Title

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Journal

The Lancet Haematology, 3(4)

ISSN

2352-3026

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Publication Date

2016-04-01

DOI

10.1016/s2352-3026(16)00002-8

Peer reviewed

HHS Public Access

Author manuscript

Lancet Haematol. Author manuscript; available in PMC 2017 January 31.

Published in final edited form as:

Lancet Haematol. 2016 April ; 3(4): e176–e185. doi:10.1016/S2352-3026(16)00002-8.

Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC)

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Declaration of interests: We declare no competing interests.

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Summary

Background—Results from case-control studies have shown an increased risk of acute lymphoblastic leukaemia (ALL) in young children born by caesarean delivery, and prelabour caesarean delivery in particular; however, an association of method of delivery with childhood leukaemia subtypes has yet to be established. We therefore did a pooled analysis of data to investigate the association between childhood leukaemia and caesarean delivery.

Methods—We pooled data from 13 case-control studies from the Childhood Leukemia International Consortium done in nine countries (Canada, Costa Rica, Egypt, France, Germany, Greece, Italy, New Zealand, and the USA) for births from 1970-2013. We analysed caesarean delivery overall and by indications that probably resulted in prelabour caesarean delivery or emergency caesarean delivery. We used multivariable logistic regression models, adjusted for child's birthweight, sex, age, ethnic origin, parental education, maternal age, and study, to estimate odds ratios (ORs) and 95% CIs for the risk of ALL and acute myeloid leukaemia (AML) in children aged 0-14 years at diagnosis.

Findings—The studies provided data for 8780 ALL cases, 1332 AML cases, and 23 459 controls, of which the birth delivery method was known for 8655 (99%) ALL cases, 1292 (97%) AML cases, and 23 351 (>99%) controls. Indications for caesarean delivery were available in four studies (there were caesarean deliveries for 1061 of 4313 ALL cases, 138 of 664 AML cases, and 1401 of 5884 controls). The OR for all indications of caesarean delivery and ALL was 1.06 (95% CI 0.99–1.13), and was significant for prelabour caesarean delivery and ALL (1.23 [1.04-1.47]; p=0.018). Emergency caesarean delivery was not associated with ALL (OR 1.02 [95% CI 0.81-1.30]). AML was not associated with caesarean delivery (all indications OR 0.99 [95% CI 0.84-1.17]; prelabour caesarean delivery 0.83 [0.54-1.26]; and emergency caesarean delivery 1.05 [0.63-1.77]).

Interpretation—Our results suggest an increased risk of childhood ALL after prelabour caesarean delivery. If this association is causal, maladaptive immune activation due to an absence of stress response before birth in children born by prelabour caesarean delivery could be considered as a potential mechanism.

Introduction

Leukaemia is the most common childhood malignant disease, accounting for around a third of cancers diagnosed in children aged 0-14 years.[1] There is strong evidence that acute lymphoblastic leukaemia (ALL), the most common subtype, is initiated in utero with a secondary event necessary to trigger carcinogenesis.[2] Hypotheses suggest involvement of immune development and responses to infection in the development of childhood ALL.[3] Findings from studies of proxies of exposure to infection, including day-care attendance,[4] birth order,[5] and timing of birth,[6] lend support to the concept of an infectious cause. Additionally, children who develop ALL might have developmental differences in immune function from birth,[7] suggesting that early immune development could be important for risk of disease.

Mounting evidence suggests that birth by caesarean delivery affects both short-term and long-term outcomes onset of labour.[9]

Meta-analyses have reported small (odds ratio <1.50) but significant associations between birth by caesarean delivery and subsequent risk of immune-related disorders, including asthma[10] and type 1 diabetes.[11] An association of childhood leukaemia with caesarean delivery has not been established, although many studies might be underpowered to detect a small association. Several previous studies have reported null associations between caesarean delivery and ALL,[12–17] but findings from one study suggested increased odds of ALL after caesarean delivery.[18] Furthermore, two studies have done subgroup analyses and shown raised effect estimates when stratifying by disease subtypes or type of caesarean delivery. In what was, to our knowledge, the first study to investigate the role of prelabour caesarean delivery in childhood leukaemia, investigators showed an increased risk of overall ALL and precursor B-cell ALL in children aged 0–3 years after prelabour caesarean delivery,[19] whereas another study reported increased risk of common ALL (defined as ALL with expression of CD10 and CD19 surface antigens and diagnosis occurring between age 2 and 5.9 years), particularly in Hispanic people, after caesarean delivery.[20]

The Childhood Leukemia International Consortium (CLIC) is a multinational collaboration of epidemiological and genetic studies of childhood leukaemia.[21] In this collaborative study, we used pooled CLIC data to comprehensively investigate the association between childhood leukaemia and caesarean delivery.

Methods

Selection criteria and data inclusion

We invited all principal investigators of studies currently included in CLIC consortium to participate in this analysis. Participation depended on availability of data about method of birth, and the ability of the study teams to provide data by the end of June, 2014. 13 case-control studies done in nine countries (Canada, Costa Rica, Egypt, France, Germany, Greece, Italy, New Zealand, and the USA) in variable periods including births from 1970 to 2013 contributed data to the pooled analyses. Study design and characteristics of participants in individual studies have been described elsewhere.[21] The data we requested included the child's sex, age at diagnosis or recruitment, ALL immunophenotype, year of birth, birthweight, gestational age, ethnic origin, maternal age at child's birth, maternal and paternal education level, breastfeeding, method of delivery, and, if available, indication for caesarean delivery. We also requested the variables used in the matching or selection of participants. All studies were approved by institutional ethics committees.

Data were checked in collaboration with investigators from each study and standardised across studies for the pooled analyses. In particular, categorical variables were created for ethnic origin (white, black, Asian, Hispanic, other), highest level of education obtained by either parent (none or primary, secondary, or tertiary [roughly equivalent to 0-9 years, 10-12 years, and ≥13 years of education, respectively]), and birthweight (≤2499 g, 2500-3999 g, ≥4000 g). Breastfeeding was classified as either yes or no on the basis of whether the child was ever breastfed. In the few studies that did not obtain information about ethnic origins,

we classified ethnic group based on the predominant ethnic group of each country, after consultation of the respective principal investigators. For the purpose of stratified analyses, we created a categorical variable for gestational age (early preterm [<34 weeks], late preterm [34-36 weeks], early term [37-38 weeks], full term [39-40 weeks], and late term [>40 weeks]). Implausible values for birthweight (<500 g) and gestational age (<20 weeks or >44 weeks) were deemed as missing.

The primary exposure variable, method of birth, was obtained by questionnaire for all studies except two US studies (Washington and the California Childhood Leukemia Study [CCLS]) that obtained information from birth-registry records. From four studies (Canada, France [Etude cas-témoins sur les cancers de l'enfant; ESTELLE], Greece, and US [the Children's Cancer Group (CCG)]) that provided indications for caesarean delivery, data were obtained by questionnaire in response to questions such as “What was the reason for having a caesarean section?”. When the reason given was previous caesarean delivery or multiple births, we regarded these indications as likely to have resulted in scheduled prelabour caesarean delivery. Although the questionnaires contained data elsewhere for whether the index child was part of a multiple birth or whether the mother had undergone a previous caesarean delivery, we only judged births as probably prelabour caesarean delivery when these indications were explicitly given as the reason that a caesarean delivery took place. The France (ESTELLE) and Greece studies contained sufficient detail in the indication for a caesarean delivery variable to also classify caesarean births as probably emergency caesarean delivery. We categorised births as emergency caesarean delivery when the indication for caesarean delivery was fetal distress, prolonged labour, failure in labour progression, cord prolapse, or obstructed labour due to malposition, malpresentation, or shoulder dystocia. The main outcome of our analysis was an association of either ALL or AML with caesarean delivery due to all indications, prelabour caesarean delivery, or emergency caesarean delivery. We also examined the risk of ALL with caesarean delivery by subgroups (immunophenotypes, age, year of birth, gestational age, and child's ethnic origin).

Statistical analysis

Analyses were restricted to children aged 0-14 years at diagnosis. We used multivariable logistic regression models to estimate study-specific and pooled odds ratios (ORs) and 95% CI for the association of ALL and AML with caesarean delivery due to all indications, prelabour caesarean, and emergency caesarean. To test for interactions, we included models with cross-term products for method of delivery and all stratification variables. Controls were individually matched (mostly by age and sex, and, in four studies, region) to cases in eight studies and frequency matched (mostly by age and sex) to cases in five studies. In the estimation of study-specific ORs for studies that used individual matching, we retained original matched sets and used conditional logistic regression; unconditional logistic regression was used to calculate study-specific ORs for studies with a frequency matched design. For the estimation of pooled ORs, we used unconditional logistic regression to increase statistical power because it enabled us to include all participants with complete data,[22] and at least three of the individual studies had used this method in their original analyses.[23-25] All models were adjusted for child's age, sex, ethnic origin, birthweight, maternal age, parental education, and study. For ALL cases, we did the analyses by B-cell

and T-cell immunophenotype subgroups, and stratified analyses by age at diagnosis (using categories 0, 1-5, 6-10, and 11-14 years to show age-related cytogenetic profiles of ALL cases),[26] decade of birth, and gestational age. We also did analyses restricted to children aged 0-3 years to replicate the analyses from the Greek study.[19] Separately, we stratified analyses by child's ethnic origin within ALL cases overall and then restricted analysis to children aged 2-5 years with ALL to replicate analyses from the California study.[20] For stratification by ethnic origin, we used data from the four US-based studies because these contained the most detailed data for ethnic origin. Because caesarean delivery is associated with lower rates of breastfeeding,[27] which is in turn associated with increased risk of childhood leukaemia,[28] we regarded breastfeeding as a potential mediator of the effect of caesarean delivery on leukaemia risk. To assess this possibility, we did separate analyses controlling for breastfeeding to calculate the direct effect of caesarean delivery and prelabour caesarean delivery on leukaemia risk (emergency caesarean delivery was not included in these analyses). Finally, we combined study-specific ORs in fixed-effects meta-analysis models and produced summary ORs, 95% CIs, forest plots, and I^2 statistics. We tested between-study heterogeneity by Cochran's Q test. We did sensitivity analyses by systematically removing one study at a time from the pooled analyses. For all instances, we did a complete participant analysis.[29] Data were analysed with SAS 9.4 and R 3.0.2.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (ELM) and last author (LGS) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The 13 participating studies provided data for 8780 ALL cases, 1332 AML cases, and 23 459 controls aged 0-14 years (table 1). Delivery method was known for 8655 (99%) ALL cases, 1292 (97%) AML cases, and 23 351 (>99%) controls (table 2). Information about indication for caesarean delivery was provided by four studies (Canada [Quebec], France [ESTELLE], Greece [NARECHEM], and USA [CCG]), there were caesarean deliveries for 1061 of 4313 ALL cases, 138 of 664 AML cases, and 1401 of 5884 controls. The percentage of caesarean delivery in controls varied substantially between studies, from 7% (20 of 303) in New Zealand to 38% (449 of 1176) in Greece (appendix p 1). We also noted substantial variation in the frequency of caesarean delivery between ALL and AML cases. For children born by caesarean delivery, the study-specific frequency of prelabour caesarean delivery ranged from 17% (43 of 255 in France [ESTELLE]) to 28% (126 of 449 in Greece) for controls and 13% (16 of 122 in France [ESTELLE]) to 36% (142 of 391 in Greece) for ALL cases (table 3).

Caesarean delivery due to any indication was associated with a slightly increased point estimate for ALL (OR 1.06 [95% CI 0.99-1.13]), mainly driven by the B-cell immunophenotype (table 4), however this finding was not significant. Study-specific ORs for ALL ranged from 0.61 to 1.88 (appendix p 2) but we did not detect evidence of

heterogeneity (I^2=0.02%). We did not note an association between caesarean delivery and AML (OR 0.99 [95% CI 0.84-1.17], table 4), and no associations were apparent between caesarean delivery due to any indication and ALL for any subgroups. After inclusion of cross-term products for method of delivery and all stratification variables we noted no significant interaction p values (data not shown).

By contrast, prelabour caesarean delivery was significantly associated with ALL (OR 1.23 [95% CI 1.04-1.47], p=0.018; table 4). Study-specific ORs for ALL and prelabour caesarean delivery ranged from 0.85 to 1.38 (appendix p 3) and we did not detect evidence of heterogeneity (I^2=0.00%). The effect estimate was similar for B-cell ALL (p=0.039) but lower for T-cell ALL (table 4). We did not note an association between prelabour caesarean delivery and AML (table 4). We noted an increased risk of ALL in children aged 0-3 years after prelabour caesarean delivery (p=0.0079; table 4), but no other associations for ALL with any other subgroup.

Emergency caesarean delivery was not associated with ALL (all cases OR 1.02 [95% CI 0.81-1.30]; B-cell immunophenotype 0.99 [0.77-1.28]; T-cell immunophenotype 1.19 [0.71-1.99]) or AML (1.05 [0.63-1.77]; appendix p 4). When we controlled for breastfeeding, the results remained stable for the associations between caesarean delivery overall and ALL (OR 1.04 [0.97-1.12]) and prelabour caesarean delivery and ALL (1.22 [1.02-1.45]; appendix p 5). The exclusion of one study at a time from caesarean delivery analyses only altered our effect estimates by less than 10% for all estimates (appendix p 6). Because of the small sample sizes in prelabour caesarean delivery analyses, we did sensitivity analyses excluding each study one by one only for the association between ALL and prelabour caesarean delivery. Results were highly consistent with those based on all four studies, with ORs within 5% of the original estimate (appendix p 6).

Discussion

We examined the association between childhood leukaemia and caesarean delivery in the largest sample of cases assembled to date, using studies from CLIC. We did not note an association between overall caesarean delivery and ALL or AML; however, in the four studies for which indication of caesarean delivery was available, ALL was associated with prelabour caesarean delivery (defined as indications of multiple births and previous caesarean delivery).

Although leukaemia is the most common cancer in children aged 0-14 years, it remains rare and difficult to study epidemiologically, and achieving sufficient power in studies to detect modest associations is a particular challenge. Previous studies have been generally limited by inadequate sample sizes to detect modest associations and many did not have either the power or data availability to stratify by disease subtype or type of caesarean delivery. In this context, both null,[12,14-16] and marginally significant positive associations between ALL and overall caesarean delivery[1820] have been shown. Similarly, studies that did not distinguish between leukaemia subtypes also reported null[13,17] or small positive[37] associations. One study distinguished between emergency and prelabour caesarean delivery and reported null associations for caesarean delivery overall and for prelabour caesarean delivery in children

diagnosed at age 0-14 years, but reported moderate positive associations for children aged 0-3 years between ALL—particularly B-cell ALL—and both all-caesarean deliveries and prelabour caesarean delivery.[19] By contrast, no association was identified with emergency caesarean delivery.[19] Finally, one study investigated common ALL and reported a positive association between this subtype and caesarean delivery, especially in Hispanic people.[20] Our findings suggest that prelabour caesarean delivery increases risk of ALL. Results of meta-analyses (appendix) were consistent with those of pooled analyses, thus we chose to present findings from the pooled analyses of individual data.

Several mechanisms might underlie the apparent association between ALL and prelabour caesarean delivery. First, labour and delivery elicit a substantial stress response in the fetus. Both catecholamine and cortisol concentrations are increased by a factor of 1.5-3.0 times in neonates born by vaginal delivery compared with those born by caesarean delivery before the onset of labour.[38,39] By contrast, neonates born by emergency caesarean delivery show post-partum cortisol concentrations that are similar to those noted in neonates born by vaginal delivery.[40] Increased cortisol concentrations at birth activate the hypothalamic–pituitary–adrenal (HPA) axis, which has a negative feedback relationship with immune and inflammatory reactions.[41] The role of the HPA axis and increased cortisol concentrations in reducing risk of ALL was previously postulated by Schmiegelow and colleagues[42] as part of the adrenal hypothesis of ALL causes. This hypothesis seeks to provide a causal framework to account for the negative association between early-life infections and childhood ALL, and suggests that infections increase plasma cortisol concentrations through changes in the HPA axis and that cortisol destroys leukaemic or preleukaemic cells. Glucocorticosteroids are powerful antileukaemic agents,[43] and cortisol concentrations during infection-related stress can reach those obtained in glucocorticosteroid-based therapy.[44,45] Indeed, adrenocorticotropic hormone treatment can stimulate cortisol secretion, which results in morphological remission of ALL.[46] Thus, increased cortisol exposure in early life could directly eliminate leukaemic and preleukaemic cells. Furthermore, increased cortisol might suppress the T-helper-1-mediated proinflammatory response to infections by promoting production of anti-inflammatory T-helper-2 cytokines, including interleukin 4 and interleukin 10.[42] This effect on the T-helper-1–T-helper-2 balance might reduce the proliferative stress on extant preleukaemic cells. In this context, exposure to the substantial cortisol concentrations during labour and delivery might have a role in mitigating ALL risk for those with preleukaemic cells that have arisen in utero. Children born by vaginal delivery and emergency caesarean delivery are generally exposed to similar cortisol concentrations during labour and delivery, whereas children born by prelabour caesarean delivery are expected to have significantly reduced cortisol exposure at birth.[39,40] Since we noted increased risk of ALL only in children born by prelabour caesarean delivery, our findings are consistent with the role of early-life cortisol exposure in the causes of ALL.

A second potential mechanism for the association is differential microbiota colonisation after birth by caesarean delivery versus vaginal delivery. Mounting evidence suggests a crucial role of the gut microbiome, broadly in human health, and particularly in the development of the immune system.[47] Findings from studies of germ-free mice showed an impaired development of the mucosal immune system and diminished numbers of both IgA-producing plasma cells and IgG in germ-free animals compared with animals of the same

strain that are free of only specific pathogens.[48,49] These mice also displayed abnormalities of the spleen and lymph nodes, including altered structure and poorly formed B-cell and T-cell zones.[50] Intestinal microbiota affect early postnatal immune development via interactions with intestinal Toll-like receptors and production of suppressive cytokines, transforming growth factor-β, and interleukin 10, which direct a balanced T-helper-1 and T-helper-2 immune response.[51,52] Colonisation of the microbiota occurs during the first moments of life, and the method of birth delivery has been shown to alter both composition[53] and diversity[54] of the intestinal microbiota in human beings. These differences persist through the first 6 to 12 months of life,[55] a crucial period for immune-system development. Furthermore, findings from studies have suggested that differential microbiome colonisation could affect the risk of autoimmune disorders,[56] chronic diseases,[57] infection,[58] and many types of adult cancer.[59] It is common in prelabour caesarean delivery for the amniotic membrane to remain intact until surgery, and without membrane rupture, bacterial exposure is greatly reduced compared with caesarean deliveries with amniotic-membrane rupture.[53] Findings from one study[60] showed that maternal prenatal stress and cortisol concentrations were associated with infant intestinal microbiota composition. The mechanism for this association is unknown and might be unique to prenatal stress rather than cortisol concentrations during labour and delivery. However, if maternal cortisol does have a universal effect during the perinatal period on offspring microbiota, this effect might be another pathway through which caesarean delivery alters ALL risk. Additionally, caesarean delivery might alter constitution of the microbiome, not only by an absence of exposure to vaginal flora, but also through altered breastfeeding practices after caesarean delivery. Infants born by vaginal delivery are breastfed earlier and are more likely to be breastfed than those born by caesarean delivery.[27] Breastmilk contains diverse microbes from the mother's gut and has been shown to play an important part in early microbiota colonisation.[61] Controlling for breastfeeding did not change our results. This method needs the assumption that there are no uncontrolled confounders of the relationships between exposure and outcome or mediator and outcome, and many potential confounders (ethnic origin, maternal age, and socioeconomic indicators such as parental education) were already included in our analyses. Although the possibility of unmeasured confounders remains, our analysis suggests that differential breastfeeding practices did not account for our reported association between prelabour caesarean delivery and ALL.

Incidence of caesarean delivery has risen sharply over the past several decades, both in the USA and worldwide.[62] WHO recommends that no more than 15% of births should happen by caesarean delivery;[63] however, most developed regions have caesarean delivery rates above that number, some as high as 40%.[64] The risks of caesarean delivery without medical indication to both mother and fetus have been well documented, and include both short-term and long-term effects on the offspring such as impaired lung function, altered metabolism and blood pressure during infancy, increased risk of obesity, and hepatic-related and immune-related disorders during childhood and adulthood.[8] We noted a wide range of caesarean delivery rates in participating studies. Because the rise in caesarean delivery rates is a global trend spanning about four decades, some of the differences in rates are probably due to the varying birth-years represented among studies, in addition to differences in obstetric practices between countries.

Our study had several limitations. Since all participating studies were case-control in design, some control groups might not have been representative of the source population for cases with respect to exposure distribution, and this might be a particular concern in studies that use hospital-based control recruitment. Our sensitivity analyses excluding each study one at a time did not alter the associations, suggesting that results were not driven by biases inherent to individual studies. Furthermore, the estimates were unchanged when we excluded both studies that used hospital-based control recruitment. Additionally, the caesarean delivery rates noted in the controls show the expected trend based on the rates in each country for the birth-years represented. Most of the participating studies relied on maternal recall of our primary exposure variable, method of birth and indication for caesarean delivery, although findings from studies have shown that maternal recall of both method of birth and events in labour and delivery are highly accurate when compared with medical records (sensitivity and specificity for method of birth >99%).[65,66] Our main findings for the association between ALL and prelabour caesarean delivery are based on two specific indications (previous caesarean delivery and multiple births). The four studies included in prelabour caesarean delivery analyses had varying levels of detail about indications for caesarean delivery. Information about previous caesarean delivery and multiple births was obtained for each study and, when listed as the indication for caesarean delivery, were regarded as highly likely to have resulted in prelabour caesarean delivery for all countries and years of birth represented in our dataset. Specifically, the data suggest that for mothers who have a repeat caesarean delivery, more than 80% of these are prelabour in both France[67] and Greece[68] (appendix p 7). Although some women in the prelabour caesarean delivery group might have undergone a trial of labour and were therefore misclassified, available data suggest that most of these births were correctly classified as prelabour caesarean delivery. Because misclassification of this dichotomous variable is expected to be non-differential and independent of other errors, any resultant bias would drive our reported effect toward the null.

High birthweight is known to be associated with ALL[69] and is also a predictor of caesarean delivery,[70] and macrosomia has been previously suggested as an indication for elective prelabour caesarean delivery,[71] although this practice has been discouraged in recent years (from the early 2000s in the USA).[72] To account for potential confounding by birthweight, we adjusted for this variable in all analyses. We cannot preclude the possibility that the associations are due to confounding by indication or other unmeasured confounding factors. It is possible that some maternal or fetal pathological changes that increase the risk of caesarean delivery also predispose the child to leukaemia. The data in our study did not include sufficient information to assess the possibility of confounding by indication; however, we have offered several plausible biological mechanisms that could account for the association if it is indeed causal.

Because of our large study size, we were able to investigate leukaemia subtypes, types of caesarean delivery, and ethnic origin in stratified analyses. Among the strengths of our study is that, by including both published and unpublished data, we avoided the risk of publication bias. Although both cortisol exposure and microbiota colonisation might play a part in the association between ALL and prelabour caesarean delivery, our findings that prelabour caesarean delivery, but not emergency caesarean delivery, could confer increased risk for

ALL lend support to a role for cortisol exposure affecting risk of disease in susceptible infants, as proposed by the adrenal hypothesis. Future studies with more detailed and reliable information on caesarean delivery and its indication might be helpful in further elucidating this association. If the association between ALL and prelabour caesarean delivery is causal, and assuming an average global exposure prevalence of around 20% and an effect size of 1.25, about 5% of ALL cases could be attributable to prelabour caesarean delivery, although more research needs to be done to determine whether this is the case. Birth cohorts and population-based epidemiological studies with data from medical records about indications for caesarean delivery and occurrence of caesarean delivery before or during labour, especially if enriched with data for leukaemia subtypes and molecular markers, and biomarker information about stress hormones will be useful for doing a thorough analysis of the association between ALL and prelabour caesarean delivery. Comparisons of the number of preleukaemic cells and CD34 positive cells, and HPA axis activity and epigenetic changes in neonates born by vaginal delivery, caesarean delivery, and prelabour caesarean delivery will also be valuable in elucidating the effect of method of birth on cells susceptible to malignant transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Childhood Leukemia International Consortium (CLIC) administration, annual meetings, and pooled analyses are partly supported by the National Cancer Institute (NCI), USA (grant R03 CA132172), National Institute of Environmental Health Sciences (NIEHS), USA (P01 ES018172, R01 ES009137, R13 ES021145, R13 ES022868, R13 ES024632 and R13 ES021145-01), the US Environmental Protection Agency (USEPA), USA (RD83451101), as part of the Center for Integrative Research on Childhood Leukemia and the Environment, Children with Cancer, (CwC UK; 2010/097), Alex's Lemonade Stand Foundation (ALSF; 20140461), and the Sao Paulo Research Foundation (FAPESP). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIEHS, NCI, USEPA, CwC UK, ALSF, or FAPESP. ELM and SSF were supported by postdoctoral fellowships from the National Institutes of Health, NCI (T32CA099936, and T32CA151022, respectively). We thank Alice Y Kang (project manager of CLIC), Somdat Mahabir (National Cancer Institute, USA), and Denis Henshaw and Katie Martin (CwC UK) for the scientific and administrative support to CLIC; and the families for their participation in each individual CLIC study. Additional acknowledgments for CLIC studies are in the appendix.

Funding: National Cancer Institute

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Research in Context

Evidence before this study

Acute lymphoblastic leukaemia (ALL) is the most common cancer in children. Immune development and early life exposures such as breastfeeding and infections are probably associated with the risk of ALL. Mounting evidence suggests that birth by caesarean delivery affects outcomes for the neonate, including development of the immune system; indeed, findings from two studies have suggested a heightened risk of ALL in children born by caesarean delivery. The first study showed an increased risk of the common ALL subtype after caesarean delivery, and the second noted an increased risk of B-cell ALL diagnosed at an earlier age specifically in children born by prelabour caesarean delivery.

Added value of this study

We did a pooled analysis of 13 case-control studies from the Childhood Leukemia International Consortium to investigate the association between childhood leukaemia and caesarean delivery. Our findings showed a significant association between prelabour caesarean delivery and childhood ALL. By contrast, acute myeloid leukaemia was not associated with caesarean delivery. Because of the large sample sizes and data available, we were able to separately examine subgroups of ALL and, in a subset of studies, caesarean deliveries that probably happened before the onset of labour. We substantiated the increased risk of B-cell ALL after birth by prelabour caesarean delivery, augmented in children diagnosed at age 0–3 years.

Implications of all the available evidence

The pooled analysis of CLIC studies suggest a role of prelabour caesarean delivery in development of ALL, specifically B-cell ALL. If confirmed in studies with detailed indications of caesarean delivery, these findings add to existing evidence suggesting adherence to guidelines for caesarean deliveries for the benefit of the child's health. Future studies could consider the absence of stress response before birth in children born by prelabour caesarean delivery as a potential mechanism.

Table 1

Summary of the 13 case-control studies included in the pooled analysis by country (study name), and years of case accrual

	Method of assessment	Cases			Controls	
		Source	ALL (n)	AML (n)	Source	n
Canada (Quebec), 1980–2000[30]	Questionnaire	Province-wide hospitals	790	0	Province-wide population-based health-insurance registry	790
Costa Rica, 2001-03[31]	Questionnaire	Cancer registry and hospitals	252	40	Birth registry	577
Egypt (CCHE), 2009–11 (no publication yet)	Questionnaire	One hospital	299	0	Region-wide, population-based registry	351
France (ESCALE), 2003–04[32]	Questionnaire	Cancer registry	648	101	Nationwide population quotas	1681
France (ESTELLE), 2010–11[16]	Questionnaire	Cancer registry	636	100	Nationwide population quotas	1421
Greece (NARECHEM), 1996–2013[19]	Questionnaire	Cancer registry	1045	114	Hospital-based registry	1176
Germany (GCCR), 1980–96[23]	Questionnaire	Cancer registry	751	130	Population-based registry	2455
Italy (SETIL), 1998–2001[24]	Questionnaire	Cancer registry	601	82	Population-based registry	1044
New Zealand (NZCCS), 1990–93[25]	Questionnaire and medical records	Cancer registry	97	22	Birth registry	303
USA (CCLS), 1995–2013[33]	Questionnaire	Hospitals	840	145	Statewide birth registry	1226
USA (CCG), 1989–93[34]	Questionnaire	CCG clinical trials	1842	450	Random digit dialling *	2497
USA (Texas), 2003–13[35]	Questionnaire and medical records	One hospital	212	1	One hospital	339
USA (Washington), 1974–2009[36]	Birth records	Cancer registry	767	147	Statewide birth registry	9599
Total	..	..	8780	1332	..	23 459

Data are numbers of cases and controls aged 0–14 years contributing to the study sample. ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. CCHE=Children's Cancer Hospital Egypt. ESCALE=Etude cas-témoins sur les cancers de l'enfant. ESTELLE=Etude cas-témoins sur les cancers de l'enfant. GCCR=German Childhood Cancer Registry. NARECHEM=NAtionwide REgistry for Childhood HaEmatological Malignancies. SETIL=Studio sulla Eziologia dei Tumori Infantili Linfoemopoietici. NZCCS=New Zealand Childhood Cancer Study. CCLS=California Childhood Leukemia Study. CCG=Children's Cancer Group.

* Controls were individually matched on telephone area code and exchange.

Table 2
Birth and demographic characteristics of study participants

	Controls (n=23 351)	ALL cases (n=8655)	AML cases (n=1292)
Child's sex			
Male	12 516 (54%)	4886 (57%)	677 (52%)
Female	10 835 (46%)	3769 (44%)	615 (48%)
Child's age (years)			
0–1	4143 (18%)	1000 (12%)	381 (30%)
2–5	10 916 (47%)	4806 (56%)	340 (26%)
6–10	5244 (23%)	2013 (23%)	330 (26%)
11–14	2920 (13%)	834 (10%)	239 (19%)
Missing	128	2	2
Child's ethnic origin			
White	18 069 (78%)	6723 (78%)	978 (76%)
Black	760 (3%)	177 (2%)	49 (4%)
Asian	820 (4%)	212 (3%)	61 (5%)
Hispanic	2476 (11%)	965 (11%)	152 (12%)
Other	1011 (4%)	553 (6%)	47 (4%)
Missing	215	25	5
Birthweight (g)			
≤2499	1316 (6%)	450 (5%)	73 (6%)
2500–3999	18 960 (83%)	6866 (82%)	1045 (82%)
≥4000	2644 (12%)	1068 (13%)	156 (12%)
Missing	431	271	18
Gestational age (weeks)			
<34	347 (2%)	115 (2%)	16 (2%)
34–36	1005 (6%)	431 (6%)	66 (6%)
37–38	3293 (18%)	1274 (18%)	157 (15%)
39–40	9342 (51%)	3624 (51%)	556 (52%)
>40	4260 (23%)	1650 (23%)	276 (26%)
Missing	5104	1561	221
Mother's age at delivery (years)			
<26	8179 (35%)	2918 (34%)	464 (36%)
26–30	7854 (34%)	2913 (34%)	422 (33%)
31–35	5081 (22%)	1961 (23%)	286 (22%)
36–40	1754 (8%)	661 (8%)	96 (7%)
>40	306 (1%)	98 (1%)	22 (2%)
Missing	177	104	2
Parental education *			

	Controls (n=23 351)	ALL cases (n=8655)	AML cases (n=1292)
None or primary	2082 (11%)	1054 (13%)	178 (15%)
Secondary	7414 (40%)	3558 (43%)	557 (46%)
Tertiary	9159 (49%)	3644 (44%)	473 (39%)
Missing	4696	399	84
Breastfeeding[†]			
Yes	9428 (69%)	5049 (66%)	468 (70%)
No	4153 (31%)	2624 (34%)	203 (30%)
Missing	9770	982	621
Method of delivery			
Vaginal	18 583 (80%)	6601 (76%)	1020 (79%)
Caesarean	4768 (21%)	2054 (24%)	272 (21%)
Type of caesarean[‡]			
Prelabour because of previous caesarean delivery or multiple births	325	309	34
Other or unknown	1076	752	104

Data are for numbers of participants with complete data for method of delivery (%). ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia.

[*] Data for 4230 controls, 335 ALL cases, and 66 AML cases are missing from the US (Washington) study, in which data on parental education were not obtained before 1992.

[†] Data for 8499 controls, 680 ALL cases, and 128 AML cases are missing from the US (Washington) study, in which breast-feeding data were not obtained before 2003.

[‡] Data are shown for the Canada, France (ESTELLE), Greece, and US (CCG) studies that had information about the indication for caesarean delivery. Only absolute counts are shown because data are for a subset of participants.

Table 3

Frequency of type of caesarean delivery, by study

	All participants aged up to 14 years			Participants aged 0–3 years		
	Controls	**ALL cases**	**AML cases**	**Controls**	**ALL cases**	**AML cases**
Canada, Quebec						
Caesarean delivery	136	137	..	63	74	..
Prelabour	27 (20%)	42 (31%)	..	11 (18%)	27 (37%)	..
Other or unknown	109 (80%)	95 (69%)	..	52 (83%)	47 (64%)	..
France (ESTELLE)						
Caesarean delivery	255	122	16	114	39	8
Prelabour	43 (17%)	16 (13%)	1 (6%)	16 (14%)	5 (13%)	0
Emergency	85 (33%)	52 (43%)	7 (44%)	45 (40%)	13 (33%)	4 (50%)
Other or unknown	127 (50%)	54 (44%)	8 (50%)	53 (47%)	21 (54%)	4 (50%)
Greece						
Caesarean delivery	449	391	40	207	196	24
Prelabour	126 (28%)	142 (36%)	16 (40%)	56 (27%)	66 (34%)	12 (50%)
Emergency	108 (24%)	83 (21%)	11 (28%)	47 (23%)	39 (20%)	6 (25%)
Other or unknown	215 (48%)	166 (43%)	13 (33%)	104 (50%)	91 (47%)	6 (25%)
USA (CCG)						
Caesarean delivery	561	411	82	223	189	42
Prelabour	129 (23%)	109 (27%)	17 (21%)	42 (19%)	50 (27%)	11 (26%)
Other or unknown	432 (77%)	302 (74%)	65 (79%)	181 (81%)	139 (74%)	31 (74%)

Data are n (%). ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. ESTELLE=Etude cas-témoins sur les cancers de l'enfant. CCG=Children's Cancer Group.

Table 4

Risk of childhood leukaemia associated with caesarean delivery and prelabour caesarean delivery

	Caesarean delivery (all indications)						Prelabour caesarean delivery					
	Number of studies	Controls		Cases		OR* (95% CI)	Number of studies	Controls		Cases		OR* (95% CI)
		CD	VD	CD	VD			PLCD	VD	PLCD	VD	
Outcome												
ALL	13	3812	14 184	1877	6000	1.06 (0.99–1.13)	4	325	4467	306	3238	1.23 (1.04–1.47), p=0.018
AML	11	3179	11 917	251	937	0.99 (0.84–1.17)	3	298	3815	34	525	0.83 (0.54–1.26)
ALL immunophenotype†												
B-cell	10	3411	12 641	1324	4091	1.07 (0.99–1.15)	3	267	3394	208	1867	1.23 (1.01–1.50), p=0.039
T-cell	10	3411	12 641	150	519	0.97 (0.80–1.18)	3	267	3394	26	275	1.11 (0.72–1.72)
Risk of ALL by subgroup†												
Age at diagnosis (years)‡												
0	13	312	1155	62	190	1.14 (0.79–1.64)	4	13	305	11	96	2.62 (0.96–7.19)
0–3	13	1883	6327	927	2679	1.05 (0.95–1.17)	4	125	1743	148	1405	1.42 (1.09–1.83), p=0.0079
1–5	13	2411	7979	1293	3769	1.04 (0.96–1.14)	4	210	2454	201	1982	1.19 (0.96–1.47)
6–10	13	732	3269	386	1430	1.12 (0.96–1.30)	4	63	1024	64	775	1.32 (0.91–1.93)
11–14	12	339	1706	136	611	1.00 (0.78–1.27)	4	39	684	30	385	1.13 (0.65–1.94)
Year of birth												
1970–79	4	85	543	55	329	1.06 (0.70–1.60)	2	17	386	11	304	1.13 (0.46–2.80)
1980–89	9	806	3489	535	2049	1.01 (0.89–1.15)	3	119	1870	122	1523	1.30 (0.99–1.72)
1990–99	13	1613	6439	690	2300	1.07 (0.95–1.19)	4	77	1045	75	703	1.25 (0.88–1.78)
2000–09	9	1237	3528	575	1296	1.12 (0.98–1.28)	2	102	1015	91	688	1.09 (0.79–1.50)
2010–13	4	71	185	22	26	1.54 (0.69–3.42)	2	10	151	7	20	3.92 (0.98–15.70)
Gestational age												
Early preterm	12	137	154	49	53	1.12 (0.66–1.91)	4	6	46	6	35	0.88 (0.19–4.10)
Late preterm	12	299	591	140	254	1.07 (0.81–1.42)	4	18	165	17	113	1.39 (0.61–3.14)
Early term	12	773	2152	375	837	1.11 (0.94–1.31)	4	82	588	92	422	1.35 (0.95–1.93)
Full term	12	1473	6759	671	2786	1.01 (0.90–1.13)	4	142	2212	135	1709	1.23 (0.95–1.59)

	Caesarean delivery (all indications)						Prelabour caesarean delivery					
	Number of studies	Controls		Cases		OR* (95% CI)	Number of studies	Controls		Cases		OR* (95% CI)
		CD	VD	CD	VD			PLCD	VD	PLCD	VD	
Late term	11	649	3220	296	1308	1.04 (0.88–1.22)	4	15	985	8	641	0.85 (0.34–2.11)
Child's ethnic origin§¶												
White	4	1237	4316	472	1569	1.04 (0.91–1.19)	..	..	..	..	..	..
Black	4	122	306	37	113	0.74 (0.44–1.24)	..	..	..	..	..	..
Asian	4	102	383	26	121	0.85 (0.48–1.51)	..	..	..	..	..	..
Hispanic	4	300	1178	146	467	1.14 (0.89–1.47)	..	..	..	..	..	..
Other	4	43	165	20	67	1.23 (0.62–2.45)	..	..	..	..	..	..
Child's ethnic origin (age 2–5 years)§¶												
White	4	685	2198	295	862	1.06 (0.88–1.26)	..	..	..	..	..	..
Black	4	65	148	18	47	0.65 (0.29–1.44)	..	..	..	..	..	..
Asian	4	57	208	17	77	0.91 (0.43–1.89)	..	..	..	..	..	..
Hispanic	4	137	632	90	272	1.36 (0.97–1.92)	..	..	..	..	..	..
Other	4	28	83	11	40	0.86 (0.32–2.27)	..	..	..	..	..	..

OR=odds ratio. CD=caesarean delivery. VD=vaginal delivery. PLCD=prelabour caesarean delivery. ALL=acute lymphoblasic leukaemia. AML=acute myeloid leukaemia.

*Adjusted for birthweight, sex, ethnic origin, maternal age, child's age at diagnosis or reference date, parental education, and study.

†Analyses include ALL cases only.

‡ORs adjusted for birthweight, sex, ethnic origin, maternal age, parental education, and study.

§Analyses include the four US studies only.

¶ORs adjusted for birthweight, sex, maternal age, child's age at diagnosis or reference date, parental education, and study.