OBSTETRICS

Relationship between interpregnancy interval and congenital anomalies

Innie Chen, MD; Gian S. Jhangri, MSc; Sujata Chandra, MD, MSc

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 congenital anomalies; and, secondarily, to determine the relationship between interpregnancy intervals and specific categories

★ EDITORS' CHOICE ★

From the Department of Obstetrics and Gynecology (Dr Chen), University of Ottawa Faculty of Medicine, and School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, and the School of Public Health (Mr Jhangri) and Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine and Dentistry (Dr Chandra), University of Alberta, Edmonton, Alberta, Canada.

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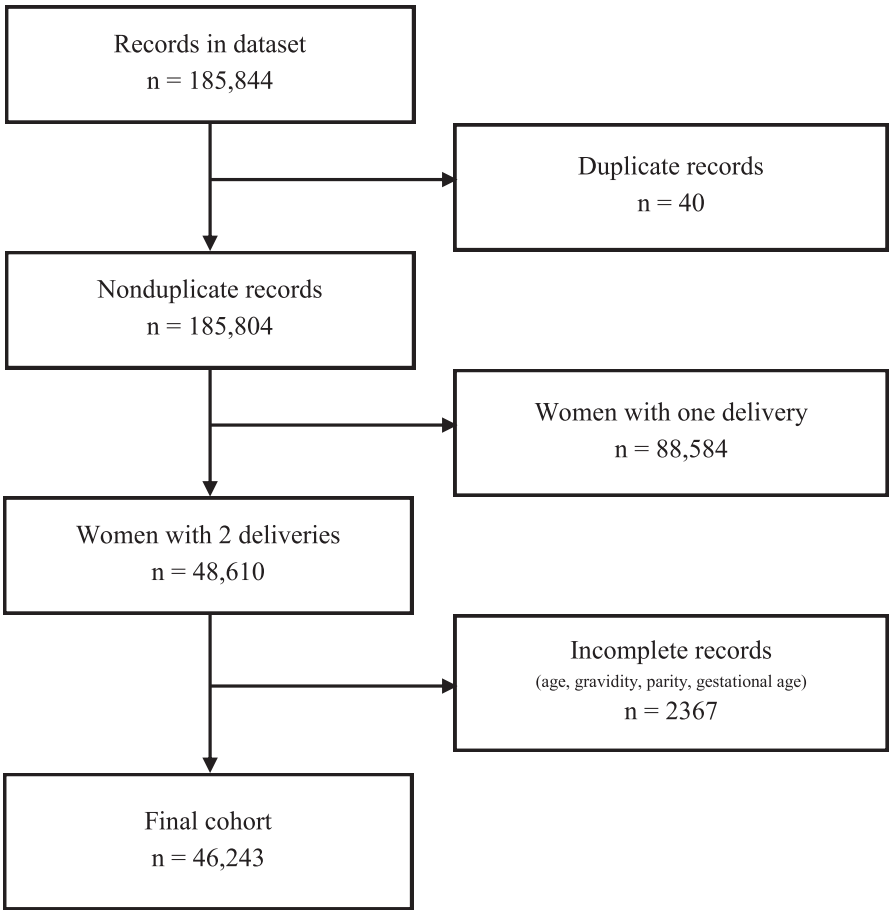
FIGURE 1
Selection of study cohort from linked dataset, Alberta, 1999-2007



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