Published in final edited form as:

Cancer Causes Control. 2011 August ; 22(8): 1197–1204. doi:10.1007/s10552-011-9798-4.

Maternal exposure to household chemicals and risk of infant leukemia: A report from the Children's Oncology Group¹

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Abstract

Objective—Utilizing data from the largest study to date, we examined associations between maternal preconception/prenatal exposure to household chemicals and infant acute leukemia.

Methods—We present data from a Children's Oncology Group case-control study of 443 infants (<1 year of age) diagnosed with acute leukemia (including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)) between 1996-2006 and 324 population controls. Mothers recalled household chemical use one month before and throughout pregnancy. We used unconditional logistic regression adjusted for birth year, maternal age, and race/ethnicity to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—We did not find evidence for an association between infant leukemia and eight of nine chemical categories. However, exposure to petroleum products during pregnancy was associated with AML (OR=2.54; 95% CI:1.40-4.62) and leukemia without mixed lineage leukemia (*MLL*) gene rearrangements (“*MLL*-”) (OR=2.69; 95% CI: 1.47-4.93). No associations were observed for exposure in the month before pregnancy.

Conclusions—Gestational exposure to petroleum products was associated with infant leukemia, particularly AML and *MLL*- cases. Benzene is implicated as a potential carcinogen within this exposure category, but a clear biological mechanism has yet to be elucidated.

Keywords

epidemiology; infants; leukemia; chemical; prenatal

¹Funding: Research supported by National Institutes of Health Grants R01 CA79940, T32 CA99936, U10 CA13539, and U10 CA98543, U10 CA98413, P30 CA77598 (University of Minnesota Masonic Cancer Center shared resource: Health Survey Research Center), and the Children's Cancer Research Fund, Minneapolis, MN.

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Introduction

Leukemia in infants (<1 year of age) is rare, with an annual incidence of about 40 cases per million children in the United States. It is the second most common cancer after neuroblastoma in this young age group [1]. Unlike infant neuroblastoma and leukemia in older children (ages 1 to 4 years), which have 5-year survival rates of 93% and 87%, respectively, the 5-year survival rate for infants with leukemia is only 50% [2].

A notable characteristic of infant leukemia is the presence of mixed lineage leukemia (*MLL*) gene rearrangements (“*MLL+*”). These genetic translocations are present in only 5% of all childhood leukemias diagnosed after 1 year of age and in 10% of adult acute myeloid leukemias (AMLs), but are found in up to 80% of infant ALLs and 60% of infant AMLs [3,4,5]. *MLL* status is thought to represent distinct etiologies, in part because *MLL+* cases of infant ALL generally have much poorer survival rates than *MLL-* cases [6,7]. Previous findings from studies of identical twins [8] and stored neonatal blood spots [9,10] indicate that *MLL* rearrangements are initiated *in utero*. This evidence has led to investigations into prenatal exposures suspected to be involved in leukemogenesis, including certain household chemicals.

Both prenatal and postnatal residential exposure to paints, petroleum products, solvents, pesticides, and metals have been associated with childhood leukemia in a number of prior epidemiologic studies [11,12]; however, the epidemiologic evidence has been inconsistent and fairly inconclusive (reviewed in [5]). Of note, there have been very few studies specifically examining infant leukemia. A study of 202 infant leukemia cases observed a positive association with household pesticides [13], while a study of 136 cases noted a similar association with Baygon/mosquitocides [14]. To expand upon the existing literature, we present data from the largest case-control study of infant leukemia to date.

Materials and Methods

Study population

Details regarding subject recruitment and data collection for this study have been described elsewhere [15,16,17]. Briefly, infants diagnosed with acute leukemia at <1 year of age were identified at Children's Oncology Group (COG) institutions between January 1, 1996 and October 13, 2002 (phase I) and between January 1, 2003 and December 31, 2006 (phase II). Cases were eligible for this study if they did not have Down syndrome, if their biological mother was available for a telephone interview in English (phase I and II) or Spanish (phase II only), and if they were diagnosed or treated at a participating COG institution in the U.S. or Canada. Mothers of deceased cases were eligible for participation.

Sources of controls differed for the two phases described above. Phase I controls were selected from the U.S. and Canada using a standardized random digit dialing (RDD) procedure [18,19] and were frequency matched to cases on year of birth. During phase II, controls were randomly selected from 15 U.S. state birth registries and were frequency matched to cases on year of birth and region of residence (Canadian cases were matched as

close as possible to northern U.S. controls) based on the geographical and annual birth distribution of phase I cases [15]. All controls were required to have a biological mother who was available for a telephone interview in English (phase I and II) or Spanish (phase II only); children with Down syndrome were ineligible. As phase I and II controls were similar to each other based on maternal and infant characteristics[15] they were combined into one control group for this analysis.

Data collection

Exposure data were collected for all participants through structured, computer-assisted telephone interviews of mothers. Interviews were successfully completed for 443 (64%) eligible cases (264 ALL, 172 AML, and 7 biphenotypic and acute undifferentiated leukemia) and 324 (47%) eligible controls (254 of 430 in Phase I and 70 of 270 in Phase II). Rates and reasons for non-participation for each study phase have been reported previously [15,16,20]. Interview questions included items on demographics, reproductive history, family history of disease, and exposures during pregnancy with the index (case or control) child. Additionally, pathology and cytogenetic reports from diagnosis were obtained for cases, and *MLL* gene rearrangement status (*MLL*+, *MLL*-, or indeterminate) was determined through central review by a panel of three independent reviewers, as described previously [20].

The exposure variables of interest in the current analysis comprised nine separate categories of household chemicals: insecticides, moth control, rodenticides, flea or tick control, herbicides, insect repellants, professional pest exterminations, paints/stains/lacquers, and petroleum products. To facilitate accurate recall, interview guides describing these exposures, including specific examples, were mailed to all participants prior to telephone interviews. For example, the petroleum products category included the following: gasoline (not including pumping gas, unless gasoline got on skin), kerosene, lubricating oils, and spot removers (See Appendix for complete description). For each of the nine categories, mothers were asked whether or not they came in contact with the product(s) one month prior to and/or during their pregnancy. Respondents indicating any exposure were also asked how many times they came in contact with the product(s) both in the month before the index pregnancy and during the pregnancy, respectively.

Study procedures were approved by institutional review boards at the University of Minnesota and participating COG institutions. The study was also reviewed and approved by health departments for states providing birth certificates, as applicable. Informed consent was provided by all mothers prior to participation.

Statistical analysis

Differences between cases and controls in baseline characteristics and potential covariates were assessed using the chi-square test for categorical variables and the t-test for two means for continuous variables. Controls were compared to infant leukemia subgroups defined by leukemia type (ALL and AML) and *MLL* status (*MLL*+ and *MLL*-).

Unconditional logistic regression was used to evaluate associations between preconception/prenatal exposure to household chemicals and development of infant leukemia. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for each of the nine categories for

any preconception/prenatal exposure and for exposure by time period (month before pregnancy, during pregnancy). There was no evidence of a linear trend, or dose response, for any of the categories when exposure frequency (i.e. number of times in contact with product) was modeled as tertiles (none; >0, median; >median). Therefore, we converted all frequency responses into dichotomous variables ("any exposure" vs. "no exposure"). We repeated all analyses upon stratification by leukemia type and *MLL* status. All models were adjusted for maternal age (continuous) and race/ethnicity (white or non-white), and child's year of birth (ordinal), a matching factor. Child's gender, household income, maternal education, maternal smoking, and region of residence were also considered potential confounders but were not included in the final multivariable models because their inclusion did not change natural log odds ratio estimates by >10%. All analyses were conducted using SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Descriptive characteristics for controls and ALL and AML subgroups are provided in Table 1. Cases and controls did not differ significantly with respect to child's gender, household income, or mother's education level. Compared to controls, cases were more likely to be non-white (24% of ALL and AML cases vs. 16% of controls), and mothers of ALL cases tended to be younger at the time of the child's birth compared to mothers of controls (mean_{cases} = 28.7 years vs. mean_{controls} = 29.8 years).

Adjusted ORs and 95% CIs for maternal household chemical exposures are presented in Table 2. No statistically significant associations were found for eight of nine categories of chemical exposures. Any exposure to petroleum products during the preconception or prenatal period was significantly associated with infant leukemia among AML (OR=2.33; 95% CI: 1.30-4.18) and *MLL*- cases (OR=2.48; 95% CI: 1.37-4.48) examined separately, after adjustment for birth year, maternal age, and maternal race/ethnicity. Similarly, exposure to petroleum products during pregnancy was associated with AML (OR=2.54; 95% CI: 1.40-4.62) and *MLL*- leukemia (OR=2.69; 95% CI: 1.47-4.93). There were no significant associations observed for exposure in the month before pregnancy.

Upon further stratification, significant associations were detected for any petroleum product exposure among ALL *MLL*- (OR=2.21; 95% CI: 1.04-4.67) and AML *MLL*- cases (OR=2.48; 95% CI: 1.16-5.31), but not among ALL *MLL*+ (OR=1.30; 95% CI: 0.68-2.49) nor AML *MLL*+ cases (OR=1.32; 95% CI: 0.52-3.33). Likewise, exposure during pregnancy was associated with leukemia among ALL *MLL*- (OR=2.39; 95% CI: 1.12-5.11) and AML *MLL*- cases (OR=2.67; 95% CI: 1.24-5.78) but not among ALL *MLL*+ (OR=1.23; 95% CI: 0.62-2.43) nor AML *MLL*+ cases (OR=1.39; 95% CI: 0.55-3.54). As before, no significant associations were observed for exposure in the month before pregnancy. However, these results should be interpreted with caution due to small cell counts (as low as 5).

A sensitivity analysis, as outlined by Greenland and Lash [22], was performed to describe the potential role of exposure misclassification in our study (data not shown). Using a range of sensitivities (0.60 to 0.99) and specificities (0.86 to 0.97), the corrected ORs produced were generally *greater* in magnitude than our unadjusted estimates. A separate sensitivity

analysis was conducted to uncover potential bias due to the differing methods of control recruitment and potential secular trends in chemical exposures across the two study phases; ORs retained the same direction and general magnitude after excluding phase II participants. Furthermore, standard regression adjustment for phase did not change ORs by more than 10%.

Discussion

We utilized data from the largest case-control study of infant leukemia conducted to date to examine preconception/prenatal household chemical exposures as potential risk factors for leukemia. Any exposure to petroleum products, as well as exposure during the index pregnancy, were each associated with infant leukemia among AML and *MLL*- cases analyzed separately and among ALL *MLL*- and AML *MLL*- subgroups after further stratification. No other statistically significant associations with other chemicals were apparent in any time period. However, distinguishing exposure during the month before pregnancy compared to early pregnancy may be difficult since many women may not be aware of early stage pregnancy, thus some caution is warranted in interpretation of findings between these periods.

The petroleum products considered in this study contain or used to contain some amount of benzene. Benzene exposure has been consistently associated with positive dose response relationships for adult AML across cohort and case-control study designs [11,23,24]. An exact mechanism of benzene leukemogenesis has yet to be established, perhaps because benzene and its metabolites are able to generate numerous types of chromosomal aberrations [10]. Nonetheless, there is strong evidence from studies of chromosomal changes found in highly exposed individuals with AML, which supports at least three potential pathways involving chromosomes 5 and/or 7. In these pathways, 5q-/-5 and 7q-/-7 represent possible first genetic hits in the leukemogenic process. In contrast, there is currently little evidence supporting a mechanism by which benzene induces *MLL* gene rearrangements. It is therefore notable that we observed no evidence of an association between petroleum products and *MLL*+ leukemia in this study. In fact, it has been suggested that leukemias with *MLL* translocations constitute a distinct disease type with a characteristic gene expression profile and unique etiology [21].

In contrast to adult studies, a clear association between environmental benzene exposure and childhood leukemia has not been observed (reviewed in [25]). Most studies have failed to stratify by *MLL* status or any other cytogenetic abnormalities, which may help explain the lack of consistent findings. However, a recent study of household exposure to petroleum solvents (including paint thinner, spot remover, paint remover, glue, solvent, gasoline, kerosene, or lubricating oil) and risk of childhood ALL or AML did stratify by cytogenetic subtype [26]. They found that overall exposure (before/during pregnancy and/or after birth) was significantly associated with AML but not ALL. Although statistical significance was lost after stratifying by cytogenetic subtype, the association was strongest among the “good prognosis” cytogenetic subtypes (OR=3.49; 95% CI: 0.92-13.2), which supports our current findings for *MLL*- leukemia.

No known studies have reported on maternal exposure to petroleum products and/or benzene in relation to infant leukemia, although benzene has been shown to cross the placental barrier [27]. Our results suggest that infant *MLL*- leukemia might be similar to AML in older individuals in that benzene exerts its leukemogenic effects through pathways independent of the *MLL* gene. This suggestion is further supported by results of gene expression profiling studies, in which pediatric and adult AML cases with the same chromosomal aberrations, including *MLL* translocations, had similar gene expression signatures [28]. Individuals exposed *in utero* may be more vulnerable to adverse effects compared to adults, however [29,30]. Further research will be required to confirm that these findings are not due to chance.

The null results for the other eight categories of household chemicals were surprising and do not support positive associations observed in previous epidemiological studies [11,13,14,31]. In 2007, Infante-Rivard and Weichenthal reviewed the literature and concluded that studies generally support an association between pesticide exposure and childhood leukemia, especially for childhood exposure to household insecticides and parental exposure to pesticides before and during pregnancy [31]. Two studies have considered infant leukemia apart from other age groups and have noted significant associations with household pesticides [13] and Baygon/mosquitocides [14].

Making comparisons between studies is difficult due to the variation in etiologic time periods, subcategories of exposure, and case subgroups examined. Studies that failed to find significant increases in risk, including the present one, may have suffered from methodological limitations, such as small numbers of exposed individuals (especially among subgroups) or incomplete and/or biased exposure assessment. In addition, chemical exposure categories can have overlapping carcinogenic exposures (e.g., pesticides often contain solvents) and do not always provide details on specific chemicals, which could lead to exposure misclassification. In an attempt to address this concern, we conducted a sensitivity analysis examining the effect of potential misclassification, as described above. We found that the corrected ORs were generally *larger* in magnitude than the observed ORs, indicating the true associations might actually be stronger if exposures could be measured more accurately.

In general, future studies may benefit from improving their methods of exposure assessment. Methods used in studies of farmers or other occupational groups, in which very detailed information on chemical exposures can often be obtained, could help inform researchers aiming to improve exposure measurement in other populations. For example, investigators from the Northern California Childhood Leukaemia Study conducted a comprehensive assessment of residential pesticide exposure including quality control of self-reports, home pesticide inventory and linkage to the Environmental Protection Agency to obtain data on active ingredients, collection and laboratory analyses of home dust samples, use of geographic information from environmental databases to assess exposure to agricultural pesticides, and large-scale genotyping to evaluate the role of genetics in pesticide metabolism and transport [32]. The use of biomarkers of exposure, as they become available, is another important avenue for future consideration.

Recall bias is also a concern, especially in light of the potential health effects of pesticides (including childhood cancers) discussed in the mainstream media [33]. Further, mothers of cases might be expected to report these types of exposures more often than control mothers based solely on their knowledge of these associations [34]. In our study, the potential for recall bias might be lessened by the use of mailed interview guides and by the relatively short interval between birth and interview (on average, 2.5 years for cases and 3.5 years for controls), particularly when compared to studies that include children diagnosed at older ages. Additionally, mothers were recalling events from a relatively specific, brief, and potentially very memorable time period (i.e., pregnancy). Upon further investigation, no apparent trends were observed in the prevalence of maternally reported chemical exposures from phase I to phase II, indicating any potential time trends in public awareness were not a major factor in this study.

Because of low response rates among both cases (64%) and controls (47%), selection bias is another concern. For cases, selection bias was minimized by the use of COG institutions for case ascertainment, since they treat the majority of leukemia patients diagnosed in the U.S. under the age of 5 years [35,36]. In a prior analysis, we evaluated potential selection bias among our control groups. In that analysis, both RDD and birth certificate controls were compared to U.S. National Center for Health Statistics data for all births in the year 2000 [15]. Control mothers were older, more often white, more often married, and had more years of education compared with the U.S. population; control children were more likely to be born at term and to weigh more at birth. In the present analysis, control mothers were more often white compared with case mothers, but were similar with regard to other measured demographics. We controlled for maternal race/ethnicity and age in our analyses in an attempt to minimize the potential effects of selection bias, but cannot rule out residual confounding.

There were also numerous comparisons, and our statistically significant results could be due to chance. The absence of a clear dose response is an added limitation. However, we had ORs near or above 2.0, relatively narrow confidence intervals, consistent significance patterns (significance in the same two time period categories among AML and *MLL*⁻ cases, respectively), a low probability of systematic differences in exposure recall across *MLL*⁺ and *MLL*⁻ case mothers, and supporting evidence from prior studies of benzene exposure.

Despite these limitations, this study provides an important contribution to the limited amount of existing literature linking infant leukemia and maternal exposure to household chemicals. We found evidence of an association between infant leukemia and maternal prenatal exposure to petroleum products in and around the home. This association was specifically detected among *MLL*⁻ cases and for exposure occurring during, rather than before, pregnancy. Benzene was implicated as a potential carcinogen among the petroleum product category, but a clear mechanism has yet to be elucidated. Infant leukemia was not associated with any of the other household chemical exposures examined. Future research, especially that which utilizes improved exposure assessment methods, is needed to verify these results and provide additional insight into potential biological pathways in infant leukemogenesis.

Acknowledgments

The authors would like to thank Cindy K. Blair and Michelle A. Roesler for their helpful comments and suggestions.

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Table 1

Selected characteristics of 264 infant ALL cases, 172 infant AML cases, and 324 controls.

	Controls (N = 324)		ALL (N = 264)		AML (N = 172)	
	N (%)		N (%)	P	N (%)	P
Infant characteristics						
Gender						
Male	156 (48.1)		133 (50.4)	0.59	84 (48.8)	0.88
Female	168 (51.9)		131 (49.6)		88 (51.2)	
Maternal characteristics						
Age at index child's birth (years)						
Mean $\pm$ SD	29.8 $\pm$ 5.4		28.7 $\pm$ 5.6	0.02	29.7 $\pm$ 5.9	0.79
Race/Ethnicity						
White	273 (84.5)		199 (75.7)	0.007	130 (75.6)	0.02
Non-White	50 (15.5)		64 (24.3)		42 (24.4)	
Educational attainment						
High school graduate	91 (28.2)		94 (35.7)	0.12	53 (30.8)	0.31
Some post-high school	112 (34.7)		76 (28.9)		48 (27.9)	
College graduate	120 (37.1)		93 (35.4)		71 (41.3)	
Household income						
\$30,000	95 (29.6)		100 (38.2)	0.09	54 (31.8)	0.43
\$30,000 - \$75,000	145 (45.2)		105 (40.1)		82 (48.2)	
>\$75,000	81 (25.2)		57 (21.7)		34 (20.0)	

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia

Adjusted associations between maternal household chemical exposure and infant acute leukemia

Table 2

	Controls		ALL		AML		MLL+		MLL-	
	N	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)	N
Household chemical exposure										
Insecticides										
Any	117	94	1.01 (0.71-1.45)	69	1.30 (0.86-1.94)	79	1.06 (0.72-1.55)	54	0.95 (0.62-1.46)	54
Month before pregnancy	100	78	0.95 (0.65-1.38)	40	0.72 (0.46-1.12)	57	0.80 (0.53-1.21)	38	0.71 (0.45-1.14)	38
During pregnancy	91	77	1.08 (0.74-1.58)	58	1.35 (0.88-2.07)	63	1.07 (0.71-1.61)	46	1.05 (0.67-1.65)	46
Moth control										
Any	15	15	1.39 (0.64-3.01)	9	1.38 (0.57-3.35)	8	0.84 (0.34-2.11)	8	1.41 (0.56-3.55)	8
Month before pregnancy	10	6	0.85 (0.29-2.49)	4	0.89 (0.26-2.99)	2	0.30 (0.06-1.48)	4	0.98 (0.29-3.34)	4
During pregnancy	11	15	1.89 (0.82-4.37)	8	1.70 (0.64-4.48)	7	0.95 (0.34-2.63)	8	1.92 (0.72-5.11)	8
Rodenticides										
Any	11	13	1.43 (0.61-3.40)	5	0.74 (0.24-2.27)	8	0.97 (0.36-2.64)	5	0.88 (0.28-2.71)	5
Month before pregnancy	9	8	1.17 (0.42-3.26)	5	1.04 (0.33-3.32)	3	0.43 (0.11-1.76)	5	1.20 (0.37-3.85)	5
During pregnancy	9	10	1.19 (0.46-3.08)	4	0.65 (0.19-2.26)	6	0.75 (0.25-2.28)	3	0.54 (0.14-2.13)	3
Flea or tick control										
Any	60	55	1.24 (0.80-1.91)	36	1.30 (0.79-2.14)	50	1.30 (0.82-2.06)	26	0.95 (0.56-1.64)	26
Month before pregnancy	49	46	1.25 (0.79-1.99)	31	1.29 (0.76-2.19)	44	1.34 (0.82-2.19)	23	1.06 (0.60-1.88)	23
During pregnancy	47	47	1.40 (0.87-2.24)	28	1.28 (0.74-2.21)	40	1.41 (0.85-2.34)	23	1.05 (0.59-1.87)	23
Herbicides										
Any	70	49	1.00 (0.65-1.53)	36	1.15 (0.70-1.88)	40	0.96 (0.60-1.53)	31	1.12 (0.68-1.86)	31
Month before pregnancy	45	27	0.75 (0.44-1.28)	17	0.76 (0.41-1.42)	20	0.64 (0.35-1.16)	17	0.83 (0.44-1.55)	17
During pregnancy	55	42	1.14 (0.72-1.81)	33	1.45 (0.87-2.44)	36	1.16 (0.70-1.92)	27	1.34 (0.78-2.30)	27
Insect repellants										
Any	127	99	0.88 (0.62-1.26)	66	0.97 (0.64-1.45)	93	0.94 (0.65-1.37)	48	0.73 (0.47-1.14)	48
Month before pregnancy	75	62	0.96 (0.64-1.44)	37	0.90 (0.56-1.45)	57	0.99 (0.65-1.52)	29	0.75 (0.45-1.25)	29
During pregnancy	108	87	0.95 (0.66-1.37)	57	0.97 (0.64-1.49)	84	1.05 (0.71-1.54)	39	0.72 (0.46-1.14)	39
Professional pest exterminations										

	Controls		ALL		AML		MLL+		MLL-		
	(N = 324)		(N = 264)		(N = 172)		(N = 228)		(N = 146)		
	N	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)	N	OR <i>a</i> (95% CI)
Any	42	46	1.22 (0.75-1.97)	30	1.22 (0.71-2.11)	37	1.08 (0.64-1.83)	25	1.20 (0.68-2.13)		
Month before pregnancy	30	28	0.94 (0.53-1.67)	17	0.88 (0.45-1.72)	21	0.80 (0.42-1.51)	16	0.98 (0.50-1.95)		
During pregnancy	36	41	1.35 (0.81-2.24)	26	1.27 (0.71-2.26)	34	1.23 (0.71-2.13)	23	1.41 (0.78-2.55)		
Paints, stains, lacquers											
	154	128	1.03 (0.73-1.45)	87	1.08 (0.72-1.62)	105	0.88 (0.61-1.28)	78	1.30 (0.85-1.99)		
Month before pregnancy	46	36	1.17 (0.71-1.92)	27	1.23 (0.71-2.12)	36	1.41 (0.84-2.37)	22	1.27 (0.71-2.27)		
During pregnancy	141	121	1.02 (0.72-1.44)	79	0.98 (0.65-1.48)	98	0.85 (0.58-1.23)	71	1.17 (0.76-1.78)		
Petroleum products											
Any	29	33	1.56 (0.90-2.70)	29	2.33 (1.30-4.18)	28	1.38 (0.77-2.48)	27	2.48 (1.37-4.48)		
Month before pregnancy	25	24	1.31 (0.71-2.41)	16	1.42 (0.71-2.83)	19	1.14 (0.58-2.21)	16	1.65 (0.83-3.28)		
During pregnancy	26	31	1.60 (0.90-2.83)	29	2.54 (1.40-4.62)	26	1.37 (0.74-2.51)	27	2.69 (1.47-4.93)		

OR = odds ratio, CI = confidence interval, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MLL+ = mixed lineage leukemia gene rearrangement present, MLL- = no mixed lineage leukemia gene rearrangement present

^aORs adjusted for maternal age and race/ethnicity, and child's year of birth.