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The association between weight gain during pregnancy and neural tube defects and gastroschisis in offspring

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Abstract

Background—Limited information is available about the association of maternal weight gain during pregnancy and birth defects. The objective of this study was to investigate the association of maternal weight gain with neural tube defects and gastroschisis among offspring.

Methods—We used data from the National Birth Defects Prevention Study, an ongoing multi-center, population-based case-control study. Mothers of cases and controls were interviewed by phone. Analyses included 255 anencephaly, 577 spina bifida, and 648 gastroschisis cases and 5,587 controls with deliveries from 1999–2005. After subtracting birth weight, the associations of total and average weekly weight gain(kg) with each phenotype were estimated, stratified by gestational age (<37vs.≥37 weeks) and adjusted for relevant covariates

Results—Among deliveries <37 weeks gestation, mothers of anencephaly and spina bifida cases had lower weight gains compared to control mothers; no association between weight gains and gastroschisis was observed. Among deliveries ≥37 weeks, mothers of anencephaly cases had lower weight gains during pregnancy; a similar association was not observed for spina bifida; mothers of gastroschisis cases were twice as likely to have weight gains in the highest quartile. Stratification by maternal age (gastroschisis) or BMI or race/ethnicity (all phenotypes) did not alter odds ratio estimates.

Conclusion—Altered weight gain during pregnancy may be a consequence of carrying a NTD/gastroschisis affected fetus or a marker for underlying factors common to the etiology of these birth defects. It is possible that whatever mechanisms influence weight gain may also influence the development of NTDs and gastroschisis, but in opposite directions.

INTRODUCTION

Several lines of evidence suggest lower maternal weight gain during pregnancy may be associated with neural tube defects (NTD)-affected pregnancies. Results from one report suggested that weight loss during early pregnancy may be more common among pregnancies affected by an NTD (Robert and others, 1995). In another study it was observed that mothers whose pregnancies were affected by NTDs had lower weight gain during pregnancy (Shaw and others, 2001). Other studies reported associations between dieting behaviors that involved food restriction and NTDs (Carmichael and others, 2003; Suarez and others, 2011); periconceptional use of weight loss products has been associated with

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anencephaly (Bitsko and others, 2008), one of the two most common phenotypes that comprise NTDs (the other being spina bifida).

Available data regarding weight gain during pregnancies affected by NTDs are suggestive of an association, but limited. Even less information is available about the potential inter-play of weight gain during pregnancy with other nutrition-related risk factors for NTDs such as maternal pre-pregnancy obesity, vitamin supplement use and dietary nutrient intakes. It is also important to expand such investigations to other birth defects, particularly birth defects that are associated with maternal nutritional status, such as gastroschisis. Risk of gastroschisis is negatively associated with maternal pre-pregnancy body mass index (BMI). (Lam and others, 1999; Rasmussen and others, 2008; Siega-Riz and others, 2009; Stothard and others, 2009; Waller and others, 2007) and therefore provides an interesting contrast to NTDs, which are positively associated with obesity (Lam and others, 1999; Rasmussen and others, 2008; Shaw and Carmichael, 2008; Shaw and others, 1996; Stothard and others, 2009; Waller and others, 2007; Watkins and others, 2003).

Most structural birth defects occur during the process of organogenesis during early pregnancy, and therefore associations with total weight gain during pregnancy may not reflect a direct causal sequence(Institute of Medicine, 2009). However, associations between birth defects and maternal weight gain could reflect shared underlying mechanisms and as such could be informative about potential etiologies. Thus, weight gain associations merit investigation because they could provide clues to help understand underlying mechanisms in the upstream causal pathways for certain nutrition-related birth defects.

We investigated the association of maternal weight gain during pregnancy with NTDs and gastroschisis among offspring, controlling for selected weight-related factors, using data from the National Birth Defects Preventions Study (NBDPS).

MATERIALS AND METHODS

NBDPS is an ongoing multi-site, population-based case-control study of over 30 different birth defects. This analysis included NBDPS data on pregnancies with estimated dates of delivery from 1999 to 2005 (after fortification of grain products with folic acid in the U.S.). Detailed study methods have been published (Yoon and others, 2001). Cases are identified through population-based birth defects surveillance. Each site randomly selects approximately 150 liveborn controls without major birth defects per study year from birth certificates (AR 2000–2005, GA 2001–2005, IA, MA, NC, NJ, UT) or from birth hospitals (AR 1997–1999, CA, GA 1997–2000, NY, TX), to represent the population from which the cases were derived. The NBDPS is approved by the Institutional Review Boards of the participating study centers.

Case information (i.e. clinical description, surgical, or autopsy report) was reviewed and case status was confirmed by clinical geneticists at each site to establish study eligibility. Cases included in this analysis were infants or fetuses with anencephaly, spina bifida, and gastroschisis. Cases recognized or strongly suspected to have single-gene conditions or chromosomal abnormalities were ineligible (Rasmussen and others, 2003). Cases with more than one defect believed to be pathogenically related but for which the primary defect was not apparent (complex cases) were excluded to reduce heterogeneity within case groups. Infants/fetuses who had a diagnosis of a limb-body wall disruption or amniotic band sequence were excluded, again to reduce heterogeneity. Cases with both anencephaly and spina bifida were analyzed with the anencephaly group (N=3). One case with both spina bifida and gastroschisis was included in both groups.

Maternal interviews were conducted using a standardized, computer-assisted telephone interview, in English or Spanish, no earlier than six weeks and no later than 24 months after the infant's estimated date of delivery (EDD). The EDD was based on mother's self-report; if unknown, EDD was estimated from information in the medical record (less than two percent of subjects). Exposures to a variety of factors were assessed, relative to a woman's date of conception, which was derived by subtracting 266 days from her EDD. Participation in the interview was 70% among case mothers and 67% among control mothers. Interviews were conducted with 1532 mothers of NTD and gastroschisis cases and 5734 mothers of controls who had singleton deliveries. Interviews were completed within an average of 11 months from the EDD for cases and 9 months for controls. Because pregestational diabetes (i.e. type I or II) was reported to be associated with both NTDs and gastroschisis (Correa and others, 2008), cases (n=14) and controls (n=36) whose mothers had these conditions were excluded from analyses. Therefore 1518 cases and 5698 controls were included in our analyses.

Weight gained or lost during pregnancy was assessed by the question "Overall, how much weight did you gain or lose during this pregnancy?" Body mass index (BMI) was estimated for each woman based on her reported pre-pregnancy weight and height using the algorithm (Institute of Medicine, 1990), weight (kg) / height^2 (meters^2). Weight gain greater than 91 kg (200 pounds) or weight loss more than 45 kg (100 pounds) or pre-pregnancy weight minus weight loss resulting in a weight less than 34 kg (75 pounds) were all set to missing (38 cases and 111 controls). One case was further excluded due to missing gestational age. Thus, 5587 controls and 1479 unique cases with anencephaly (255), spina bifida (577), and gastroschisis (648) were available for analyses.

After subtracting infant/fetus birth weight (Schieve and others, 1999), total net maternal weight gain during pregnancy was analyzed as a continuous variable as well as a three-level categorical variable based on quartile cut-offs (≤ 25th, 25th – 75th, >75th percentile, i.e. ≤6.67 kg, 6.68–14.88 kg (ref), and >14.88 kg), based on the distribution among controls. In addition, we calculated average weekly weight gain (kg), by dividing the total weight gain (minus birth weight) with gestational duration in weeks, as an attempt to account for differences in the opportunity for weight gain attributable to length of gestation, which is particularly important for anencephaly since many cases were electively terminated (47%). Average weekly weight gain was analyzed as a continuous variable as well as a three-level categorical variable based on quartile cut-offs (≤0.17 kg, 0.18–0.39 kg (ref), and >0.39 kg), based on the distribution among controls.

A shortened version of the Willett food frequency questionnaire was used to assess frequency of intake of 58 food items during the year before pregnancy (Willett and others, 1987). Separate, more detailed questions were used to assess intakes of breakfast cereals during the three months before pregnancy. The USDA version 22 nutrient database served as the source of nutrient values (U.S.-Department-of-Agriculture-Agricultural-Research-Service, 2007). Dietary data were considered missing for 108 women with more than one missing food item and for an additional 84 women (all cases and controls combined) whose average daily kilocalorie consumption was improbably high or low, i.e., <500 or >5,000. Thus, for the adjusted logistic regression analyses, which included variables defined using nutrient values, 1427 unique cases and 5447 controls were included.

We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression (SAS 9.3). All analyses were stratified by maternal gestational age (< 37 vs. ≥ 37 weeks) given the inherent association of weight gain with duration of gestation and the preponderance of preterm deliveries among the case groups. Multivariable logistic regression analyses were conducted to examine the association of weight gain during

pregnancy (described above) with specific phenotypes adjusting for potential confounders which were selected ***a priori*** based on previously demonstrated associations with weight gain or the phenotypes under study (Abrams and others, 1995; Carmichael and others, 2003; Feldkamp and others, 2011; Mac Bird and others, 2009; Shaw and others, 2001). The covariates for NTDs were race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (< 12, 12, > 12 years), maternal pre-pregnancy BMI (< 18.5, 18.5–24.9, 25.0–29.9, ≥ 30 kg/m^2), use of folic acid-containing supplements (any versus none) during the month before and the first three months of pregnancy, maternal total energy intake (kcal/day), and dietary folate intake (dietary folate equivalents, μg/day). Gastroschisis models also included age at delivery (< 20, 20–29, ≥ 30 years), any (versus none) smoking or alcohol drinking during the month before and the first three months of pregnancy, but excluded education. We also evaluated whether associations between weight gain (e.g. average weekly weight gain) and specific phenotypes were modified by maternal prepregnancy BMI (4 categories defined above) or race/ethnicity (non-Hispanic white, Hispanic). For gastroschisis, possible effect modification by age at delivery (< 20, 20–29, ≥ 30 years) was examined because young maternal age has been consistently associated with an increased risk of gastroschisis (Kazaura and others, 2004; Loane and others, 2007; Vu and others, 2008).

RESULTS

Compared to control mothers, mothers of infants with anencephaly were more likely to be Hispanic, to be less educated, to deliver before 37 weeks, to have still births or elective terminations, and less likely to drink; mothers of infants with spina bifida were more likely to be Hispanic, to be obese, to deliver before 37 weeks, and to have elective terminations; and mothers of infants with gastroschisis were more likely to be younger and less educated, less likely to be obese, more likely to deliver before 37 weeks, and to smoke (Table 1).

Mean and standard deviation (Mean ± SD) for total gain (kg) among anencephaly, spina bifida, gastroschisis, and controls were 6.38 ± 9.03, 9.66 ± 8.73, 13.08 ± 9.57, and 11.23 ± 8.38, respectively; for weekly gain (kg) among anencephaly, spina bifida, gastroschisis, and controls were 0.24 ± 0.34, 0.27 ± 0.24, 0.37 ± 0.27, and 0.29 ± 0.22, respectively.

Among deliveries < 37 weeks gestation, mothers of cases with anencephaly and spina bifida were more likely to have lower total weight gain, and less likely to have higher gain, relative to gains in the middle two quartiles. A similar pattern was observed for average weekly weight gain, but with ORs closer to one and 95% confidence intervals (CIs) including 1.0. Among deliveries ≥ 37 weeks, we observed that total and average weekly weight gains were negatively associated with anencephaly. Mothers of anencephaly cases were more likely to have total and weekly gains in the lowest quartile, and controls were more likely to have gains in the highest quartile; the odds ratio estimate for weight gain as a continuous variable was also statistically significant. No associations were observed with weight gain and spina bifida among deliveries ≥ 37 weeks (Table 2).

For deliveries < 37 weeks gestation, ORs for gastroschisis were consistent with the null value of 1.0 for both total and average weekly weight gains. Higher total and weekly gains were more common among mothers of gastroschisis cases delivered ≥ 37 weeks when weight gain was considered as a continuous variable. Mothers of gastroschisis cases were almost twice as likely to have total and average weekly weight gains in the highest quartile, but mothers of controls were no more likely than mothers of cases to have weight gain in the lowest quartile, which suggests a possible threshold (Table 3).

A similar pattern of results was observed for each phenotype when further stratified by maternal pre-pregnancy BMI or race/ethnicity or when results for gastroschisis were stratified by maternal age at delivery (data not shown). These estimates, however, were imprecise due to sparse sample sizes in some of the strata.

Discussion

We observed an association between lower total and average weekly weight gains during pregnancy among deliveries < 37 weeks gestation and anencephaly and spina bifida, but associations were more modest for weekly gain compared to total gain with 95% CIs including 1.0. Among deliveries ≥ 37 weeks, for anencephaly, a similar association was observed with lower total and weekly gains; no association was observed between weight gain and spina bifida.

The observed association of weight gain during pregnancy with gastroschisis was in the opposite direction, in that mothers of gastroschisis cases were twice as likely to have total and average weekly weight gains during pregnancy in the top quartile relative to the middle quartiles among deliveries ≥ 37 weeks. No association between maternal weight gain during pregnancy and gastroschisis was observed for deliveries < 37 weeks.

As noted previously, most structural birth defects arise during organogenesis in early pregnancy, and therefore the associations we observed with weight gain throughout pregnancy are unlikely to reflect a direct causal sequence for an earlier determined birth defect. Our observations are not attributable to differences in birth weight among fetuses/infants with birth defects, owing to the fact that associations were observed after subtracting birth weight of the fetus/infant from the weight gain measure. The implications of the associations we observed are unclear. Our objective was to identify clues that might help elucidate previous observations regarding the association of nutritional intake and BMI with selected birth defects by investigating pregnancy weight gain measures. All of our observed results were minimally influenced by adjustment for a sizable number and variety of factors that were considered *a priori* to be relevant potential covariates, including BMI and nutrient intake. Thus, the set of factors that we were able to look at did not clarify the observed associations.

An association between lower weight gain during pregnancies and NTDs has been observed before. Data from a previous population-based case-control study in California, conducted prior to mandatory food folic acid fortification in the U.S., suggested an association between NTDs and lower maternal weight gain, with an OR of 3.6 (95% CI 2.7, 4.7) for average weight gain <0.27 kg/week compared to 0.27–0.52 kg/week (Shaw and others, 2001). The association was greater for anencephaly than for spina bifida. Our current study suggests that these associations remain in the post-fortification era.

This is the first study of which we are aware that assessed the association between maternal weight gain and gastroschisis. Higher weight gain was more common among mothers of gastroschisis cases delivering ≥ 37 weeks. Also opposite to associations observed for NTDs is the previously reported observation in the NBDPS data that gastroschisis is less common among obese women (Siega-Riz and others, 2009; Waller and others, 2007). Little is known about the pathogenic mechanisms leading to gastroschisis. Gastroschisis is strongly associated with young maternal age, which could be related to some aspect of nutritional status (Lam and others, 1999; Siega-Riz and others, 2009), but our observed associations with weight gain were not unique to young mothers.

It is notable that elevated BMI and low weight gain have both been associated with NTD-affected pregnancies, whereas lower BMI and high weight gain were associated with

gastroschisis (Lam and others, 1999; Rasmussen and others, 2008; Shaw and Carmichael, 2008; Shaw and others, 2001; Shaw and others, 1996; Siega-Riz and others, 2009; Stothard and others, 2009; Waller and others, 2007; Watkins and others, 2003). Obese women tend to have lower weight gain during pregnancy than non-obese women (Institute of Medicine, 2009), and in our study the correlation between BMI and weight gain was −0.28. Thus, it is possible that whatever mechanisms influence the association between BMI and weight gain may also influence the development of NTD and gastroschisis, but in opposite directions. What those mechanisms might be were not captured in the variables assessed in this analysis. Alternatively, the association of weight gain and BMI with these defects could be unrelated. In the earlier study (Shaw and others, 2001) of maternal weight gain and NTDs, it was suggested that lowered weight gain during pregnancy could reflect an innate metabolic abnormality or life style factors (e.g. diet, exercise, or stress) that limit weight gain. The different directions of association for weight gain with NTD and gastroschisis observed in the current study do not offer further clarification on this issue.

The strengths of this study included its large size, its population-based ascertainment of cases and controls, its geographically multi-centered US population base, and its ability to examine a variety of potential covariables, including maternal pre-pregnancy obesity, vitamin supplement use and dietary nutrient intake. We subtracted birth weight from weight gain during the pregnancy to try to account for differences in birth weight among preterm and term deliveries (i.e. birth weight accounts for a larger proportion of maternal weight gain as gestational age increases).

Our study had important limitations. The percentage of those eligible who participated was about 70%. It is unknown whether the lack of information from nonparticipants biased observations in this study. Cogswell et al. reported that control participants in the NBDPS generally were representative of their source populations (Cogswell and others, 2009). Second, accuracy of maternal self-reported weight gain during pregnancy has not been evaluated in this study. Non-differential error would tend to shift results toward the null. We were unable to determine whether reporting error varied based on case or control status. Third, placental or amniotic fluid weight was unknown and therefore not subtracted from maternal total weight gain. The implications of these measures on our observations are not known. Fourth, we were lacking information on weight gain during early pregnancy, which is the relevant embryological period for NTDs and gastroschisis. Weight gain during the entire pregnancy may be a consequence of carrying a NTD/gastroschisis affected fetus or a marker for an underlying factor in the etiology of these phenotypes. Furthermore, weight gain per week is not uniform throughout pregnancy and is likely to be lower during the first trimester (Abrams and others, 1995) and therefore potential bias from differences in length of gestation was not entirely removed, especially for anencephaly, for which terminations during earlier gestational ages were common. We stratified by gestational age to minimize this bias, but it may explain at least some of the differences we observed in OR estimates for total weight gain versus average weekly weight gain among deliveries < 37 weeks, as was seen for anencephaly and spina bifida. In these instances the estimates for total weight gain may be biased away from the null because control mothers had longer pregnancies than case mothers within this stratum. This issue is unlikely to impact deliveries occurring ≥ 37 weeks, which is supported by the agreement in point estimates we observed between the total weight gain and average weekly weight gain classifications among this stratum for spina bifida and anencephaly. Although overall sample sizes were relatively large, power for some stratified analyses was compromised.

We have described an association between weight gain during pregnancy and two nutritionally-related birth defect groups - a replicated association in terms of NTD (Shaw and others, 2001) and a new association in terms of gastroschisis. It is possible that weight

gain is a reflection of other factors that we did not measure, though what these factors might be is unknown. Factors considered most likely to contribute to such an association, given their postulated role in these two defect groups were in fact measured (e.g., BMI, nutrient intake). The implications of these associations should be interpreted as clues for further study. For example, metabolic studies may help elucidate whether these associations have biologic meaning.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the California Department of Public Health or of the Centers for Disease Control and Prevention.

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Table 1

Descriptive characteristics of case and control infants, National Birth Defects Prevention Study, 1999–2005

	Percent[1]			
	Anencephaly (n=255)	Spina Bifida (n=577)	Gastroschisis (n=648)	Controls (n=5,587)
Maternal Race/ethnicity				
Non-Hispanic White	44.7	51.6	52.5	58.6
Non-Hispanic Black	9.0	9.2	7.6	11.1
Hispanic	37.3	32.8	29.3	22.5
Other	9.0	6.1	10.5	7.3
Missing	--	0.3	0.2	0.5
Maternal age at delivery (years)				
< 20	16.1	9.9	39.8	10.5
20–29	50.2	57.7	53.0	50.5
≥ 30	33.7	32.4	7.3	39.0
Education (years)				
Less than high school	22.0	19.2	29.0	16.5
High school	30.6	28.6	39.0	24.7
More than high school	45.9	51.5	29.3	57.4
Missing	1.6	0.7	2.6	1.4
Prepregnancy BMI (kg/m^2)				
Underweight BMI (<18.5)	6.7	3.1	9.1	5.4
Normal weight (18.5 ≤BMI <25)	50.2	44.9	68.8	53.4
Overweight (25 ≤BMI <30)	21.6	23.4	15.6	21.9
Obese (≥30)	17.6	22.9	4.8	15.9
Missing	3.9	5.7	1.7	3.4
Vitamin supplement use[2]				
None	12.2	15.9	17.6	15.0
Any	87.8	83.7	81.8	84.7
Missing	--	0.3	0.6	0.3
Smoking[2]				
Any	12.2	18.2	36.6	18.8
None	86.7	81.1	61.7	80.2
Missing	1.2	0.7	1.7	1.0
Drinking[2]				
Any	26.3	32.9	39.8	36.0
None	72.2	66.0	58.2	62.5
Missing	1.6	1.0	2.0	1.5
Gestational age (weeks)				
Preterm (< 37)	75.3	27.0	59.1	8.3
Term (≥ 37)	24.7	73.0	40.9	91.7
Birth outcomes				

	Percent[1]			
	Anencephaly (n=255)	**Spina Bifida (n=577)**	**Gastroschisis (n=648)**	**Controls (n=5,587)**
Live birth	29.8	88.0	96.6	100.0
Still birth (≥ 20 weeks)	23.1	2.1	2.9	0.0
Electively terminated	47.1	9.9	0.3	0.0
Missing	--	--	0.2	--

[1] Numbers may not add to 100% due to rounding.

[2] During the month before and the first 3 months of pregnancy.

Table 2

Association of neural tube defects with weight gain during pregnancy stratified by gestational age (< 37 weeks or ≥ 37 weeks)

	Deliveries <37 weeks					Deliveries ≥ 37 weeks				
	Controls (n= 438)	Anencephaly (n= 177)		Spina Bifida (n=145)		Controls (n=4773)	Anencephaly (n= 58)		Spina Bifida (n= 382)	
	N	N	OR [1] (95%CI)	N	OR [1] (95%CI)	N	N	OR [1] (95%CI)	N	OR [1] (95%CI)
Total weight gain (kg)[2]										
Quartile 1 (≤ 6.67)	117	106	3.1 (2.1,4.7)	78	2.9 (1.9,4.4)	1132	29	2.7 (1.5,4.9)	119	1.1 (0.9,1.5)
Quartiles 2&3 (6.68–14.88)	216	62	REF	48	REF	2435	25	REF	174	REF
Quartile 4 (>14.88)	105	9	0.3 (0.1,0.6)	19	0.8 (0.4,1.4)	1206	4	0.3 (0.1,1.0)	89	1.1 (0.8,1.4)
Continuous, 25th vs. 75th percentile (8.21 unit change)	438	177	0.58 (0.47,0.72)	145	0.72 (0.59,0.88)	4773	58	0.55 (0.42,0.72)	382	0.98 (0.88,1.10)
Average weekly weight gain (kg)[2]										
Quartile 1 (≤ 0.17)	98	57	1.3 (0.8,2.0)	51	1.5 (1.0,2.4)	1120	28	2.6 (1.5,4.6)	117	1.1 (0.9,1.5)
Quartiles 2&3 (0.18–0.39)	210	85	REF	65	REF	2493	26	REF	177	REF
Quartile 4 (> 0.39)	130	35	0.7 (0.4,1.1)	29	0.7 (0.4,1.2)	1160	4	0.3 (0.1,1.0)	88	1.1 (0.8,1.4)
Continuous, 25th vs. 75th percentile (0.22 unit change)	438	177	0.87 (0.76,1.01)	145	0.88 (0.75,1.04)	4773	58	0.53 (0.40,0.71)	382	1.00 (0.90,1.12)

[1] Adjusted for maternal race-ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (<12, 12, >12 years), pre-pregnancy BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥ 30 kg/m^2), intake of folic acid-containing supplements during the month before and the first three months of pregnancy (any versus none), maternal total energy intake (kcal/day), and dietary folate intake (dietary folate equivalents, μg/day). Analyses included subjects with complete data on all covariates.

[2] Birth weight was subtracted from total weight gain, and average weekly weight gain was obtained by dividing the total weight gain (minus birth weight) with gestational duration in weeks.

Table 3

Association of gastroschisis with weight gain during pregnancy stratified by gestational age (< 37 weeks or ≥ 37 weeks)

	Deliveries <37 weeks			Deliveries ≥ 37 weeks		
	Controls (n= 438)	Gastroschisis (n= 355)		Controls (n=4767)	Gastroschisis (n= 251)	
	N	N	OR[1] (95%CI)	N	N	OR[1] (95%CI)
Total weight gain (kg)[2]						
Quartile 1 (≤ 6.67)	118	76	0.8 (0.6,1.3)	1132	33	0.9 (0.6,1.4)
Quartiles 2&3 (6.68–14.88)	215	164	REF	2427	100	REF
Quartile 4 (>14.88)	105	115	1.2 (0.8,1.8)	1208	118	1.8 (1.4,2.4)
Continuous, 25th vs. 75th percentile (8.21 unit change)	438	355	0.97 (0.84,1.13)	4267	251	1.23 (1.10,1.39)
Average weekly weight gain (kg)[2]						
Quartile 1 (≤ 0.17)	99	64	0.9 (0.6,1.5)	1119	30	0.8 (0.5,1.3)
Quartiles 2&3 (0.18–0.39)	209	149	REF	2486	104	REF
Quartile 4 (> 0.39)	130	142	1.3 (0.9,1.9)	1162	117	1.9 (1.4,2.5)
Continuous, 25th vs. 75th percentile (0.22 unit change)	438	355	0.98 (0.86,1.12)	4267	251	1.31 (1.16,1.47)

[1] Adjusted for maternal race-ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), age at delivery (<20, 20–29, ≥ 30 years), pre-pregnancy BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥ 30 kg/m^2), any (versus none) intake of folic acid-containing supplements, smoking, or drinking alcohol during the month before and the first three months of pregnancy, maternal total energy intake (kcal/day), and dietary folate intake (dietary folate equivalents, μg/day). Analyses included subjects with complete data on adjusted covariates.

[2] Birth weight was subtracted from total weight gain, and average weekly weight gain was obtained by dividing the total weight gain (minus birth weight) with gestational duration in weeks.