HHS Public Access

Author manuscript

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2016 May 04.

Published in final edited form as:

Birth Defects Res A Clin Mol Teratol. 2012 September ; 94(9): 714–720. doi:10.1002/bdra.23061.

Short Interpregnancy Interval and Gastroschisis Risk in the National Birth Defects Prevention Study

Kelly D. Getz[1,*], **Marlene T. Anderka**[1], **Martha M. Werler**[2], and **Amy P. Case**[3]

[1]Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, Massachusetts

[2]Slone Epidemiology Center at Boston University, Boston, Massachusetts

[3]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas

Abstract

BACKGROUND—The micronutrient depletion hypothesis proposes that consecutive pregnancies spaced too closely may leave insufficient time for maternal micronutrient replenishment. Short interpregnancy intervals (IPI) have been associated with an increased risk for several adverse pregnancy outcomes, but an association with gastroschisis risk has not been previously explored.

METHODS—Within a population-based, case-control study, we evaluated the association between IPI length and gastroschisis risk using multivariable logistic regression models to estimate gastroschisis odds ratios for IPI <12 months and 12 to 17 months relative to those 18 to 23 months. We further evaluated the association between IPI and gastroschisis risk stratified by maternal age, periconceptional multivitamin use, preceding pregnancy outcome, study center region, and season of conception to explore whether observed associations were compatible with the hypothesis of maternal micronutrient depletion.

RESULTS—For women with IPI <12 months, the adjusted odds ratio (aOR) was 1.7 (95% confidence interval [CI]: 1.1–2.5). The magnitude of the observed effect did not differ among strata of maternal age or periconceptional multivitamin use. However, the association was more pronounced after a miscarriage or termination (aOR: 2.5; 95% CI: 1.1–5.6) and among women who resided in northern study areas (aOR: 2.8; 95% CI: 1.3–5.9). The higher risk observed with short IPI among women in northern study areas was attenuated for spring/summer conceptions.

CONCLUSION—Short IPI was associated with an increased risk for gastroschisis, particularly among women whose preceding pregnancy resulted in a miscarriage or termination and among those who resided in northern study areas with winter/fall conception.

[*]Correspondence to: Mrs. Kelly D. Getz, Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, 250 Washington Street, 5th Floor, Boston, MA 02108. Kelly.Getz@state.ma.us.

The findings and conclusions in this report do not necessarily reflect the position of the MA Department of Public Health.

Some of the findings reported in this article were shared in a presentation to the annual meeting of the National Birth Defects Prevention Study collaborating centers in Atlanta, Georgia, on January 21, 2011, and in a poster at the annual meeting of The Society for Pediatric and Perinatal Epidemiologic Research, Montreal, Quebec, Canada, on June 21, 2011, but none of the results have been previously published as an abstract or full article.

Keywords

short interpregnancy interval; gastroschisis; IPI; case-control; NBDPS

INTRODUCTION

Gastroschisis is a birth defect in the abdominal wall from which the contents of the abdominal cavity project outside of the body at birth. Unlike omphalocele, which occurs when portions of the gut that normally protrude into the umbilicus during weeks 6 through 10 of development fail to migrate back into the abdominal cavity, gastroschisis originates from incomplete closure of the lateral wall folds by the fourth week of gestation (Sadler, 2009). Although the etiology of gastroschisis is largely unknown, its strong association with young maternal age is well established (Rasmussen and Frías, 2008). As such, research has focused on behavioral and lifestyle characteristics more common in young women as potential causal factors. Significant associations with gastroschisis have been identified for maternal cigarette smoking (Feldkamp et al., 2008a), alcohol consumption (Torfs et al., 1994), urogenital infections (Feldkamp et al., 2008b), and some medications including non-aspirin non-steroidal anti-inflammatory drugs and antihypertensive drugs (Werler et al., 2009), but none have explained the differential increase in risk observed with young maternal age.

Short interpregnancy interval has been identified as a risk factor for a number of adverse pregnancy outcomes including preterm birth, low birth weight, and neural tube defects (Zhu et al., 1999; Afflick and Hessol, 2000; Todoroff and Shaw, 2000; Zhu et al., 2001; Conde-Agudelo et al., 2005; Fuentes-Smith et al., 2003; van Eijsden et al., 2008). The leading hypothesis to explain the increased risks suggests that short intervals may be a marker for a deficiency in nutritional reserves needed to support normal fetal development (King, 2003). Maternal stores of important micronutrients such as vitamins A, B_6, B_{12}, D_3, zinc, and folate, decline during pregnancy and, although most rebound relatively shortly after delivery, folate and vitamin D_3 take several months (Bruinse and van den Berg, 1995; Holmes et al., 2009). Certain vulnerable groups may require longer intervals to replenish micronutrient stores between pregnancies. Young mothers may represent one such subpopulation given their increased nutritional requirements for their own growth and development compared with older mothers (King, 2003).

To our knowledge, this is the first study to evaluate the association between interpregnancy interval length and gastroschisis risk and explore whether the relationship is compatible with the hypothesis of maternal micronutrient depletion.

METHODS

Study Design

This study was approved by the institutional review boards of the individual National Birth Defects Prevention Study (NBDPS) study centers and the Centers for Disease Control and Prevention. The study population comprised gastroschisis case subjects and nonmalformed

control subjects born to multigravid women who enrolled in the NBDPS with expected delivery dates between October 1997 and December 2007.

The NBDPS methodology has been described in detail previously (Yoon et al., 2001). Briefly, the NBDPS is a population-based, case-control study that utilizes data from the surveillance systems in 10 states (Arkansas [AR], California [CA], Georgia [GA], Iowa [IA], Massachusetts [MA], North Carolina [NC], New Jersey [NJ], New York [NY], Texas [TX], and Utah [UT]) to identify birth defect case subjects. Birth defect cases included in the NBDPS are those determined by site clinical geneticists to meet the criteria for inclusion based upon a detailed review of medical records. Those with a known cause (i.e., single gene disorders or chromosomal disorders) are ineligible to participate in the NBDPS. Eligible gastroschisis case subjects from all sites undergo secondary review by a single clinical geneticist for classification and to ensure standardization of the eligibility criteria. Gastroschisis case subjects are classified as having an isolated malformation if the gastroschisis occurred as the only major defect or as the primary defect in a sequence. Otherwise, those with accompanying anomalies are classified as having multiple malformations. Nonmalformed control subjects are randomly selected annually among live births within the defined geographic areas of each study center from electronic birth certificates (IA, MA, NJ, NC, and UT) or from the delivery records of those hospitals contributing birth defects case subjects (CA, NY, and TX). AR and GA used hospital selection at the beginning of the study and then switched to birth certificate selection in 2001. Case and control subjects are excluded if they are adopted or in foster care and if their mother is deceased, incarcerated, or does not speak English or Spanish.

NBDPS participation rates were similar for gastroschisis case (67%) and control (66%) subjects. Mothers were interviewed within 24 months after their estimated date of delivery (EDD) by telephone about demographic and reproductive factors, pregnancy history, health behaviors, and lifestyle characteristics. On average, mothers of controls were interviewed slightly sooner after the EDD (9 months) than mothers of gastroschisis cases (10 months).

Interpregnancy Interval

Interpregnancy interval was computed as the time period of completed months between the actual date of delivery, miscarriage, or termination of the most recent recognized pregnancy preceding the study pregnancy and the estimated date of conception of the study pregnancy. The date of conception was calculated as the EDD minus 266 days or for subjects missing an EDD as the date of the last menstrual period plus 14 days. When the day was missing for the end of the previous pregnancy, the 15th of the month was used to compute interpregnancy interval (31% of cases, 19% of controls). Although both very short and very long intervals have been associated with poor pregnancy outcomes, the etiologic mechanisms of the two exposures are likely very different with the micronutrient depletion hypothesis being specific to short intervals. Our primary aim was to assess the effect of short interpregnancy intervals on gastroschisis risk, so we restricted our analyses to mothers who reported at least one previous pregnancy, or who had an interpregnancy interval <24 months in which the preceding pregnancy was a singleton (263 cases, 3025 controls). The cutoff of 24 months was selected based on previous literature assessing the effect of short

interpregnancy intervals on adverse pregnancy outcomes in which intervals of 18 to 23 months were associated with the lowest risk (Conde-Agudelo et al., 2006). Subjects were assigned to an interval category based on their computed interpregnancy interval (<12 months, 12–17 months, and 18–23 months).

Covariates

Socio-demographic factors that were evaluated as potential confounders included maternal age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), years of education (<12, ≥12), and study center region (northern: ≥37°N latitude, southern: <37°N latitude). Reproductive and pregnancy characteristics were also assessed including number of previous pregnancies (1, 2, or more), pre-pregnancy body mass index categories (underweight, normal weight, or overweight/obese), pregnancy intention (intended/ambivalent, unintended/unwanted, or missing), multivitamin use during the periconceptional period defined as the period 3 months before conception through the first month of the study pregnancy (yes, no), and the outcome of the most recent previous pregnancy (live birth, stillbirth, miscarriage, elective termination, or molar/tubal pregnancy). Behavioral and lifestyle factors were also evaluated including maternal smoking and maternal alcohol use from 1 month before conception through the first trimester (yes, no). Mothers who reported using medications or procedures for infertility (5 cases, 217 controls), those missing the outcome of the preceding pregnancy (2 cases, 10 controls), or missing information on multivitamin use (2 cases, 6 controls) were excluded.

Analyses

All analyses were performed using PC-SAS (version 9.2, SAS Institute, Cary, NC). Distributions of maternal characteristics (frequency and percents) were computed by case-control status and among nonmalformed controls by interpregnancy interval category. Simple logistic regression models were used to quantify associations between each of the covariates and gastroschisis as well as short interpregnancy interval (among controls). A covariate was considered to be associated with gastroschisis or short interpregnancy interval if the resulting odds ratio (OR) for at least one level of the covariate was <0.85 or >1.15, regardless of statistical significance. Logistic regression models were used to estimate the crude and adjusted gastroschisis ORs and associated 95% confidence intervals (CIs) for each category of interpregnancy interval using 18 to 23 months as the reference category. Relative risks were estimated from ORs. The initial multivariable model (full model) included those covariates judged to be associated with both short interpregnancy interval and gastroschisis (i.e., maternal age, maternal race/ethnicity, number of previous pregnancies, pregnancy intention, outcome of previous pregnancy, maternal smoking, maternal alcohol consumption, and multivitamin use). Each covariate was then independently removed from the full model. The covariate that resulted in the smallest change in the OR for short interpregnancy interval when removed was permanently eliminated from the full model. A similar process was used with successive models until a final model was achieved in which all retained covariates resulted in a >10% change in the OR if removed. The final model included terms for maternal age and outcome of previous pregnancy.

Maternal age was examined as a potential effect modifier, on the basis that micronutrient stores may be lower in younger mothers whose bodies are still undergoing development. Periconceptional multivitamin supplementation may help replenish depleted micronutrients in women with short interpregnancy intervals. Therefore, the association between short interpregnancy interval and gastroschisis risk was evaluated separately among mothers who used any multivitamin supplements during the periconceptional period and those who did not use multivitamin supplements during the periconceptional period. Although stratification by periconceptional multivitamin supplementation status is helpful in evaluating the nutritional depletion hypothesis, it is only reflective of the collective effect of micronutrients for which supplementation is a major contributor. Particularly among pregnant women who are advised to avoid a number of natural sources of vitamin D such as liver and certain fish, the predominant source of vitamin D_3 is its photo-synthetic production in response to UVB exposure (Holmes et al., 2009), which declines along a south-north gradient (Webb et al., 1988). Therefore, study center region, as a rough estimate of differential UVB exposure by latitude and, hence, vitamin D_3 status, was assessed as a potential effect modifier. NBDPS centers were classified by region based on latitude. A latitudinal cut-point of 37°N was chosen because above that latitude there is an 80 to 100% reduction in the amount of UVB photons reaching the earth's surface in winter and, as a result, little to no vitamin D_3 is produced (Cockburn et al., 1980). In contrast, more vitamin D_3 synthesis occurs year-round at latitudes below 37°N (Holick, 2004). NBDPS centers with study areas at latitudes 37°N or above were classified as northern (IA, MA, NJ, NY, and UT) and those with study areas located at latitudes below 37°N were classified as southern (CA, AR, TX, GA, and NC). Because the 37th parallel north transects the California study area, the latitude of the center point of the study area, Fresno County, was used to classify case and control subjects from the California center as southern. To account for the seasonal variation in UVB exposure, analyses by region were further stratified by season of conception (winter/fall, spring/summer). Effect measure modification by outcome of the previous pregnancy was also examined (live birth, miscarriage, or termination) because there may be less nutritional demand for very short pregnancies.

RESULTS

Examination of the entire distribution of interpregnancy interval lengths revealed that the majority of both cases (~61%) and controls (~55%) had interpregnancy intervals <24 months. Similar to findings previously reported for other adverse pregnancy outcomes (e.g., preterm birth and low birth weight), the overall relationship between interpregnancy interval length and gastroschisis risk was J-shaped with intervals <12 months and >36 months exhibiting the highest risk (Fuentes-Afflick and Hessol, 2000; Zhu et al., 2001; Smith et al., 2003; Conde-Agudelo et al., 2005; van Eijsden et al., 2008).

A total of 254 cases of gastroschisis and 2792 nonmalformed controls born to mothers with at least one previous pregnancy and interpregnancy intervals <24 months were included in the analyses of the effect of short interpregnancy interval on gastroschisis risk. The distribution of maternal demographic, reproductive, and lifestyle characteristics for gastroschisis cases and nonmalformed control subjects are provided in Table 1. Compared with control mothers, gastroschisis case mothers were younger, less likely to have a high

school diploma, and less likely to be overweight/obese before the index pregnancy. They also were more likely to have an unintended pregnancy, to have a preceding pregnancy that resulted in a termination or miscarriage, to have smoked or binge drank, and to have used multivitamin supplements in the periconceptional period. Among nonmalformed control subjects, mothers with interpregnancy intervals <12 months were younger, had fewer previous pregnancies, were more likely to have an unintended pregnancy, and to have smoked or binge drank. They also were less likely to be underweight or to have a preceding pregnancy that resulted in a live birth.

The crude and adjusted odds ratios (aORs) by interpregnancy interval are presented in Table 2. Overall, women with interpregnancy intervals <12 months had an increased risk of gastroschisis relative to those with intervals of 18 to 23 months (aOR: 1.7; 95% CI: 1.1–2.5).

To evaluate the nutritional depletion hypothesis, we first stratified by maternal age and found that the increased risk observed for short interpregnancy intervals was evident in both mothers under 25 years of age (aOR: 1.8; 95% CI: 1.1–2.9) and those 25 years of age or older was (aOR: 1.7; 95% CI: 0.8–3.7). We then stratified by the use of multivitamin supplementation in the periconceptional period (Table 3). Among mothers who did not use multivitamin supplements during the periconceptional period, those with interpregnancy intervals <12 months had an adjusted 1.8-fold higher risk of gastroschisis (95% CI: 1.0–3.0). A similar association was observed among mothers who did use multivitamin supplements in the periconceptional period but it was not statistically significant (aOR: 1.5; 95% CI: 0.7–2.9). Next, we stratified by study center region. Interpregnancy intervals <12 months were associated with a 2.8-fold increase in the risk of gastroschisis in northern study areas (95% CI: 1.3–5.9), but no significant increase in risk was observed in southern study areas (aOR: 1.3; 95% CI: 0.8–2.2). Results were unchanged in a subanalysis of southern study areas excluding California, the only NBDPS state that is intercepted by the 37th parallel cutoff (aOR: 1.3; 95% CI: 0.7–2.5). Analyses by region were further stratified by season of conception (Table 4). This joint stratification by center region and season of conception showed that among women residing in northern center regions, the elevated gastroschisis risk observed for short interpregnancy intervals was more pronounced for those with winter/fall conceptions (aOR: 4.1; 95% CI: 1.4–12.3) than for those with spring/summer conceptions (aOR: 1.8; 95% CI: 0.7–5.3). Last, we stratified by the outcome of the preceding pregnancy. Among women whose preceding pregnancy resulted in a miscarriage or termination, interpregnancy intervals <12 months were associated with a 2.5-fold higher gastroschisis risk (95% CI: 1.1–5.6). In contrast, we observed no association between short interpregnancy and gastroschisis risk among those whose preceding pregnancy outcome was a live birth (aOR: 1.3; 95% CI: 0.8–2.2). Due to sample size limitations, we were unable to independently assess the association between interpregnancy interval and gastroschisis for other previous pregnancy outcomes (i.e., stillbirths).

Analyses restricted to women with no family history of major birth defects were not materially different from analyses including all women; therefore, the latter are presented to take advantage of the larger sample size. Analyses were performed using all gastroschisis case subjects meeting the study inclusion criteria, then the final models were reevaluated using only those with isolated gastroschisis. Following this restriction, the ORs for

gastroschisis comparing interpregnancy intervals <12 months to those of 18 to 23 months did not change by more than 10% from those obtained using the full dataset; therefore, only the results based on the full analysis dataset are presented here.

DISCUSSION

In this population-based, case-control study, women with interpregnancy intervals <12 months were 1.7 times as likely to have an infant with gastroschisis compared to women with intervals of 18 to 23 months. Further analyses of this association in various subgroups did not suggest that the observed association is due to general nutritional depletion. We surmised that women under 25 years of age, those who did not use multivitamins in the periconceptional period, and those whose preceding pregnancy was a live birth were most vulnerable to micronutrient depletion, but the association between short interpregnancy interval and gastroschisis risk was not further elevated in these women. The effect of short interpregnancy interval was more pronounced among women who resided in northern study areas (aOR: 2.8; 95% CI: 1.3–5.9) particularly those who conceived during fall/winter months.

That periconceptional multivitamin use did not offset the observed association with short interpregnancy interval led us to consider a role for vitamin D_3, because previous studies have identified vitamin D_3 insufficiency among pregnant women despite multivitamin supplementation (Cockburn et al., 1980; Holmes et al., 2009). The association between short interpregnancy interval and gastroschisis risk was restricted to mothers giving birth in study areas above 37°N latitude suggesting differences in vitamin D_3 status may be involved in the association between short interpregnancy interval and gastroschisis. Although the differential effect by region may be due to other factors that exhibit a north-south gradient (e.g., fruit and vegetable consumption [Agudo et al., 2002]), that the effect of short interpregnancy interval on gastroschisis risk observed among women in northern areas was restricted to those with winter/fall conceptions and was attenuated among those with spring/summer conceptions provides additional support for involvement of vitamin D_3.

We unexpectedly found a more pronounced effect of short interpregnancy interval on gastroschisis risk among women whose previous pregnancy was a miscarriage or termination, which we assumed to result in less maternal micronutrient depletion than preceding pregnancies of longer duration. Why a greater gastroschisis risk relative to short interpregnancy interval would be observed for pregnancies preceded by a miscarriage or termination is unclear. It is possible that a causal mechanism through which short interpregnancy interval may lead to gastroschisis may also be associated with miscarriage and terminations. For example, vitamin D_3 has important immunomodulatory functions (Holick, 2007) and immunologic imbalances have been implicated as a risk factor for miscarriage (Evans et al., 2004). Additionally, vitamin D_3 depletion may occur as a result of excessive inflammatory responses to uterine trauma after elective terminations. It is also possible that women whose preceding pregnancy resulted in miscarriage or termination represent subpopulations with greater risk for poor pregnancy outcomes overall. Our findings that short interpregnancy intervals were most strongly associated with an increased risk of gastroschisis among women who may be more likely to be vitamin D_3 deficient and

among women whose preceding pregnancy was a miscarriage/termination are compatible with results of others who have suggested that a possible immunologic or inflammatory mechanism may be involved in the etiology of gastroschisis (Chambers et al., 2007; Rittler et al., 2007; Draper et al., 2008; Feldkamp et al., 2008a; Feldkamp et al., 2008b).h

Advantages of this study include its population-based case ascertainment, case classification by clinical geneticists, and detailed information on reproductive histories and multiple potential confounders. Although we relied on self-reported dates for the pregnancy preceding the study pregnancy to calculate interpregnancy interval, we expect that recall of dates of previous pregnancy outcomes would be of similar accuracy for both case and control mothers. However, there are limitations to our study. Estimates of interpregnancy interval were based on recognized pregnancies only. It is possible that there may have been early pregnancy losses between the previous recognized pregnancies and the study pregnancies resulting in interpregnancy intervals being similarly misclassified as longer for both case and control mothers. As a result, the association between short interpregnancy interval and gastroschisis risk may be underestimated. Controls participating in the NBDPS are comparable to the base population with respect to many maternal characteristics, but there are small differences in distributions related to maternal race/ethnicity and education level (Cogswell et al., 2009). If short interpregnancy interval is associated with maternal race/ethnicity or education level, then the distribution of interpregnancy intervals included in our study may not be representative of the base population. Participation rates were 67% for cases and 66% for controls. In a subanalysis of Massachusetts center participants and nonparticipants, we found that participants were more likely to have short interpregnancy intervals than nonparticipants, especially among cases. Consistent with this trend, the association between short interpregnancy interval and gastroschisis occurrence was attenuated when both MA participants and nonparticipants were included (OR = 3.0; 95% CI: 0.9–7.9) compared with those observed among MA participants only (OR = 4.0; 95% CI: 0.9–17.7). If participation is related to interpregnancy interval in the same fashion for all NBDPS centers, then our results may be an overestimate of the association that would be observed using all eligible subjects. In the absence of a better surrogate, we used study region above or below 37°N latitude as an indicator of vitamin D_3 status. This is a crude proxy and may represent other unmeasured factors that exhibit a north-south gradient. Studies using more accurate measures of vitamin D_3 status are needed to substantiate our findings. Additionally, in our stratified analyses, some exposure categories included small numbers of gastroschisis cases and sample size limitations precluded our ability to stratify by multiple factors simultaneously. Last, although we assessed the potential for confounding by a number of maternal socio-demographic, reproductive and behavioral characteristics, residual confounding by uncontrolled or poorly controlled factors is always a possibility.

A number of studies have shown that short interpregnancy intervals are associated with adverse pregnancy outcomes including preterm birth (Smith et al., 2003; van Eijsden et al., 2008), low birth weight (van Eijsden et al., 2008) and neural tube defects (Todoroff and Shaw, 2000). The current study suggests a similar association with gastroschisis.

Acknowledgments

Supported by a grant for The National Birth Defects Prevention Study from the Centers of Disease Control and Prevention (U01DD000493).

The authors thank National Birth Defects Prevention Study staff from Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah for data collection, data cleaning, and case classification.

References

Agudo A, Slimani N, Ocké MC, et al. Consumption of vegetables, fruit and other plant foods in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. Public Health Nutr. 2002; 5:1179–1196. [PubMed: 12639226]

Bruinse HW, van den Berg H. Changes of some vitamin levels during and after normal pregnancy. Eur J Obstet Gynecol Reprod Biol. 1995; 61:31–37. [PubMed: 8549845]

Chambers CD, Chen BH, Kalla K, et al. Novel risk factor in gastroschisis: change of paternity. Am J Med Genet A. 2007; 143:653–659. [PubMed: 17163540]

Cockburn F, Belton NR, Purvis RJ, et al. Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. Br Med J. 1980; 281:11–14. [PubMed: 7407476]

Cogswell ME, Bitsko RH, Anderka M, et al. Control selection and participation in an ongoing, population-based, case-control study of birth defects: the National Birth Defects Prevention Study. Am J Epidemiol. 2009; 170:975–985. [PubMed: 19736223]

Conde-Agudelo A, Belizán JM, Norton MH, Rosas-Bermúdez A. Effect of the interpregnancy interval on perinatal outcomes in Latin America. Obstet Gynecol. 2005; 106:359–366. [PubMed: 16055588]

Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Birth spacing and risk for adverse perinatal outcomes: a meta-analysis. JAMA. 2006; 295:1809–1823. [PubMed: 16622143]

Draper ES, Rankin J, Tonks AM, et al. Recreational drug use: a major risk factor for gastroschisis? Am J Epidemiol. 2008; 167:485–491. [PubMed: 18063593]

Evans KN, Bulmer JN, Kilby MD, Hewison M. Vitamin D and placental-decidual function. J Soc Gynecol Investig. 2004; 11:263–271.

Feldkamp ML, Alder SC, Carey JC. A case control population-based study investigating smoking as a risk factor for gastroschisis in Utah, 1997–2005. Birth Defects Res A Clin Mol Teratol. 2008a; 82:768–775. [PubMed: 18985693]

Feldkamp ML, Reefhuis J, Kucik J, et al. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997–2003. BMJ. 2008b; 336:1420–1423. [PubMed: 18558640]

Fuentes-Afflick E, Hessol NA. Interpregnancy interval and the risk of premature infants. Obstet Gynecol. 2000; 95:383–390. [PubMed: 10711549]

Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004; 80(6 Suppl):1678S–1688S. [PubMed: 15585788]

Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266–281. [PubMed: 17634462]

Holmes VA, Barnes MS, Alexander HD, et al. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. Br J Nutr. 2009; 102:876–881. [PubMed: 19331703]

King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. J Nutr. 2003; 133(5 Suppl 2):1732S–1736S. [PubMed: 12730491]

Rasmussen SA, Frías JL. Non-genetic risk factors for gastroschisis. Am J Med Genet C Semin Med Genet. 2008; 148C:199–212. [PubMed: 18655102]

Rittler M, Castilla EE, Chambers C, Lopez-Camelo JS. Risk for gastroschisis in primigravidity, length of sexual cohabitation, and change in paternity. Birth Defects Res A Clin Mol Teratol. 2007; 79:483–487. [PubMed: 17358037]

Sadler, TW. Langman's medical embryology. 11. Baltimore, MD: Lippincott William & Wilkins; 2009.

Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. BMJ. 2003; 327:313. [PubMed: 12907483]

Todoroff K, Shaw GM. Prior spontaneous abortion, prior elective termination, interpregnancy interval, and risk of neural tube defects. Am J Epidemiol. 2000; 151:505–511. [PubMed: 10707919]

Torfs CP, Velie EM, Oechsli FW, et al. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. Teratology. 1994; 50:44–53. [PubMed: 7974254]

van Eijsden M, Smits LJ, van der Wal MF, Bonsel GJ. Association between short interpregnancy intervals and term birth weight: the role of folate depletion. Am J Clin Nutr. 2008; 88:147–153. [PubMed: 18614735]

Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 1988; 67:373–378. [PubMed: 2839537]

Werler MM, Mitchell AA, Moore CA, et al. Is there epidemiologic evidence to support vascular disruption as a pathogenesis of gastroschisis? Am J Med Genet A. 2009; 149A:1399–1406. [PubMed: 19533769]

Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116(Suppl 1):32–40. [PubMed: 11889273]

Zhu BP, Haines KM, Le T, et al. Effect of the interval between pregnancies on perinatal outcomes among white and black women. Am J Obstet Gynecol. 2001; 185:1403–1410. [PubMed: 11744916]

Zhu BP, Rolfs RT, Nangle BE, Horan JM. Effect of the interval between pregnancies on perinatal outcomes. N Engl J Med. 1999; 340:589–594. [PubMed: 10029642]

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2016 May 04.

Table 1

Distribution (%) of Demographic, Reproductive, and Lifestyle Characteristics for Gastroschisis Case Subjects and Nonmalformed Control Subjects and by Length of Interpregnancy Interval among Control Subjects, National Birth Defects Prevention Study 1997–2007

	Overall		Interpregnancy interval[a]		
Maternal demographics	**Cases (N = 254)**	**Controls (N = 2792)**	**<12 m (N = 1441)**	**12–17 m (N = 796)**	**18–23 m (N = 632)**
Maternal age, years					
<25	76.4	32.3	34.7	32.5	26.7
≥25	23.6	67.7	65.3	67.5	73.3
Race/ethnicity					
Non-Hispanic white	51.6	59.3	56.7	63.4	60.0
Non-Hispanic black	8.3	11.3	13.3	8.8	10.3
Hispanic	31.1	21.2	21.2	21.4	20.7
Other	9.1	7.8	8.3	6.1	8.8
Missing	0	0.4	0.5	0.4	0.2
Education level, years					
0–12	64.2	39.6	40.0	38.4	40.0
>12	33.4	59.1	58.4	60.8	58.7
Missing	2.4	1.3	1.6	0.8	1.3
Reproductive/pregnancy factor					
Number of previous pregnancies					
1	47.2	38.2	35.6	40.5	41.3
2 or more	52.8	61.8	64.4	59.5	58.7
Pre-pregnancy body mass index					
<18.5 (underweight)	6.7	4.9	4.7	4.0	6.6
18.5–24.9 (normal weight)	67.7	52.3	49.9	56.8	52.9
≥25 (overweight/obese)	23.2	39.2	42.1	35.3	37.5
Missing	2.4	3.6	3.3	3.9	4.0
Pregnancy intention					
Intended/ambivalent	41.4	53.3	52.6	50.5	58.2
Unintended/unwanted	42.1	28.7	31.6	28.2	22.7
Missing	16.5	18.0	15.7	21.3	19.1

	Overall		Interpregnancy interval[a]		
Maternal demographics	**Cases (N = 254)**	**Controls (N = 2792)**	**<12 m (N = 1441)**	**12–17 m (N = 796)**	**18–23 m (N = 632)**
Outcome of previous pregnancy					
Live birth	50.0	67.2	52.1	80.4	84.9
Miscarriage/termination	49.2	30.4	44.8	17.9	13.5
Stillbirth/tubal/molar	0.79	2.4	3.1	1.7	1.6
Behavior/lifestyle factor					
Cigarette smoking B1–P3					
Any	36.6	16.9	18.2	15.8	15.4
None	61.8	82.1	80.5	83.5	83.8
Missing	1.6	1.0	1.3	0.6	0.8
Alcohol consumption B1–P3					
Binge drinking (5 or more)	12.2	6.8	6.9	8.0	5.0
Drinking, but not binge	19.3	26.1	26.5	24.4	27.5
None	65.3	64.5	64.6	67.0	65.6
Missing	3.2	1.6	2.1	0.6	1.9
Periconceptional multivitamin use					
Any use B3–P1	38.6	52.4	53.4	51.8	50.6
No use B3–P1	61.4	47.6	46.6	48.2	49.4
Study center region					
Northern (≥37°N latitude)	40.2	47.3	45.1	49.9	49.0
Southern (<37°N latitude)	59.8	52.7	54.9	50.1	51.0

[a]Distribution of characteristics among nonmalformed control subjects by length of interpregnancy interval.

m, months; N, number; B1–P3, the time period from 1 month before conception through 1 month after conception; B3–P1, the time period from 3 months before conception through 1 month after conception.

Table 2

Overall Crude and aORs (95% CI) for Gastroschisis by Interpregnancy Interval, National Birth Defects Prevention Study 1997–2007

IPI, m	Cases	Controls	Crude OR (95% CI)	aOR[a] (95% CI)
<12	165	1394	2.38 (1.60–3.53)	1.67 (1.10–2.53)
12–17	58	776	1.50 (0.96–2.35)	1.20 (0.75–1.91)
18–23	31	622	Reference	Reference

	Maternal age <25 years			Maternal age ≥25 years		
IPI, m	Cases	Controls	aOR[b] (95% CI)	Cases	Controls	aOR[b] (95% CI)
<12	129	484	1.78 (1.08–2.95)	36	884	1.73 (0.82–3.67)
12–17	44	252	1.32 (0.76–2.32)	14	514	1.20 (0.53–2.72)
18–23	21	166	Reference	10	451	Reference

[a] Adjusted for age (continuous) and outcome of previous pregnancy.

[b] Adjusted outcome of previous pregnancy.

aOR, adjusted odds ratio; CI, confidence interval; m, months; OR, odds ratio; IPI, interpregnancy interval; m, months.

Table 3

The aORs (95% CI) for Gastroschisis by Interpregnancy Interval after Stratification by Periconceptional Multivitamin use, Region and Outcome of the Preceding Pregnancy, National Birth Defects Prevention Study 1997–2007

	Any multivitamin Use B3–P1			No multivitamin Use B3–P1		
IPI, m	**Cases**	**Controls**	**aOR[a] (95% CI)**	**Cases**	**Controls**	**aOR[a] (95% CI)**
<12	68	715	1.49 (0.75–2.95)	97	649	1.76 (1.03–3.01)
12–17	18	396	0.85 (0.39–1.86)	40	374	1.43 (0.80–2.58)
18–23	12	311	Reference	19	307	Reference

	Northern study centers (≥37°N latitude)			Southern study centers (<37°N latitude)		
IPI, m	**Cases**	**Controls**	**aOR[a] (95% CI)**	**Cases**	**Controls**	**aOR[a] (95% CI)**
<12	70	610	2.78 (1.31–5.89)	95	766	1.28 (0.77–2.14)
12–17	23	380	1.52 (0.67–3.45)	35	389	1.08 (0.61–1.91)
18–23	9	299	Reference	22	317	Reference

	Previous outcome: Live birth			Previous outcome: Miscarriage/termination		
IPI, m	**Cases**	**Controls**	**aOR[b] (95% CI)**	**Cases**	**Controls**	**aOR[b] (95% CI)**
<12	64	726	1.32 (0.80–2.17)	99	625	2.46 (1.07–5.64)
12–17	39	624	1.16 (0.68–1.98)	19	139	1.41 (0.55–3.64)
18–23	24	528	Reference	7	84	Reference

[a] Adjusted for age (continuous) and outcome of previous pregnancy.

[b] Adjusted for age (continuous).

aOR, adjusted odds ratio; CI, confidence interval; B3–P1, the time period from 3 months before conception through 1 month after conception; m, months; IPI, interpregnancy interval.

Table 4

The aORs (95% CI) for Gastroschisis by Interpregnancy Interval after Joint Stratification by Region and Season of Conception, National Birth Defects Prevention Study 1997–2007

	Northern with winter/fall conception			Northern with spring/summer conception		
IPI, m	**Cases**	**Controls**	**aOR[a] (95% CI)**	**Cases**	**Controls**	**aOR[a] (95% CI)**
<12	41	301	4.11 (1.38–12.3)	29	309	1.85 (0.65–5.30)
12–17	14	204	1.88 (0.59–6.11)	9	176	1.24 (0.39–4.02)
18–23	4	152	Reference	5	147	Reference
	Southern with winter/fall conception			**Southern with spring/summer conception**		
IPI, m	**Cases**	**Controls**	**aOR[a] (95% CI)**	**Cases**	**Controls**	**aOR[a] (95% CI)**
<12	50	397	0.92 (0.47–1.80)	45	369	1.80 (0.79–4.04)
12–17	24	204	1.27 (0.62–2.62)	11	185	0.85 (0.32–2.25)
18–23	14	155	Reference	8	162	Reference

[a]Adjusted for age (continuous) and outcome of previous pregnancy.

aOR, adjusted odds ratio; CI, confidence interval; IPI, interpregnancy interval.