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Parental infertility, infertility treatment and hepatoblastoma: a report from the Children's Oncology Group

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BACKGROUND: A recent study suggested a markedly increased risk of hepatoblastoma (HB) among children conceived with treatment for infertility. However, it is not clear whether this finding is confounded by the association between HB and low birthweight (LBW).

METHODS: Associations between parental infertility and its treatment and HB were examined using data from a case–control study conducted through the Children's Oncology Group (COG). Telephone interviews were completed for 383 mothers of cases diagnosed with HB at US COG institutions between January 2000 and December 2008 and for 387 mothers of controls recruited through state birth registries. Logistic regression was used to examine possible associations.

RESULTS: After adjusting for birthweight and other potential confounders, no significant association was found for any of the measures of parental infertility or its treatment. In HB cases conceived through assisted reproductive technology (ART), 4 of 16 also had Beckwith–Wiedemann syndrome (BWS) compared with 9 of 365 in HB cases without ART.

CONCLUSIONS: Little evidence of an association between parental infertility or its treatment and HB was found. The relationship found in a previous study could be due to LBW and BWS which are risk factors for HB and also associated with parental infertility and its treatment.

Key words: case–control studies / hepatoblastoma / infertility / selection bias

Introduction

Hepatoblastoma (HB) is a rare childhood embryonal tumor that occurs in the liver. Although few studies have been conducted concerning the etiology of this cancer, some consistent risk factors have emerged, including low birthweight (LBW: 1500–2500 g) and especially very LBW (VLBW: <1500 g) (Tanimura *et al.*, 1998; Reynolds *et al.*, 2004; Ansell *et al.*, 2005; McLaughlin *et al.*, 2006; Spector *et al.*, 2008, 2009) and congenital conditions such as Beckwith–Wiedemann syndrome (BWS) (Buckley *et al.*, 1989; DeBaun and Tucker, 1998) and familial adenomatous polyposis (Kingston *et al.*, 1983; Giardiello *et al.*, 1991; Hughes and Michels, 1992). Incidence of HB has been increasing over time with an estimated increase of ~4% per year since 1992 in the USA (Linabery and Ross, 2008).

A possible risk factor for HB is parental infertility or its treatment. The standard definition of infertility is no conception after 12 months of trying to conceive. Thus defined, infertility may resolve with or without treatment. Treatment for infertility encompasses many different medications and procedures. The most extensive treatment is assisted reproductive technology (ART), defined as treatments that handle both gametes outside the body. The majority of ART treatments involve IVF with or without ICSI.

In a recent study by McLaughlin et al. (2006), a 9-fold increase in risk of HB was observed for those with reported or inferred parental infertility treatment. There have also been reports of children diagnosed with HB after parental infertility treatment in other studies (Toren et al., 1995; Maruyama et al., 1999; Ansell et al., 2005; Kallen et al., 2010). Parental infertility and its treatment have been hypothesized to be risk factors for childhood cancer in general. Results from epidemiological studies have been mixed, with many showing no association (Doyle et al., 1998; Bruinsma et al., 2000; Lerner-Geva et al., 2000; Klip et al., 2001; Kallen et al., 2005; Lidegaard et al., 2005), but some showing an increased risk both overall and for particular cancer subtypes (Lightfoot et al., 2005; McLaughlin et al., 2006; Puumala et al., 2007; Kallen et al., 2010). HB in particular could be associated with parental infertility or its treatment, since risk factors for HB including LBW and BWS have been linked to parental infertility and/or its treatment (Olivennes et al., 2001; Schieve et al., 2002; Basso and Baird, 2003; DeBaun et al., 2003; Gicquel et al., 2003; Maher et al., 2003; Halliday et al., 2004; Chang et al., 2005; Sutcliffe et al., 2006; Bowdin et al., 2007; Doornbos et al., 2007).

Although BWS is an overgrowth syndrome, with close to 90% of children experiencing macrosomia pre- or post-natally, it has also been associated with an increase in twinning and preterm birth (Weksberg et al., 2002; Wangler et al., 2005). In a large case series of children with BWS, 49% had a normal birthweight (under the 90th percentile) and 53% were born pre-term (Elliott et al., 1994). So, while children born with BWS may be relatively large for their gestational age and birth plurality, they could still be classified as LBW.

Sorting out possible effects of birthweight, syndromes, and parental infertility and its treatment is difficult as they are all inter-related. There are several lines of inquiry that could help elucidate the pathways through which these various treatments or conditions are associated with HB. It is currently not known whether there is some etiologic factor due to parental infertility or its treatment that leads to HB or whether the association is due to the relationship with birthweight and other, yet unknown factors. If there is an independent effect of parental infertility or its treatment, we would expect to see a residual effect after effectively controlling for birthweight. In this study, we attempt to assess the effect of parental infertility and its treatment on incidence of HB, independent of birthweight, through frequency matching of cases and controls within birthweight categories.

Materials and Methods

We examined data from a case–control study of HB conducted through the Children's Oncology Group (COG). Cases were eligible if they had a confirmed diagnosis of HB at a US COG institution between January 2000 and December 2008 and were under the age of 6 years at the time of diagnosis. Cases also had to have been born in the USA and have an English- or Spanish-speaking birth mother available for an interview by telephone. The birth, rather than the biological, mother was the criterion in order to include children whose conception was the result of egg donation. Approval for the study was needed at each individual COG institution, prior to obtaining case contact information. In addition, the oncologist treating each case was contacted and asked to provide permission to contact the child's mother about study participation. Deceased cases were included in the study, since the data were gathered through maternal interview.

To be eligible for the study, controls had to have been born in the USA during 1994–2008 and to have an English- or Spanish-speaking birth mother available for a telephone interview. Controls were recruited through rosters of randomly selected births provided by 32 state birth registries (Spector et al., 2007), both because of their ability to sample based on matching factors and because random digit dialing has declined in usefulness for nationwide studies (Bunin et al., 2007). Strict adherence to case–control methodology would require excluding cases not born in states that contributed controls; however, as HB is a rare disease, we elected to use a modified strategy of grouping states into six broader regions that each contained a mixture of birth registries that did and did not participate in control selection. The six regions, with participating states in bold, were Northeast (NE: **CT**, DE, **NH**, **ME**, **MA**, MD, **NJ**, NY, **PA**, **RI**, **VT**), Southeast (SE: **AL**, DC, **GA**, **FL**, **KY**, MS, **NC**, SC, **TN**, **VA**, WV), Midwest (MW: IL, **IN**, IA, **MI**, **MN**, **OH**, WI), South Central (SC: **AR**, KS, **LA**, **MO**, OK, **TX**), Northwest (NW: AK, ID, **MT**, NE, **ND**, **OR**, SD, **WA**, **WY**) and Southwest (SW: **AZ**, **CA**, **CO**, HI, NV, NM, **UT**).

Controls were frequency matched to cases on birthweight categories ($<$1500, 1500–2500 and $>$2500 g), sex, year of birth and region. Frequencies of each matching factor were based on the characteristics of cases in the COG database for the 5 years prior to the study, except for birthweight, which was randomly assigned to strata based on previous literature (Feusner et al., 1998; Tanimura et al., 1998). Within each region, the number of requested potential controls from each participating state was proportional to the size of its pediatric population. The initial ratio of cases to controls was 1:2 for children $\leq$2500 g at birth and 1:1 for those $>$2500 g in order to increase power to investigate risk factors in the former subgroup; however, due to budget constraints the case–control ratio was later allowed to drop below 1:1 for the latter group. For each set of matching characteristics, we received a roster of between 5 and 10 potential controls. An introductory letter was sent to the first potential control providing information about the study and indicating that an interviewer would contact them by phone. Phone contact, informed consent and interview were then attempted for a period of 4 weeks. If a control was not successfully enrolled by this process, the same protocol was followed for each successive control on the list successively until an eligible control agreed to participate or subject recruitment ended.

The information used in this analysis was collected by a standardized computer-assisted telephone interview of the mothers. The interview included questions about pregnancy history, maternal exposures during pregnancy with the participating (index) child, family history of cancer and other diseases and information about the medical history of the mother. Several questions about infertility and infertility treatment were asked, including length of time to index pregnancy, history of infertility (more than 1 year of trying unsuccessfully to become pregnant), history of doctor's visits by mother or index biological father due to infertility, use of medication to treat infertility and use of ART: IVF, ICSI, gamete intrafallopian transfer, assisted hatching or donor eggs.

We employed unconditional logistic regression models to assess each exposure. Multivariate models were constructed, which included matching variables as well as additional potential confounding variables. The former included year of birth (quartiles), birthweight ($<$1500, 1500–2499 and $\geq$2500 g) and sex (male, female). Potential confounding variables included in the model were maternal age (continuous), maternal education (high school or less, some post-secondary, college graduate/advanced degree), maternal race (White, Black, Hispanic, other), birth plurality (single, multiple) and gestational age ($<$34, 34–36 and $>$36 weeks). Subgroup analysis for the normal weight group ($\geq$2500) was also performed to examine possible issues with residual confounding. Results are reported as odds ratios (OR) and 95% confidence intervals (CIs). All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA).

To assess representativeness of controls, we compared their data with US births, using data from the National Center for Health Statistics (NCHS) stratified by birthweight group (<1500, 1500–2499, ≥2500). The year 2001 was chosen as the reference year, since this was the median year of birth in the control group. Controls were compared with national data on maternal race/ethnicity, maternal age, birth plurality, gestational age and child's sex. Goodness-of-fit χ^2 tests were used to examine differences in controls from the reference population. In addition, a sensitivity analysis was conducted to help quantitatively assess the impact of selection bias. Post-stratification (PS) weights were constructed using the NCHS data and used in a weighted logistic regression model (Haneuse *et al.*, 2009). Several different PS weights were constructed based on various combinations of maternal age, maternal education and maternal race.

The study was approved by the institutional review boards at the University of Minnesota and the participating COG institutions as well as health departments for the states providing birth registry information. All participants provided informed consent prior to participating in the study.

Results

There were 771 cases of HB registered with COG who were diagnosed at 0–6 years of age during 2000–2008 and presumed to be otherwise eligible. Of these, 408 mothers consented and 383 completed the interview portion of the study. Among the remaining cases, reasons for non-participation included inability to be contacted (21.3%), no institutional IRB approval (11.2%), physician refusal (7.0%) and participant refusal (8.8%). Of cases the study had permission to contact (IRB approved institution and physician consent) 60.7% of cases participated, although the actual proportion is likely higher since an unknown proportion of cases not reached may have been ineligible due to adoption or language.

There were 5813 potential controls requested from participating states. Contact was attempted for 1718 of these, and 754 were reached, prior to the end of data collection. Out of those reached 387 (51.3%) mothers completed an interview, 229 refused participation (30.3%), 123 (16.3%) declined or were unable to complete interview after initial consent and 15 (2.0%) were ineligible due to language.

Characteristics of cases and controls are presented in Table I. Case mothers were more likely to be Hispanic (OR: 1.85, 95% CI: 1.16, 2.95) and younger (OR: 2.19, 95% CI: 1.05, 4.57 for <20 years versus 25–29 years). Case children were less likely to be part of a multiple birth (OR: 0.58, 95% CI: 0.32, 1.06) and more likely to be born pre-mature (OR: 3.35, 95% CI: 1.29, 8.65 for <34 weeks versus ≥37 weeks). A diagnosis of BWS was reported for 13 cases and no controls.

No significant association was found for any of the measures of parental infertility or its treatment and HB (Table II). However, there was a possible indication of decreased risk for history of infertility (OR: 0.72, 95% CI: 0.49, 1.04, $P = 0.08$). ORs for doctor's visit for infertility and time to pregnancy for the index child were very close to 1. Somewhat increased ORs were observed for the use of fertility drugs and ART for children with birthweights of 2500 g or more, but these were very imprecisely estimated. Results were similar in analyses that excluded cases of BWS although the OR for ART moved closer to the null (OR: 1.18, 95% CI: 0.44, 3.06) (data not shown).

ART was associated with both VLBW and BWS. Half of both cases and controls conceived through ART were VLBW compared with 13 and 15%, respectively, without ART use. Twenty-five percent of cases (4 of 16) conceived through ART had a diagnosis of BWS compared with 2.5% of cases without ART use (9 of 365).

Controls were found to differ from the US reference population with respect to maternal race, education and age in all birthweight categories (Table III). Specifically, our controls were more likely to have mothers who were white, non-Hispanic, had higher education levels and were older. We also found that our controls had a higher than expected proportion of multiple births and males for those weighing between 1500 and 2499 g at birth. Table IV presents the results of the sensitivity analysis for selection bias using PS weights based on

Table I Characteristics of cases and controls, USA, 2000–2008.

	Controls *n* (%)	Cases *n* (%)	OR[a]	95% CI
Maternal race/ethnicity				
White	284 (74.5)	261 (68.9)	Ref	
Black	33 (8.7)	18 (4.7)	0.64	0.34, 1.23
Hispanic	34 (8.9)	72 (19.0)	1.85	1.16, 2.95
Other	30 (7.9)	28 (7.4)	0.97	0.53, 1.76
Maternal age (years)				
<20	15 (3.9)	27 (7.0)	2.19	1.05, 4.57
20–24	66 (17.2)	59 (15.4)	1.03	0.64, 1.66
25–29	122 (31.8)	101 (26.4)	Ref	
30–34	113 (29.4)	127 (33.2)	1.36	0.92, 2.02
35+	68 (17.7)	69 (18.0)	1.23	0.77, 1.96
Maternal education				
≤High school	85 (22.2)	110 (28.9)	1.35	0.93, 1.97
Some post-secondary	107 (27.9)	106 (27.9)	1.10	0.76, 1.59
College graduate/ advanced degree	191 (49.9)	164 (43.2)	Ref	
Plurality				
Single	326 (84.9)	360 (94.0)	Ref	
Twins+	58 (15.1)	23 (6.0)	0.58	0.32, 1.06
Gestational age (weeks)				
<34	69 (18.0)	62 (16.3)	3.35	1.29, 8.65
34–36	50 (13.0)	25 (6.6)	1.11	0.57, 2.17
37+	265 (69.0)	293 (77.1)	Ref	
BWS				
Yes	0 (0.0)	13 (3.4)	[b]	
No	384 (100.0)	368 (96.6)		
Birthweight (g)[c]				
<1500	65 (16.8)	57 (14.9)		
1500–2499	79 (20.4)	23 (6.0)		
2500+	243 (62.8)	303 (79.1)		
Gender[c]				
Male	225 (58.1)	228 (59.5)		
Female	162 (41.9)	155 (40.5)		

[a]Adjusted for matching factors only (birthweight, year of birth (quartiles), gender).
[b]OR is not calculable.
[c]Matching factor, no OR presented.

Table II Association between parental infertility and HB, USA, 2000–2008.

	All birthweights combined						Birthweight ≥2500					
	Controls *n* (%)	Cases *n* (%)	OR[a]	95% CI	OR[b]	95% CI	Controls *n* (%)	Cases *n* (%)	OR[a]	95% CI	OR[b]	95% CI
History of infertility[c]												
Yes	109 (28.4)	82 (21.4)	0.74	0.52, 1.06	0.73	0.51, 1.07	56 (23.1)	52 (17.2)	0.70	0.45, 1.10	0.69	0.43, 1.10
No	275 (71.6)	301 (78.6)	Ref .		Ref .		186 (76.9)	251 (82.8)	Ref .		Ref .	
Time to index pregnancy												
Not trying	133 (34.6)	155 (40.5)	Ref .		Ref .		88 (36.4)	124 (40.9)	Ref .		Ref .	
<12 months	192 (50.0)	177 (46.2)	0.84	0.60, 1.18	0.89	0.62, 1.29	129 (53.3)	150 (49.5)	0.89	0.61, 1.30	0.98	0.65, 1.49
12+ months	59 (15.4)	51 (13.3)	1.01	0.63, 1.64	1.05	0.61, 1.81	25 (10.3)	29 (9.6)	0.98	0.52, 1.84	0.97	0.49, 1.94
Doctor visit for infertility												
Yes	62 (16.1)	48 (12.5)	0.94	0.60, 1.48	1.07	0.64, 1.78	23 (9.5)	27 (8.9)	1.08	0.58, 2.00	1.06	0.54, 2.08
No	322 (83.9)	335 (87.5)	Ref		Ref		219 (90.5)	276 (91.1)	Ref		Ref	
Use of infertility drugs												
Yes	45 (11.7)	34 (8.9)	0.92	0.55, 1.54	1.12	0.61, 2.04	12 (5.0)	20 (6.6)	1.57	0.73, 3.38	1.70	0.71, 4.06
No	339 (88.3)	349 (91.1)	Ref		Ref		230 (95.0)	283 (93.4)	Ref		Ref	
Use of ART												
Yes	20 (5.2)	16 (4.2)	0.94	0.44, 1.98	1.44	0.59, 3.54	3 (1.2)	7 (2.3)	2.07	0.50, 8.50	2.21	0.46, 10.70
No	367 (94.8)	367 (95.8)	Ref		Ref		240 (98.8)	296 (97.7)	Ref		Ref	

[a]Adjusted for matching factors only (birthweight, year of birth (quartiles), gender).
[b]Adjusted for birthweight, year of birth (quartiles), gender, maternal age, maternal education, maternal race, plurality and gestational age.
[c]Ever try for one year or more.

Table III Controls compared with US births (2001), stratified by birthweight categories, USA, 2000–2008.

	US births 2001			Controls			Chi-squared *P*-value		
	<1500 (%)	1500–2499 (%)	2500+ (%)	<1500 *n* (%)	1500–2499 *n* (%)	2500+ *n* (%)	<1500	1500–2499	2500+
Maternal race/ethnicity									
White	47.2	52.2	58.7	41 (66.1)	55 (70.5)	188 (78.0)	<0.001	<0.001	<0.001
Black	31.6	23.6	13.9	8 (12.9)	7 (9.0)	18 (7.5)			
Hispanic	17.1	18.2	21.6	6 (9.7)	5 (6.4)	23 (9.5)			
Other	4.1	6.0	5.8	7 (11.3)	11 (14.1)	12 (5.0)			
Maternal age (year)									
<20	14.0	13.9	11.2	3 (4.8)	4 (5.1)	8 (3.3)	0.019	0.025	<0.001
20–24	24.5	25.9	25.4	10 (15.9)	15 (19.0)	41 (16.9)			
25–29	23.4	23.2	26.5	22 (34.9)	24 (30.4)	76 (31.4)			
30–34	21.8	21.4	23.6	16 (25.4)	20 (25.3)	77 (31.8)			
35+	16.3	15.6	13.5	12 (19.0)	16 (20.3)	40 (16.5)			
Maternal education									
0–12 years	58.5	58.7	52.8	14 (22.2)	17 (21.5)	54 (22.4)	<0.001	<0.001	<0.001
13–15 years	21.1	20.1	21.7	23 (36.5)	21 (26.6)	63 (26.1)			
16+ years	20.4	21.3	25.5	26 (41.3)	41 (51.9)	124 (51.5)			
Gender									
Male	50.9	46.7	51.4	41 (63.1)	54 (68.4)	130 (53.5)	0.28	0.002	0.94
Female	49.1	53.3	48.6	24 (36.9)	25 (31.6)	113 (46.5)			
Plurality									
Single	73.9	76.8	98.5	38 (60.3)	49 (62.0)	239 (98.8)	0.11	0.02	0.99
Multiples	26.1	23.2	1.5	25 (39.7)	30 (38.0)	3 (1.2)			
Gestational age (weeks)									
<34	91.1	20.7	0.9	55 (88.7)	13 (16.5)	1 (0.4)	0.45	0.66	0.19
34–36	5.5	39.2	6.5	6 (9.7)	36 (45.6)	8 (3.3)			
37+	3.4	40.1	92.6	1 (1.6)	30 (38.0)	234 (96.3)			

various combinations of maternal race, education and age. The results based on the PS analysis were very similar to the unweighted results for each of the three weighted models used.

Discussion

We did not find a significant association between parental infertility or its treatment and HB, which was independent of birthweight in our case–control study. In analysis restricted to those of normal birthweight (≥2500 g), the ORs for use of ART were over two, but were imprecisely estimated and indicated no significant effect. We did see a possible relationship between ART, BWS and HB; while none of the controls conceived through ART had a BWS diagnosis, 25% of cases conceived through ART were affected.

Due to the rarity of HB, few etiologic studies have been performed. The use of patients treated at COG institutions enabled us to conduct one of the largest studies of HB to date. Also, since a higher proportion of children under the age of six are treated at a COG institution, our pool of potential cases was approximately population-based (Liu *et al.*, 2003). This study also collected detailed information on parental infertility and its treatment such that we were able to examine parental infertility and specific types of infertility treatment.

Since control participation was low and differed in several respects from the underlying population of interest, there is the possibility that selection bias affected our results. Overall, our controls tended to include fewer minorities, fewer younger mothers and more college-educated mothers compared with national data from 2001 (the median year of birth for controls). This potential bias might have led to an increase in the number of children conceived through ART or other infertility treatment in our control group since women who use infertility services tend to be older and have higher socioeconomic status (Chandra and Stephen, 2010). However, in our sensitivity analysis, little difference was found in OR estimates or 95% CI based on PS weights. While there are several limitations and assumptions in the sensitivity analysis, it does provide some quantitative measure of the potential impact of differential selection and it is reassuring that results changed so little.

Self-reported exposure information in case–control studies is prone to recall bias. While it seems unlikely that the use of ART would be recalled differently, given the extensive treatment and expense involved, other factors such as history of infertility or time to pregnancy may be differentially recalled. Few studies have reported on the recall accuracy of infertility or its treatment. One study of malformations found that mothers of malformed infants were more accurate

Table IV Sensitivity analysis for selection bias, USA, 2000–2008.

	OR[a]	95% CI	OR[b]	95% CI	OR[c]	95% CI	OR[d]	95% CI
History of infertility[e]								
Yes	0.73	0.51, 1.07	0.73	0.50, 1.06	0.80	0.55, 1.18	0.81	0.55, 1.19
No	Ref		Ref		Ref		Ref	
Time to index pregnancy								
Not trying	Ref		Ref		Ref		Ref	
<12 months	0.89	0.62, 1.29	0.92	0.65, 1.30	1.16	0.81, 1.67	0.88	0.61, 1.25
12+ months	1.05	0.61, 1.81	1.12	0.67, 1.87	1.62	0.97, 2.70	1.10	0.65, 1.86
Doctor visit for infertility								
Yes	1.07	0.64, 1.78	1.15	0.68, 1.94	1.44	0.85, 2.43	1.11	0.65, 1.89
No	Ref		Ref		Ref		Ref	
Use of infertility drugs								
Yes	1.12	0.61, 2.04	1.22	0.67, 2.22	1.36	0.75, 2.47	1.16	0.64, 2.12
No	Ref		Ref		Ref		Ref	
Use of ART								
Yes	1.44	0.59, 3.54	1.34	0.57, 3.13	1.60	0.67, 3.84	1.43	0.59, 3.48
No	Ref		Ref		Ref		Ref	

[a]Unweighted model, adjusted for birthweight, year of birth, gender, maternal age, maternal education, maternal race, plurality and gestational age.
[b]Post-stratification weight based on maternal age and education (model adjusted for birthweight, gender, year of birth, plurality and gestational age.
[c]Post-stratification weight based on maternal age only (model adjusted for birthweight, gender, year of birth, plurality and gestational age.
[d]Post-stratification weight based on maternal education and race (model adjusted for birthweight, gender, year of birth, plurality and gestational age.
[e]Ever try for one year or more.

in reporting of history of infertility compared with mothers of non-malformed infants (Werler *et al*., 1989). Validity studies have been performed for time to pregnancy, with some indicating good validity (Zielhuis *et al*., 1992; Joffe and Li, 1994; Joffe *et al*., 1995) but one suggesting lower validity particularly in women with a longer time to pregnancy (Cooney *et al*., 2009). Given that only null results were found in this study, it is unlikely that recall bias had an impact on the results.

Even though this study was relatively large, given the rarity of HB, small sample size reduced the precision of our estimates and we had limited power to detect small differences, especially in the subgroup analysis. However, this was the largest case–control study of HB ever conducted and one of the first to examine parental infertility and its treatment.

Our mostly null results contrast with the only other study to examine HB and infertility or its treatment. A population-based record-linkage study by McLaughlin *et al*. (2006) found a very strong association between HB and presumed parental infertility treatment (including IVF, other fertility treatments or triplet birth as recorded on birth certificates) (OR: 9.2; 95% CI: 2.1, 31.5), but this was based on only five exposed cases. The differing results between the McLaughlin study and ours could be due to several factors, including study design, matching and residual confounding. While the McLaughlin study was limited to New York, our study was nationwide and could have included cases from New York but not controls. The McLaughlin study was a record-based study, so the results were not affected by either recall or selection bias and misclassification should be non-differential. However, controlling by birthweight was most likely not fully possible in their study since two of the five cases were part of a triplet birth and likely to be LBW or VLBW. It was not known in the McLaughlin study if any of the cases of HB had BWS and this could have played a role in their findings as well. In our study, because of matching and subgroup analysis, we were able to better assess an independent association between parental infertility and its treatment and HB. We were also able to examine additional infertility and treatment variables. Our results did include ORs in the hypothesized direction in analysis limited to those with normal birthweight, but our estimates were very imprecise and consistent with no association.

Given that LBW and VLBW are both markers for underlying pathology and an indication for neonatal treatment, establishing the causal role of factors associated with birthweight is complex. This analysis suggests that there is not a direct effect of parental infertility or its treatment on HB. However, this does not imply that there is no causal relationship between parental infertility or its treatment and HB. For example, epigenetic changes could result from ART treatment and cause both LBW/VLBW and HB. Many epigenetically mediated genes are related to growth, and disruptions can cause either undergrowth (e.g. Silver–Russell Syndrome) or overgrowth (e.g. BWS). An epigenetic cause seems plausible, given the growing body of evidence showing a possible relationship between ART and BWS as well as the finding that children with BWS who were conceived through ART are more likely to have an epigenetic defect as the cause (Olivennes *et al*., 2001; DeBaun *et al*., 2003; Gicquel *et al*., 2003; Maher *et al*., 2003; Halliday *et al*., 2004; Chang *et al*., 2005; Rossignol *et al*., 2006; Sutcliffe *et al*., 2006; Bowdin *et al*., 2007; Doornbos *et al*., 2007; Gomes *et al*., 2007). In addition, reports of HB diagnosis occurring *in utero* or shortly after birth support a causal role of periconceptional exposures (Isaacs, 2007).

Overall, no increased risk was found for those whose parents indicated infertility or infertility treatment after adjustment for birth weight through matching or in the subgroup of children with normal birthweights. It is still possible that parental infertility or its treatment contributes to the etiology of HB by lowering birthweight and contributing to risk of BWS. More work is needed to understand the causes of HB and how they relate to birthweight and parental infertility and its treatment.

Authors' roles

S.E.P. performed the study analysis and helped prepare and revise all sections of the text; J.A.R. participated in the study design, supervised the laboratory aspects of the study and reviewed and revised all sections of the text; J.H.F. assisted with ascertainment of retrospective cases and contributed substantially to text revisions; G.E.T. assisted in acquiring tumor specimens and critically reviewed and revised the text; M.H.M. assisted in case enrollment, aided in acquiring tumor specimens and critically reviewed the text; M.D.K. assisted in analysis and interpretation of the data and critically reviewed the text; L.G.S. conceived of and designed the study, directed its implementation and helped prepare and revise all sections of the text.

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Conflict of interest

None declared.

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