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Maternal pregnancy events and exposures and risk of hepatoblastoma: A Children's Oncology Group (COG) study

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Abstract

Background—Hepatoblastoma is a rare childhood liver cancer with an obscure etiology, however it is potentially associated with selected pregnancy events and hepatoblastoma risk in offspring.

Methods—Adjusted unconditional logistic regression estimated odds ratios (OR) and corresponding 95% confidence intervals (CI) for self-reported pregnancy events and medication use in a sample of mothers of 383 childhood hepatoblastoma cases and 387 controls.

Results—Risk of hepatoblastoma was significantly associated with maternal first trimester weight gain (OR=1.02; 95% CI 1.00, 1.04 per 1 lb increase and nearly significantly with maternal multivitamin use (OR=0.73; 95% CI 0.51,1.03). Hepatoblastoma was not associated with other maternal weight changes, maternal illness or medication use during pregnancy.

Conclusion—We found little evidence that maternal illness or most medication use during pregnancy are associated with hepatoblastoma in offspring.

Keywords

hepatoblastoma; pregnancy complications; self medication; body weight changes; case-control studies

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Introduction

Hepatoblastoma (HB) is a rare childhood neoplasm of the liver, with only 100–150 new diagnoses annually in the United States [1]. HB accounts for 79% of all malignant liver tumors in children [1], and incidence is increasing[2]. The etiology of HB is largely unknown [1, 3], however, very low birth weight (VLBW; <1500 g) [4–9], congenital conditions such as Beckwith-Wiedemann syndrome [4, 7], and parental cigarette smoking [10, 11] are consistent risk factors.

While VLBW is strongly associated with HB, birth weight *per se* is not likely the etiologic agent, but instead is a correlate for another causal factor. Because VLBW infants frequently receive intensive medical care, postnatal iatrogenic exposures are suspected[7]. Alternatively, HB's early age of onset (< 5 years) [5] and primitive histology suggests a role for perinatal maternal events and exposures. Increased risks for HB have been reported with maternal hypertension [12], polyhydraminos [4], pre-eclampsia [4], and higher maternal body mass index (BMI) [6]. Such events and exposures could potentially act either independently of, or in concert with, low birth weight in the etiology of HB. In this study, we analyzed maternal pregnancy events and exposures including hypertension, threatened miscarriage, pre-eclampsia, maternal drug and vitamin use, and weight gain during pregnancy and risk of HB.

Materials and Methods

This case-control study has been described in detail previously. Briefly, cases were children diagnosed with HB < age six years between January 2000 and December 2008 in the United States ascertained from Children's Oncology Group (COG) institutions. Controls were identified and recruited through random selection of birth rosters provided by 32 state birth registries grouped by geographic region for the years 1994–2008 and frequency matched to cases on birth weight categories (<1500g, 1500–2500g, and >2500 g), sex, year of birth, and geographic region. Initial matching frequencies within region of 1:2 for children <2500g at birth (i.e. oversampling of LBW and VLBW controls) was dropped to 1:1 due to budget constraints approximately halfway through the recruitment period, while matching was 1:1 for birth weight >2500 g throughout the study.

Mothers completed a standardized computer-assisted telephone interview, which gathered information on health related characteristics of the mother and index child including maternal illness (hypertension, gestational diabetes, pre-eclampsia, polyhydramnios), maternal pre-pregnancy weight and weight gain during pregnancy, and maternal vitamin and drug use.

We conducted unconditional logistic regression to estimate associations between HB with each exposure. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Each multivariate model contained matching variables (year of birth: four categories; birth weight: three categories; and sex) as well as a set of pre-selected confounding variables (maternal age, maternal smoking during pregnancy, plurality, and maternal race). Results are reported as odds ratios (OR) and 95% confidence intervals (CI).

Results

Of the 771 HB eligible cases registered with COG, 408 (52.9%) mothers consented, and 383 (49.7%) completed the study's interview portion. We attempted to contact 1,718 potential controls from an initial roster of 5,813 provided by state registries. Of those contacted prior to the end of data collection (n=754), 387 (51.3%) mothers completed an interview.

Characteristics of case and control mothers and children are shown in Table 1. Case children were more likely to be of singleton births (OR: 3.43, 95% CI: 1.98, 5.95). Case mothers were more likely to be Hispanic (OR: 2.32; 95% CI: 1.49, 3.63), to have a lower education level (OR 1.54; 95% CI: 1.08, 2.19 for high school or less vs. college or more) and a lower income (OR: 1.47; 95% CI: 1.01, 2.14 for <$30,000 a year vs. >$75,000 a year).

A significant increased odds was observed for first trimester weight gain as both a continuous and categorical measure (OR: 1.02; 95% CI: 1.00, 1.04 for a one pound increase in weight and OR: 2.13; 95% CI: 1.17, 3.88 for highest vs. lowest quintile of weight gain during pregnancy) (Table 2). No other significant association with maternal weight gain or BMI and HB was found. We observed non-significantly increased ORs for all maternal illness during pregnancy except for gestational diabetes. Results were similar in analyses that compared the receipt of treatment for these ailments vs. no treatment (data not shown). Maternal vitamin use including prenatal, multivitamins, and folate use during pregnancy was not associated with HB, although there was some suggestion of a protective association of multivitamin use (OR: 0.73; 95% CI: 0.51, 1.03; P=0.07). Increased odds ratios were found for other drug use including recreational drugs, steroids, insulin, thyroid medication, and holistic treatments, but confidence intervals were wide for these estimates. Maternal use of common pain medications during pregnancy was not significantly associated with HB. In an assessment of the robustness of these results, an assumption of substantial differential mis-reporting by case mothers (at least 40%) was required in order to obtain statistically significant results. Assuming non differential under- or over-reporting by both case and control mothers did not have a substantial impact on the statistical significance of the estimated ORs, but did draw the estimates even closer to the null.

Discussion

Our analyses indicated few significant associations between maternal exposures during pregnancy and offspring risk for HB. A lack of precision yielded wide CIs around increased ORs for many of the exposures. Weight gain during early pregnancy, but not weight gain for the full pregnancy term was significantly associated with a slight increase in odds.

Due to HB's extreme rarity, this study represents the largest published epidemiology study of HB to date, comprising nearly 400 HB cases. However, low participation rates and differences in controls compared to the US reference population suggest a potential for selection bias in our results. Specifically, control mothers tended to be older, more educated, and more often Caucasian when compared with national data from 2001—the median year of birth for controls. This discrepancy in age and education may have overestimated the prevalence of multivitamin use and of complication s during pregnancy in control mothers as both increase with maternal age [13].

Furthermore, exposure measures were derived from maternal self-report and thus are prone to recall bias through differential recall between mothers of healthy and ill children. Results of a small sensitivity analysis to assess the impact that such recall error would have on our results suggest our results might be somewhat sensitive to differential under reporting illness by case mothers, however, there is no way of ascertaining whether such under reporting actually occurred. To assess under and over reporting, analyses were repeated with positive exposures restricted to mothers who reporting medical treatment for an illness during pregnancy with no substantial change in our results, however, this analysis was also on self-report data, although many--but not all--of the rates of self-reported behaviors and exposures during pregnancy were consistent with those reported in PRAMS national data[14].

Finally, we estimate that the current study had 80% power to detect an OR of approximately 2.2 or greater for a rare exposure (5% prevalence in the source population) and an OR of 1.6 or greater for a moderately common exposure (25% prevalence in the source population). As a majority of our effect sizes were considerably smaller, it is possible that our study was simply not powerful enough to detect the slight but real elevations in risk conferred by such exposures.

Overall we did not find an increased risk for maternal illness or medication/drug use during pregnancy, and only marginal evidence of an increased risk associated with maternal weight gain during pregnancy where only a small effect was found, and only for weight gain during early pregnancy.

Increased risk of HB associated with maternal adiposity as well as the birth weight of the index child has been previously reported[7], and the complex interplay between maternal weight prior to and during pregnancy, and fetal growth appears to be implicated in HB's' etiologic pathway. While higher maternal BMI was not statistically significantly different in our study as it had been in previous studies, case mothers were approximately one BMI unit higher than control mothers. We did find an association with early pregnancy weight gain, independent of the index child's weight. It is unclear why early pregnancy weight gain, but not weight gain overall, could be associated with HB, although formation of the liver bud--the site of HB--is initiated in early pregnancy, at weeks 9–10 of gestation [15], hence early pregnancy weight gain could be associated with either a cause or effect of aberrant liver cell proliferation and tumorigenesis.

These analyses indicate there is little evidence of an association between maternal events during pregnancy and risk of HB in offspring. Future research should examine alternative causal pathways involving low birth weight and HB.

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Table 1

Demographic Characteristics of Case and Control Mothers and Children from a Children's Oncology Group (COG) Study of Childhood Hepatoblastoma[a]

Maternal characteristics	Cases (n=383)		Controls (n=387)	
	n	%	n	%
pregnancy number				
1	116	31.78	130	33.94
2–4	216	59.18	216	56.40
5+	33	9.04	37	9.66
maternal age (years)				
<25	82	22.47	81	21.09
25– 29	94	25.75	122	31.77
30–34	122	33.42	113	29.43
35 +	67	18.36	68	17.71
maternal BMI[b]				
<18.5	17	4.78	26	6.81
18.5–24.9	202	56.74	233	60.99
25.0–29.9	87	24.44	75	19.63
30 +	50	14.04	48	12.57
maternal race/ethnicity				
white, non-Hispanic	248	68.70	284	74.54
black	16	4.43	33	8.66
Hispanic	**69**	**19.11**	**34**	**8.92**
other	28	7.76	30	7.87
maternal education				
high school or less	**106**	**29.28**	**85**	**22.19**
some college	101	27.90	107	27.94
college or more	155	42.82	191	49.87
maternal income				
< $30,000	**113**	**31.56**	**88**	**23.04**
$ 30,000 – $75,000	133	37.15	166	43.46
> $ 75,000	112	31.28	128	33.51
maternal smoking[c]				
yes	65	17.91	71	18.49
no	298	82.09	313	81.51
Child characteristics				
sex				
male	228	59.53	225	58.14
female	155	40.47	162	41.86
birth weight [d]				
<1500 g	57	14.88	65	16.80

Maternal characteristics	Cases (n=383)		Controls (n=387)	
	n	%	n	%
1500–2499 g	**23**	**6.01**	**79**	**20.41**
2500 + g	303	79.11	243	62.79
small for gestational age				
yes	**63**	**17.31**	**97**	**25.46**
no	301	82.69	284	74.54
gestational age				
<37 weeks	87	22.89	119	30.99
37–<42 weeks	281	73.95	253	65.89
42+ weeks	12	3.16	12	3.13
baby moved to intensive care				
yes	116	30.61	132	34.55
no	263	69.39	250	65.45
baby given oxygen therapy				
yes	112	29.71	121	31.76
no	265	70.29	260	68.24
plurality				
singleton	**347**	**95.07**	**326**	**15.10**
multiple	18	4.93	58	84.90

[a]Bold: Statistically significant difference between cases and controls

[b]Body Mass Index: Pre-pregnancy

[c]Before mother knew she was pregnant

[d]Matching variable

Table 2

Maternal Exposures and Events During Pregnancy and Odds of Hepatoblastoma in Offspring

Pregnancy Event	OR	95 % CI
maternal weight		
BMI (pre-pregnancy)	1.00	0.98, 1.04
3 month weight gain (quintiles)		
1	1.00	REF
2	1.47	0.86, 2.51
3	1.35	0.74, 2.45
4	1.64	0.92, 2.93
5	2.13	1.17, 3.88
9 month weight gain (quintiles)		
1	1.00	REF
2	1.27	0.76, 2.12
3	0.76	0.44, 1.31
4	1.05	0.62, 1.78
5	0.94	0.55, 1.61
maternal illness during pregnancy		
morning sickness	1.02	0.73, 1.42
high blood pressure	1.15	0.73, 1.81
toxemia	1.60	0.88, 2.91
threatened miscarriage	1.18	0.65, 2.13
vaginal bleeding	1.06	0.72, 1.58
gestational diabetes	0.79	0.43, 1.48
maternal medication use		
vitamins		
any vitamin yes/no	0.99	0.59, 1.67
multivitamin vs. none	0.73	0.51, 1.03
prenatal vitamin vs. none	1.26	0.85, 1.89
folate vs. none	0.88	0.48, 1.62
recreational drug use yes/no	1.68	0.76, 3.68
steroid use	1.27	0.69, 2.34
insulin	1.74	0.57, 5.37
thyroid medication use	1.43	0.56, 3.67
holistic natural medication use	1.11	0.65, 1.92
common pain medications		
aspirin	0.97	0.65, 1.46
Tylenol	0.98	0.65, 1.48
advil	1.09	0.79, 1.52