OBSTETRICS

Relationship between interpregnancy interval and congenital anomalies

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OBJECTIVE: To assess the association between interpregnancy intervals and congenital anomalies.

STUDY DESIGN: A retrospective cohort study on women who had 2 consecutive singleton births from 1999—2007 was conducted using a linked dataset from the Alberta Perinatal Health Program, the Alberta Congenital Anomalies Surveillance System, and the Alberta Health and Wellness Database. Interpregnancy interval was calculated as the interval between 2 consecutive deliveries minus the gestational age of the second infant. The primary outcome of congenital anomaly was defined using the International Classification of Diseases. Maternal demographic and obstetric characteristics and interpregnancy intervals were included in multivariable logistic regression models for congenital anomalies.

RESULTS: The study included 46,243 women, and the overall rate of congenital anomalies was 2.2%. Both short and long interpregnancy intervals were associated with congenital anomalies. The lowest rate was for the 12-17 months category (1.9%, reference category), and increased rates were seen for both short intervals (2.5% for 0-5 months; adjusted odds ratio, 1.32; 95% confidence interval, 1.01—1.72) and long intervals (2.3% for 24-35 months; adjusted odds ratio, 1.25; 95% confidence interval, 1.02—1.52). Statistically significant associations were also observed for folate independent anomalies, but not for folate dependent anomalies.

CONCLUSION: The risk of congenital anomalies appears to increase with both short and long interpregnancy intervals. This study supports the limited existing studies in the literature, further explores the types of anomalies affected, and has implications for further research and prenatal risk assessment.

Key words: birth spacing, congenital anomalies, folate deficiency, interpregnancy interval

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Birth spacing is an established independent predictor of pregnancy outcomes. Both short and long interpregnancy intervals have been shown repeatedly and in different populations to be associated with multiple adverse fetal outcomes, including fetal growth restriction, preterm birth, perinatal death,[1] and maternal morbidity and mortality.[2] Several mechanisms have been proposed to explain this prevailing phenomenon, including postpartum nutritional stress and hormone imbalance, but the folate depletion hypothesis appears to be the most commonly cited.[3-5] Serum studies have shown that women in late pregnancy and early postpartum are relatively folate-depleted.[6-7] In addition, low serum folate in pregnancy has also been associated with fetal growth restriction and preterm birth,[8-11] and this relationship appears to be mitigated by folate supplementation.[9]

Folate deficiency has been associated with increased rates of certain congenital anomalies, such as neural tube defects, cleft lip and palate, cardiovascular defects, urinary tract anomalies, and limb defects.[12] Because women with short interpregnancy intervals are relatively folate deficient, it is conceivable that women with short interpregnancy intervals may also be at risk of congenital anomalies. The association between interpregnancy interval and congenital anomaly rate was recently reported in 2 large studies. Both the Israeli retrospective cohort study[13] and the American case-control study[14] found congenital malformations to be associated with both short (0-5 months) and long interpregnancy (≥60 months) intervals. However, further information pertaining to specific categories of anomalies was not available in either study. Studies investigating specific anomalies, such as neural tube defects, have been limited by the potential confounding associated with case-control design,[15,16] as well as a high proportion of terminations and miscarriages in study populations. Furthermore, results have been conflicting, as 1 retrospective cohort study found increased risk of isolated cleft palate to be associated with long, but not short interpregnancy intervals.[17]

The purpose of this study is primarily to determine the relationship between interpregnancy intervals and all

★ EDITORS' CHOICE ★

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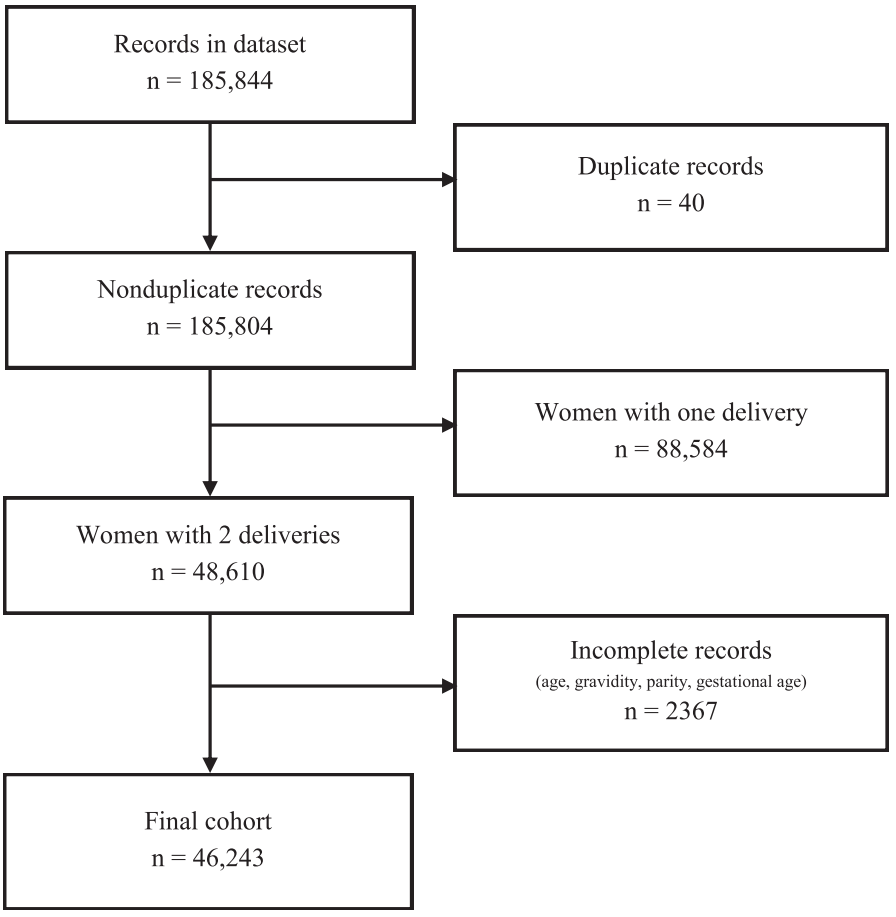
FIGURE 1
Selection of study cohort from linked dataset, Alberta, 1999-2007



From 185,844 records of women who had given birth to an infant in northern Alberta from Jan. 1, 1999 to Dec. 31, 2007, duplicate records, records with only 1 delivery, and records with missing or inconsistent information on age, gravidity, parity, and gestational age were excluded, to provide the final study cohort of 46,243 women who had 2 consecutive singleton births. Women with multiple gestations excluded prior to dataset generation.

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congenital anomalies; and, secondarily, to determine the relationship between interpregnancy intervals and specific categories of anomalies known to be associated with folate deficiency, and whether the relationship varies with folate-dependent or folate-independent anomalies.

Materials and Methods

Ethics approval

Ethics approval for this study was granted by the University of Alberta Health Research Ethics Board: Panel B (Health Services Research).

Data sources

The Alberta Perinatal Health Program is a province-wide program that collects perinatal data from provincial delivery records for all hospital births and registered midwife attended births in Alberta. Patient records from this database were linked to the Alberta Health and Wellness database, which holds extensive information on patients in the Alberta health care system, to obtain more detailed maternal demographic information, as well as the Alberta Congenital Anomalies Surveillance System, which collects information on all infant and fetal anomalies including terminations and early losses, to obtain more complete information on anomalies.

Study cohort

The study included any women who had given birth to an infant in northern Alberta, Canada, from Jan. 1, 1999, to Dec. 31, 2007, identified from the Alberta Perinatal Health Program database. The year 1999 was chosen as the start point for the study to ensure that our cohort fell completely within the Canadian mandatory folate food fortification era which began in 1998.[12,18] The study excluded women with multiple gestations. We also excluded records with incomplete information on maternal age, gravidity, parity, or gestational age, since the validation of interpregnancy intervals was dependent on this data.

Independent variables

Interpregnancy intervals were calculated as the interval between 2 consecutive deliveries minus the gestational age of the second infant. Interpregnancy intervals were categorized as follows: 0-5 months, 6-11 months, 12-17 months, 18-23 months, 24-35 months, and 36 months or more. To further characterize our study population and to evaluate potential confounders, further information was collected with respect to maternal demographic variables (age, use of social assistance) and maternal obstetric history (gravidity, parity, maternal diseases including preexisting diabetes, previous anomaly, or perinatal death).

Outcome variables

Congenital anomalies were defined according to the World Health Organization International Classification of Diseases. Cases coded as aneuploidies were not included. Our primary outcome measure was all congenital anomalies according to interpregnancy interval. Our secondary outcome measures were all folate-dependent anomalies, specific categories of folate-dependent anomalies, and all folate-independent anomalies by interpregnancy interval. Based on our national consensus guidelines,[12] folate-dependent anomalies were defined as neural tube defects, cleft lip and

TABLE 1
Description of total study population and by presence of all congenital anomalies and folate-dependent and independent anomalies

Variable	Total		All congenital anomalies		Folate-dependent anomalies		Folate-independent anomalies	
	n	%	n	%	n	%	n	%
Total	**46,243**	**100**	**1000**	**100**	**765**	**100**	**235**	**100**
Interpregnancy interval, mo								
0-5	3281	7.1	82	8.2	60	7.8	22	9.4
6-11	8397	18.2	180	18.0	134	17.5	46	19.6
12-17	10,186	22.0	190	19.0	155	20.3	35	14.9
18-23	7982	17.3	167	16.7	120	15.7	47	20.0
24-35	8961	19.4	209	20.9	162	21.2	47	16.2
36+	7436	16.1	172	17.2	134	17.5	38	14.9
Maternal age, y								
<20	1288	2.8	22	2.2	13	1.7	9	3.8
20-34	38,530	83.3	822	82.2	622	81.3	200	85.1
35+	6425	13.9	156	15.6	130	17.0	26	11.1
Gravidity								
2	23,504	50.8	488	48.8	378	49.4	110	46.8
3	11,758	25.4	258	25.8	191	25.0	67	28.5
4+	10,981	23.7	254	25.4	196	25.6	58	24.7
Parity								
1	32,544	70.4	701	70.1	531	69.4	170	72.3
2	8279	17.9	174	17.4	134	17.5	40	17.0
3+	5420	11.7	125	12.5	100	13.1	25	10.6
Prepregnancy diabetes								
No	45,122	99.1	973	98.3	746	98.3	227	98.3
Yes	417	0.9	17	1.7	13	1.7	4	1.7
Other maternal disease								
No	39,783	87.4	851	86.0	652	85.9	199	86.1
Yes	5756	12.6	139	14.0	107	14.1	32	13.9
Prior perinatal death								
No	44,594	97.9	955	96.5	729	96.0	226	97.8
Yes	945	2.1	35	3.5	30	4.0	5	2.2
Prior anomaly								
No	45,121	99.1	959	96.9	732	96.4	227	98.3
Yes	418	0.9	31	3.1	27	3.6	4	1.7
Prior small for gestation								
No	45,056	98.9	975	98.5	746	98.3	229	99.1
Yes	483	1.1	15	1.5	13	1.7	2	0.9

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(continued)

TABLE 1
Description of total study population and by presence of all congenital anomalies and folate-dependent and independent anomalies *(continued)*

Variable	Total		All congenital anomalies		Folate-dependent anomalies		Folate-independent anomalies	
	n	%	n	%	n	%	n	%
Prior large for gestation								
No	44,468	97.6	969	97.9	740	97.5	229	99.1
Yes	1071	2.4	21	2.1	19	2.5	2	0.9
Smoking in index pregnancy								
No	35,570	78.1	768	77.6	597	78.7	171	74.0
Yes	9969	21.9	222	22.4	162	21.3	60	26.0
Illicit drug(s) in index pregnancy								
No	44,904	98.6	975	98.5	752	99.1	221	96.5
Yes	635	1.4	15	1.5	7	0.9	8	3.5
Need for social assistance in index pregnancy								
No	39,681	87.6	867	86.7	661	86.4	206	87.7
Yes	5629	12.4	133	13.3	104	13.6	29	12.3
Index pregnancy outcome								
Livebirth	45,846	99.1	911	91.1	691	90.3	220	93.6
Stillbirth	231	0.5	26	2.6	21	2.7	5	2.1
Neonatal death	166	0.4	63	6.3	53	6.9	10	4.3
Index infant sex								
Female	22,480	48.7	383	38.4	290	38.0	93	39.7
Male	23,669	51.3	614	61.6	473	62.0	141	60.3
Index infant gestational age, wks								
<28	306	0.7	47	4.7	39	5.1	8	3.4
28-34	607	1.3	39	3.9	27	3.5	12	5.1
34-37	2244	4.8	91	9.1	63	8.2	28	11.9
37+	43,088	93.2	823	82.3	636	83.1	187	79.6
Index infant birthweight, g								
<1000	289	0.6	50	5.0	41	5.4	9	3.9
1000-1500	197	0.4	17	1.7	13	1.7	4	1.7
1500-2500	1424	3.1	76	7.6	55	7.2	21	9.0
2500+	44,262	95.9	854	85.7	655	85.7	199	85.4

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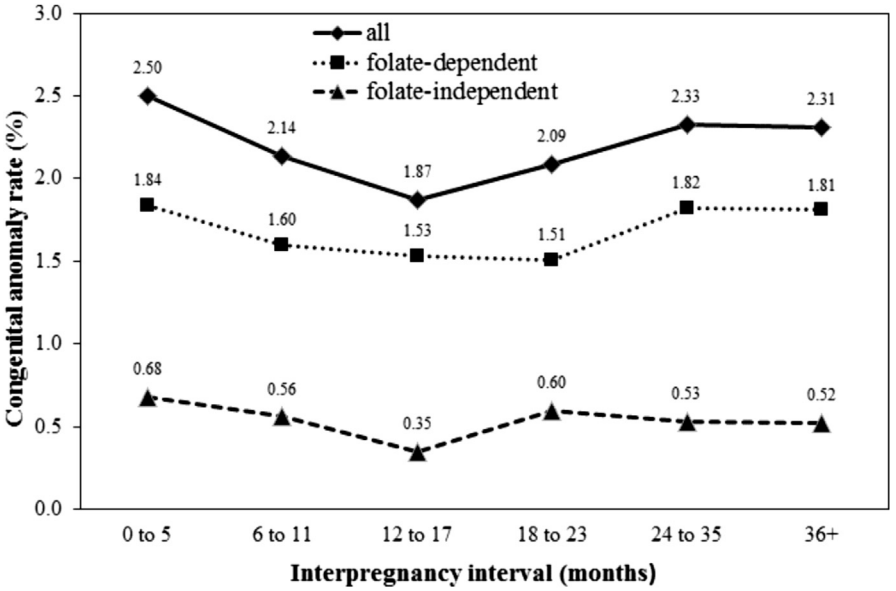
palate, cardiovascular defects, urinary tract anomalies, and limb defects. Other anomalies were classified as folate independent anomalies.

Statistical analysis

Statistical analyses were performed using SPSS 20 (SPSS Inc, Armonk, NY) and a $P < .05$ was considered for statistical significance. Results were expressed as mean ± standard deviation (SD) for continuous variables, numbers and percentages for categorical variables. The

FIGURE 2
Congenital anomaly rates by interpregnancy intervals



Both short and long interpregnany intervals were associated with congenital anomalies, with the lowest rate (1.9%) observed for 12-17 months, and increased rates for both short intervals (2.5% for 0-5 months) and long intervals (2.3% for 24-35 and 36+ months).

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χ^2 tests and logistic regression analyses were used for bivariate data analysis. Bivariate and multivariable logistic regression models were developed and the primary outcomes of interest were different congenital anomalies. Independent variables included demographic and socioeconomic characteristics as well as categorized interpregnancy interval as main variables of interest. Variables found to be statistically significant ($P < .05$) in the multivariable model and important confounding variables (ie, maternal age, parity, prepregnancy diabetes, previous pregnancy with anomaly, and index infant sex) were kept in the final model.

RESULTS

From the Alberta Perinatal Health Program Database, a dataset was generated consisting of 185,844 records of women who had given birth to an infant in northern Alberta from Jan. 1, 1999 to Dec. 31, 2007. Duplicate records and records with only 1 delivery in the study time frame were excluded. Records with missing or inconsistent information on age, gravidity, parity, and gestational age were also excluded. This resulted in a final study cohort of 46,243 women who had 2 consecutive singleton births in the study period (Figure 1).

A description of the study population is shown in Table 1. Most interpregnancy intervals (76.9%) were between 6 months and 35 months. With respect to the index pregnancy, most women were between 20-34 years of age (83.3%) and para 1 (70.4%). With respect to index

TABLE 2
Unadjusted and adjusted ORs and 95% CIs for congenital anomalies by IPIs

	OR (95% CI)					
	IPI, mo					
Congenital anomalies	0-5	6-11	12-17	18-23	24-35	36+
All (n = 1000)						
Unadjusted OR	1.35[a] (1.04–1.75)	1.15 (0.94–1.42)	1.00	1.12 (0.91–1.39)	1.26[a] (1.03–1.53)	1.25[a] (1.01–1.53)
Adjusted[b] OR	1.32[a] (1.01–1.72)	1.15 (0.93–1.41)	1.00	1.12 (0.91–1.38)	1.25[a] (1.02–1.52)	1.19 (0.97–1.48)
Folate dependent (n = 765)						
Unadjusted OR	1.21 (0.90–1.63)	1.05 (0.83–1.33)	1.00	0.99 (0.78–1.26)	1.19 (0.96–1.49)	1.19 (0.94–1.50)
Adjusted[b] OR	1.20 (0.88–1.63)	1.05 (0.83–1.33)	1.00	0.99 (0.77–1.25)	1.18 (0.94–1.47)	1.11 (0.88–1.41)
Folate independent (n = 235)						
Unadjusted OR	1.96[a] (1.15–3.35)	1.60[a] (1.03–2.48)	1.00	1.72[a] (1.11–2.66)	1.53 (0.99–2.38)	1.49 (0.94–2.37)
Adjusted[b] OR	1.86[a] (1.07–3.23)	1.61[a] (1.03–2.52)	1.00	1.74[a] (1.11–2.71)	1.57[a] (1.01–2.45)	1.58 (0.99–2.51)

CI, confidence interval; *IPI*, interpregnancy intervals; *OR*, odds ratio.

[a] $P < .05$; [b] Adjusted for maternal age, parity, prepregnancy diabetes, previous pregnancy with anomaly, and index infant sex.

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TABLE 3
Unadjusted and adjusted ORs and 95% CI for individual folate-dependent congenital anomalies by IPIs

	OR (95% CI)					
	IPI, mo					
Congenital anomalies	0-5	6-11	12-17	18-23	24-35	36+
Cleft lip and palate (n = 83)						
Unadjusted OR	1.56 (0.63–3.87)	1.65 (0.83–3.29)	1.00	1.10 (0.51–2.37)	0.90 (0.41–1.98)	1.97 (0.99–3.89)
Adjusted[a] OR	1.48 (0.59–3.71)	1.64 (0.82–3.27)	1.00	1.11 (0.51–2.40)	0.90 (0.41–1.99)	1.73 (0.85–3.50)
Cardiovascular defects (n = 228)						
Unadjusted OR	1.42 (0.84–2.41)	1.05 (0.68–1.62)	1.00	1.19 (0.78–1.83)	1.22 (0.81–1.84)	1.19 (0.77–1.84)
Adjusted[a] OR	1.42 (0.83–2.43)	1.04 (0.67–1.61)	1.00	1.19 (0.78–1.83)	1.20 (0.79–1.81)	1.12 (0.72–1.74)
Genitourinary tract (n = 279)						
Unadjusted OR	1.37 (0.83–2.27)	1.09 (0.73–1.64)	1.00	1.36 (0.92–2.00)	1.32 (0.91–1.94)	1.40 (0.95–2.08)
Adjusted[a] OR	1.33 (0.79–2.23)	1.08 (0.72–1.63)	1.00	1.34 (0.91–1.97)	1.31 (0.89–1.92)	1.33 (0.89–1.98)
Limb defects (n = 229)						
Unadjusted OR	1.20 (0.72–2.02)	0.98 (0.65–1.48)	1.00	0.66 (0.42–1.06)	1.12 (0.76–1.65)	0.98 (0.64–1.49)
Adjusted[a] OR	1.27 (0.76–2.14)	1.00 (0.67–1.50)	1.00	0.66 (0.41–1.05)	1.10 (0.75–1.62)	0.93 (0.61–1.42)

Small sample size for neural tube defects (n = 21) did not allow for meaningful interpretation of ORs for these anomalies.

CI, confidence interval; *IPI*, interpregnancy intervals; *OR*, odds ratio.

[a] Adjusted for maternal age, parity, prepregnancy diabetes, previous pregnancy with anomaly, and index infant sex.

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birth, the vast majority of infants were born at term (93.2%) and weighed more than 2500 g (95.9%).

The overall rate of congenital anomalies was 2.2%. Both short and long interpregnancy intervals were associated with congenital anomalies (Figure 2). The lowest rate (1.9%) was observed for 12-17 months, and increased rates were seen for both short intervals (2.5% for 0-5 months) and long intervals (2.3% for 24-35 and 36+ months). Compared with our reference interval of 12-17 months, significantly increased odds of all congenital anomalies were observed for intervals 0-5 months (unadjusted odds ratio [OR], 1.35; 95% confidence interval [CI], 1.04–1.75), 24-35 months (OR, 1.26; 95% CI, 1.03–1.53), and 36+ months (OR, 1.25; 95% CI, 1.01–1.53) (Table 2).

For folate dependent and folate independent anomaly subgroups, significantly increased odds were observed in the folate independent anomaly subgroup for interpregnancy intervals 0-5 months (unadjusted OR, 1.96; 95% CI, 1.15–3.35), 6-11 months (OR, 1.60; 95% CI, 1.03–2.48), and 18-23 months (OR, 1.72; 95% CI, 1.11–2.66).

Multiple logistic regression models were built for potential confounders to our primary outcome of all congenital anomalies. Maternal age, parity, and the presence of prepregnancy diabetes were considered to be important confounders to be included in the multivariable analysis, and statistical significance was seen with prepregnancy diabetes ($P < .05$). Previous congenital anomaly and male gender infant were potential confounders that were found to be statistically significant ($P < .001$ for both) and were also included in the multivariable analysis. Other variables tested but found nonsignificant were maternal nondiabetic disease, maternal anaemia, poor weight gain in pregnancy, and smoking and drug use in pregnancy. After adjustment for potential confounders, significantly increased odds were seen for the interpregnancy intervals of 0-5 months (adjusted OR, 1.32; 95% CI, 1.01–1.72) and 24-35 months (OR, 1.25; 95% CI, 1.02–1.52) for all anomalies, and for the interval of 0-5 months (OR, 1.86; 95% CI, 1.07–3.23), 6-11 months (OR, 1.61; 95% CI, 1.03–2.52), 18-23 months (OR, 1.74; 95% CI, 1.11–2.71), and 24-35 months (OR, 1.57; 95% CI, 1.01–2.45) for folate independent anomalies (Table 2).

The unadjusted and adjusted ORs of individual categories of folate dependent anomalies are shown in Table 3. Although ORs for individual folate dependent anomalies were consistently elevated for the shortest interpregnancy intervals, statistical significance was not observed.

Comment

Our study demonstrates an association between both short and long interpregnancy intervals and congenital anomalies, with the interval of 12 to 17 months associated with the lowest risk of anomaly. The results of this first Canadian study are corroborated by the aforementioned Israeli and American studies available in the literature.[13,14] Because

both short and long interpregnancy intervals were associated with increased anomaly rates, this study may also help explain the conflicting findings of studies on individual anomalies, which have shown statistical significance for either short or long intervals, but not both. Because of the broad inclusion criteria, and minimal exclusion criteria, and also because this study was conducted in the post folate food fortification period, we believe that the results are generalizable.

The folate-deficiency hypothesis is the most often cited postulated mechanism for the association between interpregnancy intervals and various adverse maternal and neonatal outcomes. Even though information on folate supplementation was not available in the databases, we were able to test this hypothesis by determining whether a differential association existed between folate dependent and folate independent anomalies. Based on the folate-deficiency hypothesis, we postulated that a stronger association would be seen with the folate dependent anomalies. Based on adjusted odds ratios relative to the reference group of 12-17 months, we observe that the association between interpregnancy intervals and congenital anomalies is in fact significant only for the folate-independent anomaly subgroup. Although the importance of folate in the prevention of neural tube defects and congenital anomalies remains undisputed, the findings from this study suggest that the mechanism for association between interpregnancy intervals and congenital anomalies is unlikely to be folate deficiency alone. This is further corroborated by the association between interpregnancy interval and congenital anomalies despite the virtual absence of folate deficiency in the Canadian population.[18] However, the lack of information regarding folate supplementation in the databases is an important limitation to this study.

Despite the exclusion of known aneuploidies from this study, we found increasing rates of congenital anomalies with advancing maternal age (1.7%, 2.1%, and 2.4% for ages <20, 20-34, and 35+ years respectively), which is consistent with reports in the literature.[22] Although it is possible that residual confounding is present despite the adjustment for maternal age, the similarity of unadjusted and adjusted odds ratios suggests that the association exists independent of maternal age.

A major strength of this study is the use of the Alberta Congenital Anomalies Surveillance System. The use of a robust, dedicated, and province-wide congenital anomalies surveillance system confers the ability to consecutively capture detailed information on individual anomalies, as well as the ability to include early fetal losses and pregnancy terminations in the dataset. However, as a potential limitation, our dataset does not include cases where maternal identifiers were not linked to early losses or termination. As our anomaly rates are similar to that of the general population,[12,19-21] the differences are likely very small.

In terms of quantifying the risk of individual categories of anomalies according to interpregnancy intervals, we observed that rates were consistently higher for intervals 0-5 months. However, despite the large sample size in this study, statistical differences were not detected because of the relative infrequency of individual anomalies, raising the possibility of a type II error. Similarly, we had initially planned for finer categorization of interpregnancy intervals, but this was not possible especially at intervals beyond 36 months because of the smaller proportion of women giving birth after this interval.

Conclusion

The results of our study suggest that both short and long interpregnancy intervals are associated with congenital anomalies, and that the main mechanism for this relationship is unlikely to be folate deficiency alone. This study corroborates the limited existing studies in the literature and further explores the types of anomalies affected. These findings have broad implications for further research, prenatal risk assessment and counseling regarding birth spacing and nutritional supplementation. ■

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