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ORIGINAL PAPER

Maternal and birth characteristics and childhood rhabdomyosarcoma: a report from the Children's Oncology Group

Philip J. Lupo · Heather E. Danysh · Stephen X. Skapek · Douglas S. Hawkins · Logan G. Spector · Renke Zhou · M. Fatih Okcu · Karin Papworth · Erik B. Erhardt · Seymour Grufferman

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Abstract
Purpose Previous assessments of childhood rhabdomyosarcoma have indicated maternal and birth characteristics may be associated with tumor development; however, much work remains to identify novel and confirm suspected risk factors. Our objective was to evaluate the associations between maternal and birth characteristics and childhood rhabdomyosarcoma.
Methods This case–control study included 322 cases and 322 pair-matched controls. Cases were enrolled in a trial run by the Intergroup Rhabdomyosarcoma Study Group. Population-based controls were identified using random digit dialing and were individually matched to cases on race, sex, and age. Families of the case and control subjects participated in a telephone interview, which captured information on maternal characteristics (birth control use, number of prenatal visits, anemia, and abnormal bleeding during pregnancy) and birth characteristics [birth weight, preterm birth, and type of delivery (vaginal vs. cesarean)]. Conditional logistic regression models were used to calculate an odds ratio (OR) and 95 % confidence interval (CI) for each exposure, adjusted for age, race, sex, household income, and parental education. As the two most common histologic types of rhabdomyosarcoma are embryonal ($n = 215$) and alveolar ($n = 66$), we evaluated effect heterogeneity of these exposures.
Results The only characteristic that was associated with childhood rhabdomyosarcoma, and statistically significant, was abnormal vaginal bleeding during pregnancy (OR 1.75, 95 % CI 1.12–2.74). Birth control use (OR 1.45, 95 % CI 0.96–2.18), anemia during pregnancy (OR 1.27, 95 % CI 0.81–1.99), and preterm birth (OR 2.51, 95 % CI 0.74–8.49) were positively associated with childhood rhabdomyosarcoma, but were not statistically significant. Low birth weight [adjusted odds ratios (aOR) 4.46, 95 % CI 1.41–14.1] and high birth weight (aOR 2.41, 95 % CI 1.09–5.35) were strongly associated with alveolar rhabdomyosarcoma. However, these factors did not display significant effect heterogeneity between histologic types ($p > 0.15$ for all characteristics).

P. J. Lupo (✉) · H. E. Danysh · R. Zhou · M. F. Okcu
Department of Pediatrics, Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA
e-mail: philip.lupo@bcm.edu

S. X. Skapek
Children's Medical Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

D. S. Hawkins
Seattle Children's Hospital, University of Washington, and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

L. G. Spector
Division of Pediatric Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

K. Papworth
Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

E. B. Erhardt
Department of Mathematics and Statistics, University of New Mexico, Albuquerque, NM, USA

S. Grufferman
Division of Epidemiology and Biostatistics, Department of Internal Medicine, University of New Mexico, Albuquerque, NM, USA

Conclusions Overall, we found little evidence that these maternal and birth characteristics are strongly associated with childhood rhabdomyosarcoma.

Keywords Abnormal vaginal bleeding · Epidemiology · Rhabdomyosarcoma · Soft tissue sarcoma

Background

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and young adults <20 years of age, with most cases occurring before 10 years of age [1, 2]. Rhabdomyosarcoma is a malignant tumor that originates primarily in connective tissues, such as muscle tissue, and therefore can develop anywhere in the body. There are two major rhabdomyosarcoma histologic subtypes including embryonal, with a peak incidence in children <5 years of age, and alveolar, which has an incidence evenly distributed throughout the childhood and adolescence [1]. The overall 5-year survival for childhood rhabdomyosarcoma is approximately 60–70 % [3] and has made only modest improvements since the 1980s, likely due to the lack of new effective therapies [4].

Due to the rarity of childhood rhabdomyosarcoma and possible heterogeneity between the subtypes, very little is known about the etiology of childhood rhabdomyosarcoma. Birth defects and familial genetic syndromes, including Li–Fraumeni syndrome and neurofibromatosis type 1, are associated with a small proportion of childhood rhabdomyosarcoma cases [5–8]. Because the causes of most cases remain unknown, the majority of which occur in the first decade of life, recent epidemiological studies evaluating possible risk factors for childhood rhabdomyosarcoma have centered on exposures in utero and early life as well as pregnancy and birth characteristics. Previous studies have suggested few potential risk factors for childhood rhabdomyosarcoma including advanced maternal age [9], parental drug use [10], prenatal exposure to X-rays [11], as well an inverse relationship with childhood atopic exposures [12]. The associations between early life exposures and childhood rhabdomyosarcoma indicate that characteristics associated with the perinatal and neonatal periods may be important in understanding the etiologies of childhood rhabdomyosarcoma.

Birth characteristics have previously been found to be associated with childhood malignancies, including leukemia and central nervous system tumors [7, 9, 13–19]. In addition, several studies have evaluated birth characteristics and childhood rhabdomyosarcoma and suggest that increased birth weight [20], increased maternal age [13, 20–22], increased paternal age [20, 22], being born large for gestational age [20], and late or lack of prenatal care [22] are associated with an increased risk of childhood rhabdomyosarcoma. Similar to other childhood cancers, high birth order (3+) is suggested to have a protective effect on childhood rhabdomyosarcoma [9, 20]. A previous report indicated that being born as a twin or a multiple may be associated with higher risk of childhood rhabdomyosarcoma, but this finding was not statistically significant [22]. Few studies have assessed the associations between maternal characteristics and risk of childhood rhabdomyosarcoma, primarily focusing on prior pregnancy losses and risk of childhood rhabdomyosarcoma [21, 23, 24]. Two of these studies yielded inconsistent results on the association of prior miscarriages and rhabdomyosarcoma risk [21, 24]; however, these had small sample sizes; another study reported that maternal history of at least one stillbirth was associated with a nearly fourfold increased risk of childhood rhabdomyosarcoma [23].

The largest studies evaluating the association of birth characteristics and childhood rhabdomyosarcoma to date have primarily relied on a large dataset consisting of a pool of cancer registry data linked to birth records from five states across the USA [9, 13, 18, 20, 25]. This pooled dataset has provided sufficient statistical power to assess potential risk factors for rare childhood cancer types, and often their histologic subtypes; however, linkage studies may be subject to selection bias, as children who are born and diagnosed in separate states due to residential mobility are often excluded. Furthermore, it is common for many cases identified in cancer registries to have incomplete linkage to other databases. One study reported that only 77 % of childhood cancer cases identified from the Texas Cancer Registry were able to be linked to their birth certificates, therefore excluding approximately 25 % of cases [26]. In addition, information on exposures experienced by the mother before and during pregnancy is often not available on birth records.

To our knowledge, no study has extensively evaluated the associations between maternal characteristics and childhood rhabdomyosarcoma; additionally, there is a need to validate previous findings related to birth characteristics. The objective of this study is to explore maternal and birth characteristics as potential risk factors for childhood rhabdomyosarcoma. This evaluation is novel in that it uses data from one of the largest childhood rhabdomyosarcoma case–control studies to date, which include detailed questionnaire information on pregnancy characteristics, birth outcomes, and maternal obstetric history from the families of both childhood rhabdomyosarcoma cases and pair-matched controls.

Methods

Study population

Cases and controls were enrolled in a trial previously coordinated by the Intergroup Rhabdomyosarcoma Study

Group (IRSG), which became part of the Children's Oncology Group in 2000 and coordinated treatment protocols for 80–85 % of all childhood rhabdomyosarcoma cases in the USA [27]. The details regarding the case–control study have been previously described [7, 10, 11]. In summary, the cases were 0–20 years old when they were consecutively enrolled in the IRS-III study at the time of their rhabdomyosarcoma diagnosis in April 1982–July 1988. Central expert pathology review confirmed all rhabdomyosarcoma diagnoses as well as the histologic subtype (i.e., embryonal, alveolar, or other). Of the 511 childhood rhabdomyosarcoma patients enrolled in IRS-III during the study period, 440 cases were eligible for the current study and 351 had completed interviews. Of the 71 ineligible cases, 29 had no home telephone, 9 were not USA citizens, 15 were from families that did not speak English or Spanish, 18 were treated in institutions where the study was not approved by the institutional review board. An additional 89 cases did not participate due to parental ($n = 41$) or physician ($n = 30$) refusal, and 18 families could not be located. Seventy-three percent ($n = 322$) of eligible cases were interviewed and pair-matched with controls [7, 10, 11].

Controls were identified by random digit telephone dialing during the same period [7, 10, 11]. Specifically, the area code and first five digits of the each case's phone number were used with two randomly selected terminal digits to search for a matching control. Controls were individually matched to cases on race (White, Black, or Other), sex, and age (within 1 year for cases aged 0–5 years at diagnosis, and within 3 years for cases aged 5–20 years at diagnosis). On average, 50 phone numbers were dialed and 118 calls were made to find a matching control for each case. Seventy-eight percent of homes with a matching child agreed to participate, a response rate which is comparable to that of other Children's Oncology Group studies that utilized random digit dialing methods for control group selection in 1980s [28]. Controls could not be identified for eight percent of cases, and therefore, these cases were excluded from this analysis [7, 10, 11].

Data collection and variables

Data were collected from case and control families by telephone interview using a structured questionnaire. The child's mother and father were asked to participate in the interview, which for case and control families lasted on average 70 and 68 min, respectively. Interviews were conducted in English and Spanish (six case families and two control families were Spanish-speaking). The interview included questions about childhood environmental exposures, parental occupational exposures, family demographic characteristics, parental lifestyle and behavioral characteristics, and medical history. On average, parents were asked to recall exposures, which occurred 8–9 years prior to the interview.

For the current study, we focused on the assessment of maternal and birth characteristics as potential risk factors for childhood rhabdomyosarcoma. We evaluated the following questionnaire items directed to the child's mother, as they relate to maternal characteristics during pregnancy: "Did you take fertility medicine to help you become pregnant with [index child]?"; "Were you using birth control when you became pregnant with [index child]?"; "Did you get prenatal care when you were pregnant with him/her?"; "How many prenatal visits did you have?"; "Did you have amniocentesis done during the pregnancy?"; "Did you have any spotting, cramping, or abnormal vaginal bleeding during the pregnancy?"; and "While you were pregnant with [index child] did you have any of the following: high blood pressure, nausea or vomiting, anemia, cold or flu." In addition, the mother was asked about her obstetric history: "Did you ever use any kind of birth control before [the index child]'s birth?"; "How many times have you been pregnant? Include all live births, stillbirths, miscarriages, and abortions." We evaluated the following questionnaire items to assess birth characteristics: "How much did [index child] weigh at birth?"; "Was the baby delivered vaginally or by cesarean section?"; "Was [index child] born prematurely? Was s(he) overdue?." In addition, we evaluated birth order (1, 2, $\geq$3) and parental age at the time of birth.

Covariates for this analysis were selected a priori and included total annual household income (categorized as $<$\$20,000, \$20,000–\$39,999, $\geq$\$40,000), and maternal and paternal educational level (total number of completed years). All statistical models were adjusted for these covariates as well as the matching factors including the child's sex (male or female), age at diagnosis (in years), and race (categorized as White, Black, or other). Birth weight and pregnancy length were highly correlated, and, therefore, models evaluating these variables were mutually adjusted.

Statistical analysis

Descriptive statistics were used to characterize the demographic variables among the case and control groups. Frequency distributions were tabulated for categorical variables, and means and standard deviations were calculated for continuous variables. Conditional logistic regression was used to evaluate maternal and birth characteristics and their associations with childhood rhabdomyosarcoma by generating adjusted odds ratios (aOR), 95 % confidence intervals (CI), and p values. An association was considered statistically significant if $p < 0.05$.

Because the rhabdomyosarcoma histologic subtypes are suspected to have heterogeneous etiologies and possibly different risk factors, we used polytomous logistic regression to evaluate effect heterogeneity (as described by Glynn and Rosner [29]) between birth and maternal characteristics and the rhabdomyosarcoma histologic subtypes, embryonal and alveolar rhabdomyosarcoma. The polytomous logistic regression models included a term to account for the intra-class correlation introduced by the pair-matched cases and controls. All analyses were conducted using STATA 12.1 (StataCorp LP, College Station, TX).

Results

The demographic characteristics among the case and control groups are presented in Table 1. The matching factors of sex, age at diagnosis/enrollment, and race were balanced between the 322 childhood rhabdomyosarcoma cases and 322 controls. One-fourth of the sample (28.6 %) had an annual household income of less than $20,000, with a higher proportion of the case group falling in this category compared to the control group (32.8 vs. 24.3 %, respectively; $p = 0.014$). Maternal and paternal education levels were similar between the case and control groups, where approximately half of the sample had a maternal and paternal education level higher than high school (46.5 and 50.2 %, respectively). The majority of cases in this sample were diagnosed with embryonal rhabdomyosarcoma (66.7 %), whereas 20.5 % were diagnosed with alveolar rhabdomyosarcoma and 12.8 % are not otherwise specified (NOS).

Maternal characteristics during pregnancy and their associations with childhood rhabdomyosarcoma are presented in Table 2. Among the maternal characteristics evaluated, the occurrence of spotting, cramping, or abnormal vaginal bleeding during pregnancy was associated with increased risk for childhood rhabdomyosarcoma (aOR 1.75, 95 % CI 1.12–2.74). Overall, the maternal characteristics evaluated in this assessment were not significantly associated with childhood rhabdomyosarcoma risk, including 12+ prenatal visits (aOR 1.16, 95 % CI 0.77–1.76), anemia during pregnancy (aOR 1.27, 95 % CI 0.81–1.99), high blood pressure during pregnancy (aOR 0.66, 95 % CI 0.36–1.22), and having an amniocentesis during pregnancy (aOR 0.90, 95 % CI 0.33–2.44). Interestingly, there was a positive association with birth control use at the time of pregnancy (aOR 1.53, 95 % CI 0.61–3.87) and childhood rhabdomyosarcoma risk, as well as with ever birth control use and childhood rhabdomyosarcoma risk (aOR 1.45, 95 % CI 0.96–2.18); however, these associations are not statistically significant.

Table 1 Demographic characteristics of childhood rhabdomyosarcoma cases and controls

Characteristic	Controls $n = 322$	Cases $n = 322$
Sex of child, *n* (%)		
Male	215 (66.8)	215 (66.8)
Female	107 (33.2)	107 (33.2)
Race of child, *n* (%)		
White	291 (90.4)	287 (89.1)
Black	21 (6.5)	20 (6.2)
Other	10 (3.1)	15 (4.7)
Ethnicity of child, *n* (%)		
Non-Hispanic	307 (95.9)	303 (94.7)
Hispanic	13 (4.1)	17 (5.3)
Age at diagnosis/enrollment (years), mean (SD)	7.5 (5.4)	7.6 (5.3)
Maternal education, *n* (%)		
<High school	39 (12.2)	45 (14.1)
High school	126 (39.4)	132 (41.4)
>High school	155 (48.4)	142 (44.5)
Paternal education, *n* (%)		
<High school	37 (11.8)	54 (17.1)
High school	111 (35.5)	112 (35.3)
>High school	165 (52.7)	151 (47.6)
Total annual household income, *n* (%)		
<$20,000	77 (24.3)	104 (32.8)
$20,000–$39,999	155 (48.9)	131 (41.3)
≥$40,000	85 (26.8)	82 (25.9)
Histologic subtypes, *n* (%)		
Embryonal		215 (66.7)
Alveolar		66 (20.5)
NOS[a]		41 (12.8)

[a] Not otherwise specified

Birth characteristics and their associations with childhood rhabdomyosarcoma are presented in Table 3. Overall, there were no statistically significant associations detected; however, the results show positive associations with childhood rhabdomyosarcoma risk for low birth weight (aOR 1.69, 95 % CI 0.71–4.01), high birth weight (aOR 1.35, 95 % CI 0.77–2.37), preterm birth (aOR 2.51, 95 % CI 0.74–8.49), and being delivered by cesarean (aOR 1.44, 95 % CI 0.90–2.31). There were no apparent associations with childhood rhabdomyosarcoma risk and birth order, maternal age, or paternal age.

The results of our evaluation of the effect for heterogeneity between selected maternal and birth characteristics with embryonal and alveolar rhabdomyosarcoma, the major histologic subtypes, are presented in Table 4. Tumors classified as NOS were not included in this analysis due to possible within-group heterogeneity. When evaluating embryonal rhabdomyosarcoma alone and

Table 2 Associations of maternal characteristics with childhood rhabdomyosarcoma

Characteristic	Controls	Cases	OR[a]	95 % CI	*p* value
Using birth control when became pregnant, *n* (%)	9 (3.1)	13 (4.4)	1.53	0.61–3.87	0.365
Used fertility medications to help become pregnant, *n* (%)	7 (7.2)	5 (1.6)	0.71	0.22–2.27	0.556
Number of prenatal visits, *n* (%)					
<12	79 (25.8)	66 (21.4)	1.00	Reference	
≥12	227 (74.2)	242 (78.6)	1.16	0.77–1.76	0.476
Amniocentesis	12 (3.8)	11 (3.5)	0.90	0.33–2.44	0.835
Spotting/cramping/abnormal vaginal bleeding, *n* (%)	37 (11.8)	67 (21.1)	1.75	1.12–2.74	0.014
High blood pressure during pregnancy, *n* (%)	37 (11.8)	28 (8.8)	0.66	0.36–1.22	0.190
Nausea or vomiting during pregnancy, *n* (%)	160 (51.0)	151 (47.5)	0.84	0.59–1.18	0.308
Anemia during pregnancy, *n* (%)	46 (14.7)	53 (16.8)	1.27	0.81–1.99	0.306
Cold or flu during pregnancy, *n* (%)	101 (35.1)	104 (34.7)	1.02	0.70–1.48	0.927
Ever used any birth control, *n* (%)	226 (70.9)	237 (74.3)	1.45	0.96–2.18	0.078
Stillbirths/miscarriages/abortions, *n* (%)					
0	196 (68.3)	195 (73.0)	1.00	Reference	
1	70 (24.4)	49 (18.4)	0.84	0.51–1.39	0.504
≥2	21 (7.3)	23 (8.6)	1.05	0.52–2.14	0.893

OR odds ratio, *CI* confidence interval

[a] Adjusted for sex, age, race, household income, and maternal and paternal education

Table 3 Associations of birth characteristics with childhood rhabdomyosarcoma

Characteristic	Controls	Cases	OR[a]	95 % CI	*p* value
Birth order, *n* (%)					
1st	138 (43.3)	138 (43.4)	1.00	Reference	
2nd	101 (31.7)	102 (32.1)	0.94	0.64–1.37	0.731
≥3rd	80 (25.1)	78 (24.5)	0.94	0.61–1.44	0.779
Birth weight[b], *n* (%)					
Normal (2,500 g to < 4,000 g)	267 (86.1)	247 (77.7)	1.00	Reference	
LBW (< 2,500 g)	10 (3.2)	29 (9.1)	1.69	0.71–4.01	0.236
HBW (≥ 4,000 g)	33 (10.7)	42 (13.2)	1.35	0.77–2.37	0.287
Length of pregnancy[c], *n* (%)					
Normal	258 (81.4)	258 (81.1)	1.00	Reference	
Premature	9 (2.8)	26 (8.2)	2.51	0.74–8.49	0.137
Overdue	50 (15.8)	34 (10.7)	0.70	0.41–1.18	0.177
Type of delivery, *n* (%)					
Vaginal	273 (85.8)	260 (81.3)	1.00	Reference	
Cesarean	45 (14.2)	60 (18.8)	1.44	0.90–2.31	0.132
Paternal age (years) at child's birth, mean (SD)	29.0 (6.4)	29.0 (5.9)	0.99	0.96–1.02	0.395
Maternal age (years) at child's birth, mean (SD)	26.3 (5.2)	26.2 (5.2)	0.99	0.96–1.02	0.435

OR odds ratio, *CI* confidence interval, *LBW* low birth weight, *HBW* high birth weight

[a] Adjusted for sex, age, race, household income, and maternal and paternal education

[b] Adjusted for length of pregnancy

[c] Adjusted for birth weight

associations with selected maternal and birth characteristics, there were no statistically significant associations with the exception of abnormal vaginal bleeding during pregnancy (aOR 1.80, 95 % CI 1.10–2.92) and being born via cesarean (aOR 1.60, 95 % CI 1.00–2.56). There were strong positive associations with alveolar rhabdomyosarcoma and low birth weight (aOR 4.46, 95 % CI 1.41–2.41), high birth weight (aOR 2.41, 95 % CI 1.09–5.35), and

Table 4 Evaluation of effect heterogeneity among selected maternal and birth characteristics and childhood rhabdomyosarcoma histologic subtypes

Characteristic	Embryonal RMS $n = 215$		Alveolar RMS $n = 66$		p for heterogeneity
	OR[a]	95 % CI	OR[a]	95 % CI	
Ever used any birth control	1.19	0.80–1.79	1.41	0.75–2.62	0.624
Using birth control when became pregnant	1.51	0.59–3.90	1.13	0.23–5.40	0.706
Spotting/cramping/abnormal vaginal bleeding	1.80	1.10–2.92	2.49	1.25–5.00	0.357
Anemia during pregnancy	1.17	0.72–1.88	1.26	0.61–2.62	0.842
Type of delivery					
Vaginal	1.00	Reference	1.00	Reference	
Cesarean	1.60	1.00–2.56	1.18	0.53–2.63	0.449
Birth weight[b]					
Normal (2,500 to <4,000 g)	1.00	Reference	1.00	Reference	
LBW (<2,500 g)	1.64	0.62–4.32	4.46	1.41–14.1	
HBW (≥4,000 g)	1.61	0.93–2.79	2.41	1.09–5.35	0.169
Length of pregnancy[c]					
Normal	1.00	Reference	1.00	Reference	
Premature	2.47	0.93–6.59	0.95	0.23–4.00	
Overdue	0.58	0.33–1.02	0.95	0.44–2.08	0.155

RMS rhabdomyosarcoma, *OR* odds ratio, *CI* confidence interval, *LBW* low birth weight, *HBW* high birth weight

[a] Adjusted for sex, age, and race

[b] Adjusted for length of pregnancy

[c] Adjusted for birth weight

abnormal vaginal bleeding during pregnancy (aOR 2.49, 95 % CI 1.25–5.00). Overall, there are no statistically significant differences in effects between embryonal and alveolar rhabdomyosarcoma and their associations with selected maternal and birth characteristics. Although these associations are not statistically significant, there appears to be potential differences in magnitude of effect between the risk of embryonal and alveolar rhabdomyosarcoma and several characteristics, including preterm birth (embryonal: aOR 2.47, 95 % CI 0.93–6.59; alveolar: aOR 0.95, 95 % CI 0.23–4.00), being born past term (embryonal: aOR 0.58, 95 % CI 0.33–1.02; alveolar: aOR 0.95, 95 % CI 0.44–2.08), low birth weight (embryonal: aOR 1.64, 95 % CI 0.62–4.32; alveolar: aOR 4.46, 95 % CI 1.41–14.1), and high birth weight (embryonal: aOR 1.61, 95 % CI 0.93–2.79; alveolar: aOR 2.41, 95 % CI 1.09–5.35). The p for heterogeneity was greater than 0.150 for all exposures.

Discussion

The objective of this assessment was to evaluate maternal and birth characteristics as potential risk factors for childhood rhabdomyosarcoma. Overall, in our analyses, these exposures do not seem to be strongly associated with childhood rhabdomyosarcoma. Our analysis showed that cramping, spotting, or abnormal vaginal bleeding during pregnancy was positively associated with an increased risk of childhood rhabdomyosarcoma. A previous assessment by Grufferman et al. evaluated prenatal X-ray exposure and childhood rhabdomyosarcoma using the same data (study population) as that used in the current assessment. In the previous report, it was noted that there were more case mothers who reported abnormal vaginal bleeding compared to control mothers, and the authors suggested that abnormal vaginal bleeding during pregnancy may lead to increased exposure to X-ray examinations and therefore increased fetal X-ray exposure [11]. This may explain the association between abnormal vaginal bleeding and childhood rhabdomyosarcoma risk in the current assessment, as it was concluded by Grufferman et al. [11] that prenatal X-ray exposure contributes to an increased risk of childhood rhabdomyosarcoma. In addition, abnormal vaginal bleeding may be a marker for gynecological inflammation [30], inducing oxidative stress and DNA damage and, therefore, predisposing the fetus to developing a malignancy in childhood. Conversely, another report found that abnormal vaginal bleeding during pregnancy had a protective effect on leukemia risk in children with Down

syndrome, potentially due to early immune response activation [31]. The differential effects of abnormal vaginal bleeding on childhood cancer risk suggest that distinguished etiological mechanisms are responsible for the development of leukemia and rhabdomyosarcoma. Further studies evaluating samples independent from that of our assessment are needed to confirm the findings reported here. If these associations are consistent with our findings, more work is needed to understand the potential mechanism.

While maternal characteristics have not been extensively studied, there are a few previous studies reporting on maternal history of stillbirths or miscarriages and risk of childhood rhabdomyosarcoma. Grufferman et al. [21] reported a statistically non-significant positive association of history of miscarriage and risk of childhood rhabdomyosarcoma (OR 1.9, 95 % CI 0.6–6.2); however, there were only 33 cases included in this assessment. An assessment by Ghali et al. [23] included 103 rhabdomyosarcoma cases and reported a strong positive association between maternal history of at least one stillbirth and risk of childhood rhabdomyosarcoma (OR 3.7, 95 % CI 1.5–8.9). In contrast, Hartley et al. [24] found that mothers of children with rhabdomyosarcoma ($n = 27$) had fewer prior miscarriages compared to mothers of control children ($p = 0.008$). Our results show no association between maternal history of total pregnancy losses and risk of childhood rhabdomyosarcoma. Additionally, there is previous evidence suggesting that assisted fertilization may increase the risk rhabdomyosarcoma in children [32]; however, no association was detected between maternal use of fertility medications and childhood rhabdomyosarcoma risk in our sample. This may be due do limitations in sample size or differences in current fertility treatments and those used in the 1980s and before, the birth period of all subjects included our sample.

Although there is a deficit of studies evaluating maternal characteristics and risk of childhood rhabdomyosarcoma, several studies have assessed the effect of various birth characteristics. A series of studies evaluating birth characteristics and childhood cancer using pooled cancer registry data from five states in the USA [9, 13, 18, 20], included two studies which reported a possible protective effect of low birth weight on childhood rhabdomyosarcoma risk (OR 0.66, 95 % CI 0.38–1.14); however, the associations in both studies were not statistically significant [18, 20]. In addition, a study using data from the California Cancer Registry found no relationship between birth weight and childhood rhabdomyosarcoma (OR 1.00, 95 % CI 0.71–1.40) [22], and, similarly, a case–control study conducted in England found no difference in median birth weight among cases diagnosed with a soft tissue sarcoma and unaffected controls [24]. Conversely, our results suggest that low birth weight may possibly increase the risk of childhood rhabdomyosarcoma (OR 1.69, 95 % CI 0.71–4.01); however, these findings are not statistically significant. This association was particularly strong in the alveolar histologic subtype (aOR 4.46, 95 % CI 1.41–14.1).

Previous work of other birth characteristics have suggested an inverse relationship between birth order and childhood rhabdomyosarcoma risk [9, 20] and a positive association between older maternal age at birth [13, 20–22] and older paternal age at birth [20, 22] and childhood rhabdomyosarcoma risk. However, Hartley et al. [24] found no difference in median parental age at birth among soft tissue sarcoma cases and unaffected controls, and Johnson et al. [13] found no association between paternal age at birth and risk of childhood rhabdomyosarcoma. Associations for birth order and parental age were not detected for childhood rhabdomyosarcoma in our sample. The variation in the results reported in our study compared to previous studies may be due to differences in study design, sample size, confounders adjusted for in the regression models, and the years and ages in which the cases were diagnosed.

Although some investigators have looked at birth characteristics and maternal exposures during pregnancy in relation to childhood rhabdomyosarcoma, the largest of these studies have relied on the same set of cancer registry data. While registry data can be informative, use of these data requires linkage to birth records, which do not adequately capture maternal exposures during pregnancy. Our assessment relied on a case–control study design, which included extensive questionnaire data about the child as well as detailed information about previous parental exposures including the mother's exposures during pregnancy and her obstetric history. Furthermore, selection bias may be introduced into linkage studies as only cases with a matching birth certificate are included; these studies often exclude those who were born outside the state where they were diagnosed. This case–control study drew rhabdomyosarcoma cases from the IRSG, which coordinated treatment for 80–85 % of the all childhood rhabdomyosarcoma cases diagnosed in the USA in April 1982 through July 1988. Inclusion in this study did not rely on linkage to birth records reducing the likelihood of this form of selection bias.

There are several limitations to consider when interpreting the results presented in this report. First, as with any study that relies on questionnaire data, there is the potential for recall bias where mothers of cancer patients may be more likely to accurately report adverse pregnancy and birth outcomes in light of their child's cancer diagnosis. Recall bias may also explain the significant finding reported in the current study that abnormal vaginal

bleeding during pregnancy is positively associated with childhood rhabdomyosarcoma. It is impossible to know whether recall bias influenced the results reported here as information from birth certificates and medical records were not available; however, a study evaluating the associations of maternal and birth characteristics with childhood leukemia reported good agreement between maternal interview and birth certificates with respect to maternal age, birth weight, and birth order [14]. Furthermore, it is possible that maternal recall could be differential across the varying ages of children at the time of interview, where mothers may have more accurate responses when reporting on a more recent pregnancy compared to those reporting on a more distant pregnancy. In this assessment, cases and controls were pair-matched by age at diagnosis/interview; therefore, if recall bias were present in those reporting on older pregnancies, the effect sizes would be biased toward the null.

Although the case–control sample used in this assessment is one of the largest available for childhood rhabdomyosarcoma that includes extensive questionnaire information, it is possible that there was not sufficient power to detect the associations under evaluation. This may be particularly true for the subanalyses of the associations with the individual rhabdomyosarcoma histologic subtypes (embryonal: $n = 215$; alveolar: $n = 66$). Childhood rhabdomyosarcoma is a rare disease, which creates challenges in obtaining sufficient sample sizes to detect more subtle associations, particularly with exposures during the perinatal period, which requires data beyond that which is available from birth records.

In conclusion, our study evaluated maternal and birth characteristics as potential risk factors for childhood rhabdomyosarcoma. This assessment suggests that cramping, spotting, or abnormal bleeding during pregnancy may increase the risk of childhood rhabdomyosarcoma; however, this finding must be validated in an independent population. With this exception, there were no other maternal or birth characteristics in this assessment that were significantly associated with childhood rhabdomyosarcoma. Further studies are required to confirm these results and to further investigate potential risk factors for childhood rhabdomyosarcoma. Identifying risk factors for childhood rhabdomyosarcoma and furthering our understanding of the etiologies behind childhood rhabdomyosarcoma may inform future prevention strategies.

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Conflict of interest The authors declare that they have no conflict of interest.

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