Title:
Mode of Delivery and Risk of Childhood Leukemia

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Running Title:
Caesarian Delivery Increases Risk of Common Acute Lymphoid Leukemia

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Main Text: 1780
Tables: 3

Abstract:

Background: Childhood infection and immune response have long been suspected in the etiology of childhood leukemia, specifically acute lymphoblastic leukemia (ALL). Normal primary inoculation of the core human microbiome is circumvented by caesarian section (CS) delivery, which is a proposed modulator of both immune response and early life infection.

Methods: In this study we examined CS delivery and the risk of childhood leukemia using data from the California Childhood Leukemia Study (CCLS) case-control study and additive logistic regression models.
**Results:** We observed no association between CS and acute myeloid leukemia (AML; OR= 0.96, CI=0.52-1.55). We observed a suggestive association for ALL and CS (OR= 1.22, CI=0.97-1.54). When examining common ALL (cALL), defined as ALL with expression of CD10 and CD19 surface antigens and diagnosis occurring between 2 and 5.9 years of age, we found a significant association with CS (OR 1.44 CI=1.0-2.06). ALL subjects that are not cALL showed a similar risk as ALL overall (OR= 1.15, CI=0.91-1.44). Because of previous findings suggesting effect modification, we stratified cALL subjects by Hispanic status. While we observed no relationship for CS in non-Hispanics (OR= 1.14, CI=0.72-1.79), we did observe a strong association between cALL and CS in Hispanics (OR=2.34, CI=1.23-4.46).

**Conclusion:** Within the CCLS, CS delivery appears to be associated with cALL and Hispanic subjects may be driving the association.

**Impact:** Further research combined with investigations into response to early infection and the microbiome are warranted.

(230 words)

**Introduction:**

Despite decades of research, the causes of the most common childhood cancer, acute leukemia, remain uncertain. It is clear that for the most common subtype of childhood leukemia, acute lymphoblastic leukemia (ALL), the pre-leukemic state is initiated in utero(1), yet a low concordance rate between monozygotic twins suggests a secondary
trigger (2). One such proposed trigger is infection. Two related hypotheses posit etiologic mechanisms (2, 3). The delayed infection hypothesis of Greaves suggests that early life immunologic isolation leads to aberrantly strong reactions to infection later in childhood, contributing to leukemia risk (4), whereas the population mixing hypothesis of Kinlein suggests that leukemia is a rare response to infections that are new to a community (5). Commonly studied variables that are related to the timing of infection and associated with leukemia risk include daycare attendance and birth order and suggest that frequency and variety of exposures of infections reduces risk of ALL (6-8). Studies have shown that children developing any medically diagnosed infection (i.e. an infection leading to clinically fulminant symptoms) within the first year of life have an increased odds of developing common ALL (cALL) defined as ALL with expression of CD10 and CD19 surface antigens (pre B cell ALL) and diagnosis occurring between 2 and 5.9 years of age (9) (10). Recent work from our group showed significant differences in neonatal cytokines measured in Guthrie cards at birth between children who later contract ALL and controls (11). These findings suggest developmental differences in immune function might also contribute to development of disease.

Mounting evidence suggests a key role of the microbiome in human health, specifically induction of immune tolerance and adaptive and innate immune function (12, 13). Colonization of the microbiome occurs during the first moments of life (14, 15). Because mode of delivery has a profound impact on the earliest microbiome type of childbirth itself provides a surrogate measure of microbiome colonization (16). Three previous studies of CS and childhood leukemia without examining sub types of ALL reported no association (17-19). We cannot preclude the possibility of additional null
findings that were not reported. A single previous study suggested an increase in odds of
ALL associated with Cesarean Section (CS) delivery (OR=1.42, p=0.06) (20). The objective
of the current study is to determine if risk of childhood leukemia is influenced by mode of
delivery within a California population-based case-control study population and how this
risk differs by leukemia subtype and Hispanic status.

**Materials and Methods.**

The University of California Institutional Review Board and all participating
institutions approved the study. Informed consent was obtained from all participating
subjects.

The California Childhood Leukemia Study (CCLS) is described in detail elsewhere
(21) Briefly, the CCLS is an ongoing case-control study in California which commenced in
1995. The study began in the 17 counties surrounding the San Francisco Bay Area, and
now (up to 2008) encompasses most of California through collaboration with 35 pediatric
oncology centers in the state, allowing for rapid case ascertainment, usually within 72
hours from diagnosis. One or two controls are recruited using birth certificate information
from the California Department of Public Health Office of Vital Records. Controls are
matched on age, sex, Hispanic ethnicity, and maternal race.

In this analysis we examined mode of delivery as reported on California birth
certificates, approximately 93% of cases are born in California. Additional covariate
information (breastfeeding, gestational age, income, gender, maternal race, and maternal
ethnicity) was recorded during the conduct of the routine CCLS questionnaire either in
person or over the phone depending on the phase of the study. This analysis includes 732
cases and 1070 controls. Subjects with missing data (57 cases, 154 controls) on mode of delivery, gestational age, breastfeeding, or matching variables were excluded from the analysis. Subjects with Down syndrome (165) were excluded from all analyses. Cases were stratified by major subtype of leukemia; AML (n=85), ALL (n=647) and cALL (n=242). cALL is defined as ALL with expression of CD10 and CD19 surface antigens (pre B cell ALL) and diagnosis occurring between 2 and 5.9 years of age.

We used logistic regression models to examine the relationship between leukemia and CS. Matched pairs were separated in order to include all controls and increase sample size. Covariates assessed as plausible confounders were identified by obstetrical consultants. Additive regression models were determined a priori and not changed during analysis. Logistic regression models were adjusted for the influence of matching factors, household income, gestational age, and breastfeeding. A sub-analysis included separation of subjects by Hispanic status and cALL because previous research has shown effect modification in these sub-groups specifically in factors relating to immune exposure and response(1, 22).

**Results:**
Demographic variables were similar for cases and controls with the exception of household income (Table 1). This difference has been noted in previous CCLS studies as an artifact of control participant ascertainment and participation. Cases and controls did not differ significantly with regard to breastfeeding or gestational age.

Regression analyses of the three major subtypes of leukemia yielded varying results (Table 2). Logistic regression models showed marginally significant increased odds of CS in ALL subjects (OR = 1.22, p=0.09) and statistically significant odds for subjects with cALL.
There was no observed effect of CS on AML (OR=0.96, p=0.9). None of the models were significantly influenced by breastfeeding or gestational age. Interactions were tested between all covariates; the only significant interaction identified was between CS and Hispanic status.

Because previous studies within the CCLS have shown a difference in incidence and risk of childhood leukemia in children of Hispanic origin compared to non-Hispanic whites and because a statistical interaction was observed, we stratified cALL cases and controls by Hispanic status (Table 3). Logistic regression analysis showed an increase in the odds of CS by a factor of 2.3 in Hispanic cALL subjects (OR=2.34, p=0.009) while a non-significant OR was observed in non-Hispanics cALL cases (OR=1.14, p=0.56). Lymphoid leukemias that did not meet the cALL case definition showed no significant association with CS delivery overall or if stratified by Hispanic status.

**Discussion:**

Our results and the previous study by Kaye et al. examining ALL and CS (20) provide evidence that birth by CS delivery is associated with an increased risk of ALL. These findings are in contrast with three studies that found no statistically significant association between CS and ALL. The observed differences in risk in these studies may be due to variations in characteristics of the study populations of two of the studies. Our study is the only study which specifically examined cALL, and we do not observe statistical significance in ALL overall until we stratify by leukemia subtype, suggesting that the cALL subtype is driving the association. The observation of increased odds of CS in Hispanic children diagnosed with cALL is intriguing but tenuous due to the small sample available. Further studies with larger samples are needed. National and global data show that Hispanics are at
the highest risk for ALL (7). Interestingly, different ethnic groups appear to harbor unique compositions of bacteria within the mid-vagina with Hispanics exhibiting highly diverse bacteria and the highest vaginal pH of any ethnic group (23). These observations taken together suggest a different endemic microbial population and possibly varying circulating microorganisms by social/ethnic group.

Perinatal exposures to microbes, determined largely by mode of delivery, result in significant differences in composition of gut microflora for the first 6 to 12 months of life (24). This period is critical in adaptive immune development. Pioneering studies point to a role of differential microbiome colonization in autoimmune disorders (25) and other chronic diseases (26, 27), and a probable role of the microbiome in the susceptibility to infection with pathogenic organisms(28).

Mode of delivery, particularly delivery by CS, has been investigated as a risk factor in other disorders. A meta-analysis of 23 studies of childhood asthma showed a 22% increase in overall asthma risk in children delivered by CS (29). Similarly, type 1 diabetes risk is increased 23% following CS birth(30). Celiac disease and other IgE mediated food allergies have also been associated with CS, though more studies are needed for confirmation (31, 32). Associations between CS and intestinal bacterial infections have been identified in young children(33). CS may be an important factor in childhood leukemia through exposure to potentially pathogenic agents or human commensal organisms capable of modulating immune response across the life course(34).

There are many limitations in our study that limit a strong statistical inference of causality in the association of CS with ALL. We do not have data on elective versus emergency CS delivery, this may be an important factor in elucidating the mechanism of the
association. Although CS is usually recalled correctly in questionnaires in this study CS was recorded from birth certificates, where any potential bias of questionnaire derived exposure histories is deleted. Nevertheless, Hispanic status and other covariates are subject to potential misclassification biases. While we believe misclassification of Hispanic status would be equal between groups, i.e., non-differential, the possibility of differential misclassification remains. Although we control for socio-economic status (SES) in our analyses, the potential for unmeasured confounding influencing our measures of effect still remains. The cases are generally of a lower SES than our control subjects due to a lower response rate for controls versus cases. While it is impossible to fully control for the potential influence of this SES difference, our findings, after adjusting for income in the analysis, combined with the similar findings of the previous Minnesota cohort study that was presumably not subject to this type of selection bias, suggest that the association we observed is indeed real. Whether these observed differences are the result of some unmeasured confounding or bias cannot be ascertained with the current data. Replication of this association in other cohort studies will address the question more definitively.

The role of the primary population event of the infant microbiome in childhood leukemia remains unclear, but the data presented here suggest an etiologic function associated with early population of the human microbiome from the mother’s vaginal canal and raise many questions. Are there differences in elective versus emergency CS? Are certain cytogenetic subgroups affected disproportionately? What differences in colonization are associated with ALL? Does the child’s initial immune function affect future challenges by infectious agents? Does initial colonization create an ecological dominance
that modifies microbial competition? Are other social and environmental factors related to mode of delivery important?

If these results are replicated, it is possible that reduction of elective CS deliveries or CS delivery combined with alternative methods for microbial colonization of the neonatal gut may play a role in prevention of childhood leukemia. CS deliveries increased 56% in the United States from 1997-2006 rising to a rate of 32% of all births in 2006 (35). The majority of CS deliveries are elective. Additional research comparing the microbiome between children who develop leukemia and healthy children will aid in reconstructing the etiologic nature of this association. Those studies combined with epidemiologic evidence and immune profiling will help to shed further light on the etiology of this most common childhood cancer.

References

### Table 1: Distribution of Subjects in the California Childhood Leukemia Study (CCLS)

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<th>Controls (n=578)</th>
<th>P Value</th>
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*Author Manuscript Published OnlineFirst on March 11, 2014; DOI: 10.1158/1055-9965.EPI-13-1098*
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* all models adjusted for matching factors: age, sex, maternal race, income
Table 3: Mode of Delivery in cALL Subjects by Hispanic Status

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* all models adjusted for matching factors: age, sex, maternal race, income
Mode of Delivery and Risk of Childhood Leukemia

Stephen S Francis, Steve Selvin, Catherine Metayer, et al.

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