings were more nuanced. In the unconditional (between-women) models, women with short and long interpregnancy intervals were more likely to have gestational diabetes and to enter a pregnancy obese. Women with long interpregnancy intervals were more likely to have preeclampsia–eclampsia. However, in the matched analysis, the relationships that remained statistically significant were between short interpregnancy interval and gestational diabetes or entering the pregnancy obese. Given that short interpregnancy intervals provide less time to lose weight from a previous pregnancy, this may increase the likelihood of beginning the next pregnancy obese and, given the relationship between prepregnancy BMI and gestational diabetes,[13] short intervals then also increase the likelihood of developing gestational diabetes. Previous work has reported that weight retention between first and second pregnancies is

a risk factor for gestational diabetes and pregnancy-induced hypertension.[14]

Contrary to a large body of previous research,[2–4,9,13,15–19] our research does not support a relationship between short interpregnancy intervals and adverse neonatal outcomes nor does it support a relationship between long interpregnancy interval and adverse maternal outcomes.

Our research is consistent with the previous analyses by Erickson and Bjerkdal[10] reporting that the associations between interpregnancy interval and birth weight of the first birth were similar to that between interpregnancy interval and the birth weight of the second birth as well as with the more recent work by Ball et al[11] examining the relationship between interpregnancy interval and preterm birth, SGA birth, and low birth weight among women in Perth, Australia, matching interpregnancy intervals within the same mother. Ball et al[11] reported that the matched design showed no statistically significant associations between short interpregnancy interval and preterm birth, low birth weight, and SGA birth leading them to question the causal effect of short interpregnancy interval on adverse birth outcomes. However, our findings differ with respect to long interpregnancy intervals, because Ball et al reported that a long interpregnancy interval remained statistically significantly associated with SGA birth, which was not the case in our data. Rather the increased risk of a long interpregnancy interval persisted for low birth weight and neonatal intensive care use in our data (which was not an outcome studied by Ball et al). Our study additionally considers the effect of interpregnancy interval on maternal health by examining important outcomes such as gestational diabetes, beginning the pregnancy obese, and preeclampsia–eclampsia.

Our study has several limitations. We lacked data on some potentially important confounders, including data on fertility issues, pregnancy intention, and pregnancy losses before 20 weeks of gestation. Given the lack of data on pregnancy losses, we calculated our interpregnancy interval using pregnancies that resulted in either live or stillbirth at or after 20 weeks of gestation. Calculating intervals relative to pregnancy losses may change our effect estimates depending on the effects and frequency of pregnancy losses. Previous research has shown that women with a history of prior spontaneous and induced abortions are at increased risk of adverse outcomes, including preterm birth.[20] However, because this lack of data would have affected both our unmatched and matched analyses, they are unlikely to explain the differences observed between the two approaches. Our lack of data on fertility issues and unplanned pregnancies may confound our estimates because infertility is likely to increase both the length of the interpregnancy interval and the risk of adverse outcomes,[21,22] whereas unplanned pregnancies are more likely to result in either short or long interpregnancy intervals and also have been associated with increased risk of adverse outcomes[23]; however, these missing data would affect both the between-women and within-woman analyses equally. We were also limited by missing data on BMI for approximately 25% of our sample; however, our sensitivity analysis suggested that the relationships were consistent between the full sample and the 75% of the sample with complete BMI information. Finally, complete capture of neonatal intensive care data was available only for births between 2006 and 2015. Thus, our conclusions regarding neonatal intensive care use are based on a small sample size and our analyses of maternal BMI should be interpreted with caution.

Our results may not be generalizable to women in developing countries. In developing countries, it is more likely that concerns regarding nutrient depletion in pregnancy may affect the association between short interpregnancy interval and neonatal outcomes because women may have less access to the types of nutrition required to replenish folate and iron stores.[11,24] Our study is also limited by the small number of women with three or more successive deliveries in our data. It is possible that the association between interpregnancy interval and adverse pregnancy outcomes differs among the highly selected cohort of women with three or more successive deliveries. However, the consistency of the findings from the traditional logistic regression models between the women with at least two deliveries over the study period and the women with three or more deliveries suggests that it is unlikely that our results are reflective of differences in the two cohorts of women.

Despite the consistency of reports of increased risk among women with short and long interpregnancy intervals for adverse neonatal and maternal outcomes, our research suggests that much of this work may be biased as a result of important methodologic flaws. Given the current recommendations regarding interpregnancy intervals, more work is needed to clarify these relationships and to examine the generalizability of our findings so that recommendations around lengths of interpregnancy intervals will confer the most possible benefit to mothers and their neonates.

REFERENCES

1. Marston C. Report of a WHO technical consultation on birth spacing. Geneva (Switzerland): World Health Organization; 2005.
2. Chen I, Jhangri GS, Chandra S. Relationship between interpregnancy interval and congenital anomalies. Am J Obstet Gynecol 2014;210:564 e1–8.
3. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. JAMA 2006;295:1809–23.
4. Fuentes-Afflick E, Hessol NA. Interpregnancy interval and the risk of premature infants. Obstet Gynecol 2000;95:383–90.
5. King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. J Nutr 2003;133(suppl 2):1732–6S.
6. Stephansson O, Dickman PW, Cnattingius S. The influence of interpregnancy interval on the subsequent risk of stillbirth and early neonatal death. Obstet Gynecol 2003;102:101–8.
7. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Effects of birth spacing on maternal health: a systematic review. Am J Obstet Gynecol 2007;196:297–308.
8. Klebanoff MA. The interval between pregnancies and the outcome of subsequent births. N Engl J Med 1999;340:643–4.
9. 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.
10. Erickson JD, Bjerkedal T. Interpregnancy interval. Association with birth weight, stillbirth, and neonatal death. J Epidemiol Community Health 1978;32:124–30.
11. 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.
12. Frosst G, Hutcheon J, Joseph KS, Kinniburgh B, Johnson C, Lee L. Validating the British Columbia Perinatal Data Registry: a chart re-abstraction study. BMC Pregnancy Childbirth 2015; 15:123.
13. Conde-Agudelo A, Rosas-Bermudez A, Castaño F, Norton MH. Effects of birth spacing on maternal, perinatal, infant, and child health: a systematic review of causal mechanisms. Stud Fam Plann 2012;43:93–114.
14. Bogaerts A, Van den Bergh BR, Ameye L, Witters I, Martens E, Timmerman D, et al. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynecol 2013;122: 999–1009.
15. Chen I, Jhangri GS, Lacasse M, Kumar M, Chandra S. Relationship between interpregnancy interval and adverse perinatal and neonatal outcomes in northern Alberta. J Obstet Gynaecol Can 2015;37:598–605.
16. DeFranco EA, Seske LM, Greenberg JM, Muglia LJ. Influence of interpregnancy interval on neonatal morbidity. Am J Obstet Gynecol 2015;212:386.e1–9.
17. Hussaini KS, Ritenour D, Coonrod DV. Interpregnancy intervals and the risk for infant mortality: a case control study of Arizona infants 2003-2007. Matern Child Health J 2013;17: 646–53.
18. Kwon S, Lazo-Escalante M, Villaran MV, Li CI. Relationship between interpregnancy interval and birth defects in Washington State. J Perinatol 2012;32:45–50.
19. Rousso D, Panidis D, Gkoutzioulis F, Kourtis A, Mavromatidis G, Kalahanis I. Effect of the interval between pregnancies on the health of mother and child. Eur J Obstet Gynecol Reprod Biol 2002;105:4–6.
20. Makhlouf MA, Clifton RG, Roberts JM, Myatt L, Hauth JC, Leveno KJ, et al. Adverse pregnancy outcomes among women with prior spontaneous or induced abortions. Am J Perinatol 2014;31:765–72.
21. Declercq E, Luke B, Belanoff C, Cabral H, Diop H, Gopal D, et al. Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). Fertil Steril 2015; 103:888–95.
22. Doyle P, Beral V, Maconochie N. Preterm delivery, low birthweight and small-for-gestational-age in liveborn singleton babies resulting from in-vitro fertilization. Hum Reprod 1992;7: 425–8.
23. Shah PS, Balkhair T, Ohlsson A, Beyene J, Scott F, Frick C. Intention to become pregnant and low birth weight and preterm birth: a systematic review. Matern Child Health J 2011; 15:205–16.
24. Wendt A, Gibbs CM, Peters S, Hogue CJ. Impact of increasing inter-pregnancy interval on maternal and infant health. Paediatr Perinat Epidemiol 2012;26(suppl 1):239–58.