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Prepregnant Obesity and Risks of Selected Birth Defects in Offspring

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Abstract

Background—Prepregnant obesity has been shown to be related to several birth defects, most notably neural tube defects. We investigated the previously observed association between obesity and spina bifida and also possible associations between obesity and other birth defects.

Results—We conducted a case-control study of fetuses and liveborn infants among California births, July 1999 and June 2004. Of those eligible, 80% of case mothers (n = 659) and 77% of control mothers (n = 700) were interviewed. Cases were 147 infants with anencephaly, 191 with spina bifida, 142 with d-transposition of great arteries, and 181 with tetralogy of Fallot. Maternal body mass index (BMI) was based on prepregnant weight and height.

Results—The odds ratios of birth defects with obesity (BMI ≥30 relative to normal BMI) were 1.6 for anencephaly (95% confidence intervals = 1.0 –2.6); 1.4 for spina bifida (0.8–2.2); 0.7 for d-transposition of great arteries (0.4–1.4); and 0.8 for tetralogy of Fallot (0.4–1.4). Modestly elevated odds ratios were observed with obesity among women who reported weight gain in their waist before pregnancy—for anencephaly, 2.4 (1.2–5.1) and for spina bifida, 1.8 (0.9–3.6).

Conclusion—These data do not fully support earlier findings with respect to the relationships of obesity with anencephaly and spina bifida.

Obesity in the United States is a public health concern.[1,2] Obesity in women at conception has been associated with increased risks for several structural birth defects,[3–19] most notably for neural tube defects.[3–10,19] No additional factor has been identified to substantially influence the associations with obesity, including periconceptional intake of folic acid. Although insufficient nutrient intake, aberrant glucose control, or other related metabolic disorder could possibly contribute to such associations, mechanisms underlying the associations with obesity are unknown.

We investigated the previously observed association between obesity and neural tube defects in detail by exploring potential associations with numerous weight-related factors. We also investigated potential associations between prepregnant obesity and 2 specific congenital heart defects. These inquiries were made by analyzing data collected in a recent California population-based case-control study.

METHODS

This case-control study included data on deliveries that had estimated due dates from July 1999 to June 2004. Cases were liveborn, stillborn (fetal deaths at greater than 20 weeks gestation),

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and prenatally diagnosed, electively terminated pregnancies with birth defects that occurred to women residing in the California counties of Los Angeles, San Francisco, and Santa Clara.

Case information was abstracted from multiple hospital reports and medical records, following established procedures. [20] Medical records were reviewed by a clinical geneticist. Infants with trisomies were ineligible. Case groups included spina bifida, anencephaly, d-transposition of the great arteries, and tetralogy of Fallot. The latter 2 were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. Ascertainment of spina bifida and anencephaly ended with an estimated due date of 30 June 2003; ascertainment of d-transposition of great arteries, tetralogy of Fallot, and controls ended with estimated due date of 30 June 2004. Nonmalformed, liveborn controls were selected randomly from birth hospitals to represent the population from which the cases were derived.

Mothers were eligible for interview if they were the biologic mother and carried the pregnancy of the study subject, they were not incarcerated, and their primary language was English or Spanish. Maternal interviews were conducted using a standardized, computer-based questionnaire in English or Spanish, primarily by telephone, no earlier than 6 weeks after the infant's estimated due date. Information solicited from women included height, prepregnant weight, age, race/ethnicity, educational level, history of overweight, weight gain patterns (weight gain in hips, waist or both), weight change in year before pregnancy (gained ≥5 lbs, lost ≥5 lbs, or both), and family history (affected first degree relative) of any of the 4 studied birth defects. Queries specific to the periconceptional period (2 months before through 2 months after conception) included use of folic-acid containing vitamin supplements, diabetes (gestational, type I, and type II), seizure medication use, dieting to lose weight, use of treatments for weight loss, and weight change pattern (gained ≥5 lbs, lost ≥5 lbs, or both in first 2 months of pregnancy). Body mass index (BMI) was estimated for each woman based on reported prepregnant weight and height (kg/m^2). Obesity was defined as BMI ≥30.

The interview also included a modified version of the National Cancer Institute's Health Habits and History Questionnaire, a well-known, semi-quantitative food frequency questionnaire with demonstrated reliability and validity.[21,22] The food frequency questionnaire was modified to include ethnic foods appropriate to a diverse study population. This questionnaire provided information on dietary folate and energy intake.

In total, 659 case mothers (80% of eligible) and 700 control mothers (77% of eligible) were interviewed. Eleven percent of case mothers and 12% of control mothers could not be located and the remainder declined to participate. The median time between estimated date of delivery and interview completion was 10 months for cases and 8 months for controls. The 659 cases included 147 with anencephaly, 191 with spina bifida, 181 with tetralogy of Fallot, and 142 with d-transposition of great arteries (1 case had 2 eligible diagnoses- anencephaly and tetralogy of Fallot).

We estimated relative risks using odds ratios (ORs) and 95% confidence intervals (CIs), using SAS 9.1 (SAS Institute, Cary, NC). Models were constructed to assess effects associated with continuous measures of BMI, as well as the categorical designation of obese (BMI ≥3 kg/m^2) compared with normal BMI of 18.5 to 24.9 kg/m^2. Covariates in analyses included maternal race/ethnicity (Latina, foreign-born; Latina, US-born; white, non-Latina; Black, non-Latina; Asian; other), education (<12; 12; 13–15; >15 years), age (<25; 25–29; 30–34; and >34 years), weight-related factors described above, periconceptional vitamin supplement use (yes or no), dietary folate intake (μg/d), and total energy intake (kcal/d).

RESULTS

Compared with control mothers, case mothers were slightly more likely to be Latina or foreign-born, to have <12 years of education, to not use vitamin supplements, to have had diabetes, to have used seizure medications, and to have had a family history of birth defects in a first degree relative (Table 1). Further analyses excluded cases and controls whose mothers had diabetes (types I or II), used seizure medications, or reported a family history of birth defects.

Table 2 displays odds ratios from analyses of BMI considered as a continuous and categorical variable. Crude and adjusted odds ratios for the BMI category defining obesity (≥30 kg/m^2) were modestly elevated for anencephaly, relative to normal BMI (18.5–24.9 kg/m^2). Such comparisons for other defect groups generally approximated 1.0.

Owing to their associations with prepregnant obesity in previous studies, anencephaly and spina bifida were further scrutinized for a variety of weight-related factors (Table 3). A few factors revealed stratum-specific diversions from the overall observed unadjusted odds ratios associated with obesity of 1.6 for anencephaly and 1.4 for spina bifida. However, most odds ratios were imprecise. One aspect of obesity that appeared to contribute (with reasonable precision) to the increased risk for anencephaly was the distribution of weight gain. An odds ratio of 2.4 (1.2–5.1) was observed for obese women who had weight gain in their waist before pregnancy, but not among women who gained in their hips. The association for spina bifida of weight gain in the hips was more modest 1.8 (OR = [0.9–3.6]). The factors shown in Table 3 were also investigated in conjunction with the 2 heart defects. No notable pattern emerged (data not shown).

DISCUSSION

The mechanisms underlying associations between obesity and birth defects are unknown. Our objective was to explore this association further by investigating the potential modifying effects of weight-related factors. Our findings in general did not show increased risks associated with obesity and the studied phenotypes, although we did see a stronger relation between obesity and anencephaly among obese women who reported weight gain in their waist before pregnancy. A tendency toward this type of weight gain was also associated with a modest (and imprecise) increase in spina bifida. Body fat distribution has been identified as a risk predictor for other diseases. Interestingly, weight gain around the waist (abdominal adipose tissue accumulation) has been associated with diabetogenic and inflammatory metabolic pathogenesis.[23] Thus, this finding may offer a clue to underlying mechanisms for the associations of obesity with birth defect risk, given that clinical diabetes is also a risk factor for birth defects.24

A lack of an increased risk between obesity and the 2 studied heart defects is consistent with 1 previous report[9] and inconsistent with another.[3] Our results provide only weak evidence of an increased risk for spina bifida among obese women and are thus inconsistent with our previous findings for California women, as well as other findings.[3–10,19] The reason for this lack of consistency is unclear. One possibility is that, because this study was conducted during a time period when the food supply was fortified with folic acid, what we observed was a pattern of occurrence of spina bifida that was not responsive to folic acid, and the obesity relationship observed previously was a component of folic acid etiology. This explanation seems unlikely owing to the fact that previous associations between obesity and spina bifida appeared to be little influenced by folic acid intake.[4,5] In addition, a recent multistate US-based study that overlapped the fortification period and included data derived from California found a 2.1-fold increased risk for spina bifida associated with obesity.[19] The California data

from that study showed a 1.8-fold increased risk for obesity compared with BMI in the normal range (not shown).

Although not unique to this study, a potential limitation was the self-reported nature of the information on weight, height, and weight-related factors. It has been demonstrated that women underestimate weight and obese women tend to underestimate somewhat more than other women.[25] Underestimation of weight could have resulted in biased effects towards the null under the reasonable assumption that such reporting was unrelated to case and control status. With respect to self-reporting of weight-related factors, our results indicated an increased risk among obese women who reported weight gain in their waist before pregnancy. Selfreported information on anatomic location of weight gain has been shown to be valid in women.[26]

This study has several strengths. It is large, it is population- based in its ascertainment of cases and controls, and it had a relatively short period for maternal recall between periconceptional event of interest and interview. This study extends the knowledge base on obesity and heart defects, as well as indicating that risks between obesity and neural tube defects may be specific to weight-related features such as abdominal weight gain.

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TABLE 1

Characteristics of Case Infants/Fetuses and Nonmalformed Control Infants Delivered in Selected Counties in California, 1999–2004

	Cases (n = 659) No. (%)[a]	Controls (n = 700) No. (%)[a]
Maternal race/ethnicity		
Latina US-born	111 (17)	155 (22)
Latina foreign-born	279 (42)	264 (38)
White	165 (25)	144 (21)
Black	28 (4)	54 (8)
Asian	52 (8)	63 (9)
Other	17 (3)	10 (1)
Maternal age; yrs		
<25	184 (28)	215 (31)
25–29	150 (23)	161 (23)
30–34	185 (28)	194 (28)
>34	139 (21)	127 (18)
Maternal education; yrs		
<12	223 (34)	201 (29)
12	123 (19)	166 (24)
13–15	145 (22)	152 (22)
>15	161 (24)	168 (24)
Maternal vitamin use[b]		
No	278 (42)	271 (39)
Yes	380 (58)	427 (61)
Maternal diabetes		
None	580 (88)	656 (94)
Gestational	47 (7)	39 (6)
Type I	8 (1)	1 (0)
Type II	14 (2)	1 (0)
Seizure medication use		
No	656 (100)	699 (100)
Yes	3 (0)	1 (0)
Family history[c]		
No	648 (98)	698 (100)
Yes	11 (2)	2 (0)

[a] Percentages may not equal 100 owing to missing data or rounding.

[b] Refers to use of a vitamin supplement that contained folic acid in the period 2 months before through 2 months after conception.

[c] Refers to a history of one of the studied birth defects in the probands' siblings or parents.

TABLE 2

Association of Maternal Prepregnant Body Mass Index With Selected Birth Defects

Body Mass Index; kg/m^2	No. Controls	No. Cases	OR (95% CI)	Adjusted OR[a] (95% CI)
Anencephaly				
≥30	81	27	1.6 (1.0–2.6)	1.4 (0.8–2.4)
25–29.9	131	25	0.9 (0.6–1.5)	0.9 (0.5–1.5)
18.5–24.9[c]	340	71	1.0	1.0
<18.5	30	2	0.3 (0.1–1.4)	0.3 (0.1–1.4)
Missing	41	14		
Continuous measure[b]	582	125	1.04 (1.00–1.07)	1.03 (0.99–1.07)
Spina bifida				
≥30	81	28	1.4 (0.8–2.2)	1.2 (0.7–2.0)
25–29.9	131	44	1.3 (0.9–2.0)	1.3 (0.8–2.0)
18.5–24.9[c]	340	87	1.0	1.0
<18.5	30	5	0.7 (0.2–1.7)	0.7 (0.2–1.8)
Missing	41	22		
Continuous measure[b]	582	164	1.02 (0.99–1.05)	1.01 (0.98–1.05)
d-Transposition of great arteries				
≥30	93	14	0.7 (0.4–1.4)	0.8 (0.4–1.6)
25–29.9	146	35	1.2 (0.8–1.8)	1.2 (0.8–2.0)
18.5–24.9[c]	375	76	1.0	1.0
<18.5	36	3	0.4 (0.1–1.4)	0.4 (0.1–1.5)
Missing	45	8		
Continuous measure[b]	650	128	1.01 (0.97–1.04)	1.02 (0.98–1.06)
Tetralogy of fallot				
≥30	93	16	0.8 (0.4–1.4)	0.7 (0.4–1.4)
25–29.9	146	39	1.2 (0.8–1.8)	1.3 (0.8–2.0)
18.5–24.9[c]	375	85	1.0	1.0
<18.5	36	10	1.2 (0.6–2.6)	1.3 (0.6–2.7)
Missing	45	15		
Continuous measure[b]	650	150	0.97 (0.94–1.01)	0.97 (0.93–1.01)

[a] Odds ratio adjusted for race/ethnicity, education, vitamin use, total energy intake, maternal height, and dietary folate intake.

[b] Odds ratio expressed as change in risk per 1 unit change in body mass index.

[c] Reference category.

TABLE 3

Association of Maternal Prepregnant Obesity (BMI ≥30) With Anencephaly and Spina Bifida Stratified by Maternal Weight-Related Factors

		Anencephaly		Spina Bifida	
Covariables	**No. Obese Controls**	**No. Obese Cases**	**OR (95% CI)[a]**	**No. Obese Cases**	**OR (95% CI)[a]**
Diet to lose weight					
Yes	10	5	1.0 (0.3–2.8)	5	1.9 (0.5–7.8)
No	70	22	1.7 (1.0–2.9)	23	1.3 (0.8–2.2)
Used weight loss medications					
Yes	11	3	0.7 (0.1–3.7)	1	0.4 (0.1–4.3)
No	69	24	1.7 (1.0–2.9)	27	1.5 (0.9–2.6)
History of overweight					
Yes	74	25	1.8 (1.0–3.4)	25	1.4 (0.8–2.6)
No	7	2	1.3 (0.3–6.5)	3	1.6 (0.4–6.4)
Weight change in year before pregnancy					
Gained ≥5 pounds	21	8	1.9 (0.7–5.3)	9	1.7 (0.7–4.5)
Lost 5 lbs or more	24	4	1.2 (0.3–4.1)	4	0.7 (0.2–2.2)
Gained and lost ≥5 lbs	15	7	0.8 (0.3–2.6)	6	0.7 (0.2–2.3)
Neither gained nor lost ≥5 lbs	19	8	2.1 (0.9–5.3)	9	2.0 (0.9–4.8)
Weight change in first 2 mo of pregnancy					
Gained ≥5 pounds	12	5	1.8 (0.6–5.7)	5	1.5 (0.5–4.6)
Gained 1–4 pounds	5	3	2.9 (0.6–14.3)	1	0.8 (0.1–7.7)
Lost ≥5 pounds	24	9	2.6 (0.8–8.3)	8	2.0 (0.6–6.2)
Lost 1–4 pounds	5	3	2.9 (0.5–16.2)	4	6.4 (1.1–38.0)
Weight not changed	33	7	1.1 (0.4–2.9)	9	1.0 (0.4–2.3)
Weight gain pattern before pregnancy					
Gained in waist	43	18	2.4 (1.2–5.1)	20	1.8 (0.9–3.6)
Gained in hips	32	7	0.8 (0.3–2.0)	6	0.7 (0.3–1.9)
Gained both in waist and hips	1	1	—	0	—
Did not gain	4	0	—	2	1.9 (0.3–11.2)

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[a]Odds ratio for anencephaly computed for comparisons with >5 obese cases and controls combined.