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Pregnancy Maternal Infection as Childhood Leukemia Risk Factor: A Systematic Review

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Abstract
One of the most prevalent form of cancer in the pediatric population was leukemia. The initiation of childhood leukemia could possibly occur during the fetal stage, as evidenced by the presence of leukemia-associated chromosomal abnormalities at birth. The occurrence of maternal infection while pregnant is common and has the potential to induce chromosomal or immunological changes in the developing fetus, thereby increasing the likelihood of childhood leukemia. The main objective of this research is to identify a relationship between maternal infection during pregnancy and childhood leukemia. To achieve this aim, a systematic review was carried out that encompassed publications released between 2013 and 2023, sourced from various online databases including Pubmed and SagePub. There are total of 55 articles on PubMed and 73 articles on SagePub. Following the screening of titles, five studies meeting the predetermined criteria were included. The study's main discovery confirms that maternal infection during pregnancy is a possible risk factor for childhood leukemia. The transmission of infectious agents with oncogenic properties from mother to fetus may result in genomic instability.
Keywords: Maternal infection, pregnancy, childhood leukemia.

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INTRODUCTION

Leukemia, a type of cancer originating in the blood-forming tissues, accounts for approximately one third of all malignant tumors in individuals within the age group of 0-14 years. This disease is characterized by an abnormal production of white blood cells, which significantly impacts the quality of life of affected children. The most prevalent subtype of leukemia in this age group is acute lymphoblastic leukemia (ALL), representing around 80.0% of all leukemia cases diagnosed. ALL is a rapidly progressing cancer that affects the lymphoid line of blood cells, leading to a compromised immune system and increased susceptibility to infections. The incidence rate of ALL has been quantified at approximately 35.2 cases per million children under the age of 15 in Brazil, highlighting the significant burden of this disease on the pediatric population. This statistic highlights the urgent need for better diagnostic methods, treatment strategies, and supportive care for young leukemia patients. Furthermore, it is crucial to enhance public health initiatives aimed at raising awareness about leukemia symptoms and risk factors among caregivers, healthcare professionals, and the general population.(Da Rocha Paiva Maia & Filho, 2013; Gallant et al., 2023)

Notably, children under the age of five are disproportionately affected by ALL, indicating the susceptibility of this age group to the disease. Understanding the underlying factors contributing to this age-specific susceptibility is essential for developing targeted interventions and personalized treatment approaches. By explaining the molecular mechanisms promoting leukemia development in young children, researchers can pave the way for innovative therapies that offer better outcomes and improved quality of life for pediatric leukemia patients.(Da Rocha Paiva Maia & Filho, 2013; Gallant et al., 2023)

The possible risk factors related with childhood leukemia (CL) are currently subject to contradictory evidence within the scientific community. While exposure to ionizing radiation is widely acknowledged as a contributing factor to the development of leukemia, it is important to note that this explanation does not account for all cases of leukemia in children. The etiology of CL is inherently complex and complicated, involving a combination of genetic, environmental, and possibly infectious factors. It is understood that leukemic cells with genetic abnormalities typically appear prior to birth, with a significant proportion of cases attributed to translocations between chromosomes 12 and 21. This specific translocation leads to the fusion of the TEL and AML1 genes, resulting in the production of abnormal proteins that disrupt normal gene function and alter the behavior of hematopoietic stem cells in terms of self-renewal and differentiation. Notably, this genetic aberration is the most prevalent structural anomaly observed in children diagnosed with leukemia. Interestingly, research indicates that approximately 1.0% of healthy newborns have this translocation, yet only a little of them go on to develop leukemia, suggesting the presence of additional factors influencing disease progression. Furthermore, investigations into the incidence of leukemia in identical twins have revealed a low correlation, particularly in infants aged 2-6 years, further supporting the theory that leukemia may originate in utero but requires a secondary postnatal trigger to manifest fully - a concept known as the "two-hit model." Recent studies have explored the potential role of infections in the etiology of CL, proposing three primary hypotheses to explain the mechanisms through which infections may impact the development of this disease.(Da Rocha Paiva Maia & Filho, 2013; Metayer et al., 2016)

Pregnancy maternal infection has long been considered a potential risk factor associated with the development of childhood leukemia. The transmission of infectious agents carrying oncogenic properties from the mother to the fetus has been hypothesized as a probable mechanism leading to genomic instability within the developing fetus. On the other hand, it is theorized that fetal infection could potentially induce immune tolerance due to the immaturity of the adaptive immune response within the fetus. This immune tolerance scenario could create a conducive environment for the virus to stay in long-term and a conducive environment for infected cells to proliferate, consequently resulting in an increased viral load. Maternal infection can affect fetal immune system development without transplacental transmission. Variability in cytokine levels at birth varies between children who develop acute lymphoblastic leukemia (ALL) and their controls, suggesting a potential association of immune dysfunction at birth with leukemia pathogenesis. Several potential mechanisms may explain the possible connection between maternal infection and childhood leukemia onset.(Jia, 2017)

METHODS

Protocol

The researcher of this investigation accurately confirmed strict adherence to the guidelines defined by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, thereby ensuring that every aspect of the study aligned with the mandatory standards and criteria. This systematic process plays a crucial role in ensuring the accuracy and reliability of the conclusions drawn from the research undertaking.

Criteria for Eligibility

To accomplish the goal of conducting a comprehensive and detailed analysis of the existing literature, our primary focus is specifically directed towards the comparative examination and distinguishing characteristics relating to maternal infection during pregnancy in relation to the development of childhood leukemia. This

academic search involves a comprehensive exploration and critical assessment of maternal infection during pregnancy compared with the occurrence of childhood leukemia.

To participate in the study, the author had to meet specific criteria, including writing about pregnancy maternal infection and childhood leukemia in English. The papers studied had to be published after 2013 but before the systematic review period. Unacceptable studies included editorials, submissions without a DOI, previously published review articles, and papers identical to those already published.

Search Strategy

We used "Pregnancy maternal infection and childhood leukemia" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("Maternal infection"[MeSH Subheading] OR "Infection in pregnancy"[All Fields] OR "Childhood leukemia" [All Fields]) AND ("Leukemia by maternal infection"[All Fields] OR "Impact of maternal infection"[All Fields]) AND "Complications of maternal infection"[All Fields]) OR "Maternal infection and childhood leukemia" [All Fields]))* used in searching the literature.

Data retrieval

Upon completion of a systematic review of both the abstract and the title of every study included, the researchers proceeded with a review aimed at discovering which studies have a scope met the predetermined inclusion criteria. After this evaluation, the authors selecting those studies that best aligned with the objectives of the study. After examining a variety of research studies, all of which seemed to converge on a consistent result, the researchers came to a definitive conclusion regarding the focus of the study.

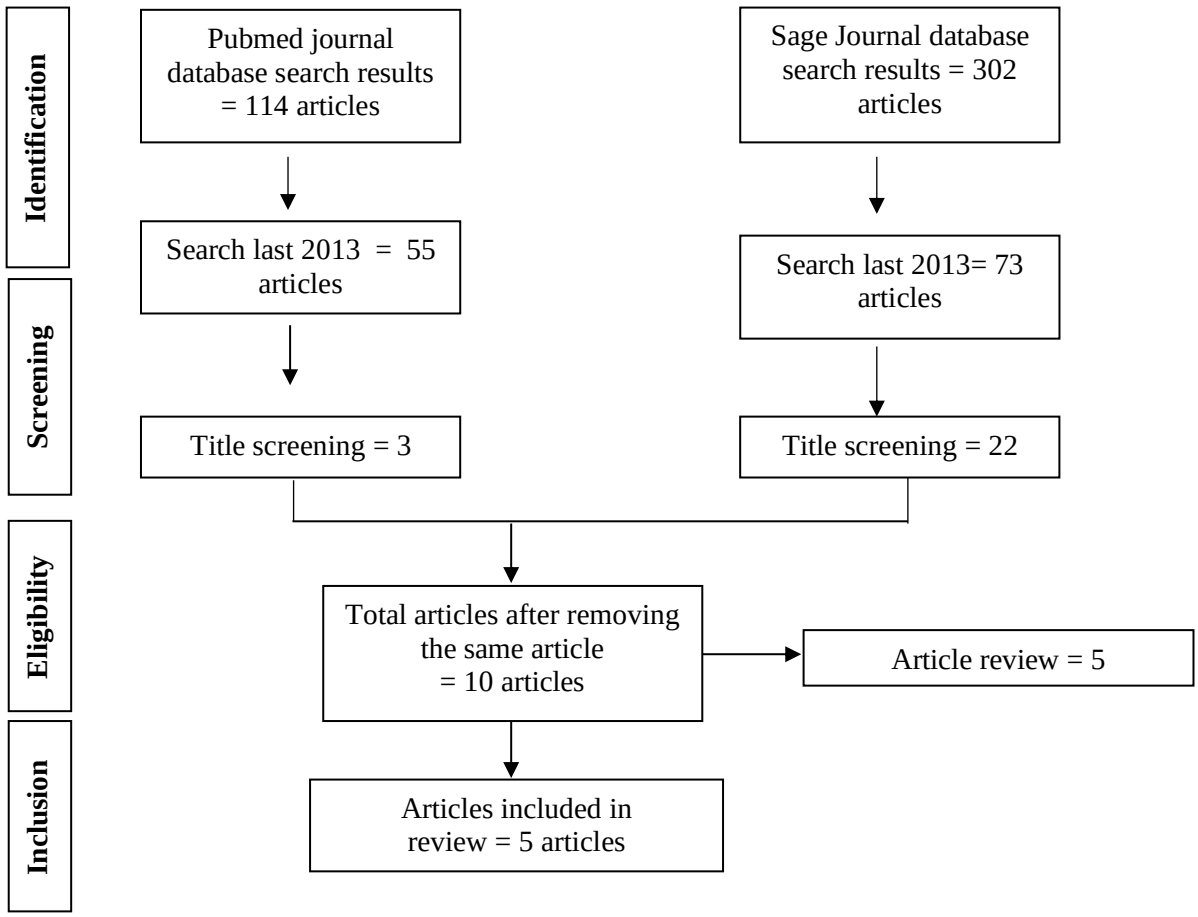

Figure 1. Article search flowchart

Only papers that met all the specified inclusion criteria were considered eligible to be included in the systematic review, thereby narrowing down the pool of results to only those directly relevant to the search query. Any study failing to meet our predetermined requirements was excluded, with a strict focus on only those meeting the criteria. Systematic analysis of the research findings was conducted to extract meaningful insights. The review for this study discovered various pieces of information such as authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

The author conducted a study on the research in the title and abstract before choosing publications for further analysis. Subsequently, the next step is to thoroughly evaluate all articles suitable for the review using the specified criteria. Subsequently, the selection of articles for the review will rely on the disclosed findings. This factor is important for choosing papers efficiently. It helps make paper selection process smoother. The focus now turns to analyzing past research efforts and the particular characteristics that made them appropriate for the review.

RESULT

Within the PubMed database, our precisely conducted search process brought to a grand total of 114 scholarly articles, exploring various research topics and findings. From the SagePub database, the findings remarkably revealed a total of 302 articles. The comprehensive study of the data from 2013 to the period of this systematic review conducted, it revealed 55 notable articles on PubMed and 73 articles on SagePub. Besides, the selective procedure of title screening, which aimed at filtering out the most relevant studies, concluded in the identification of 3 relevant articles on PubMed and 22 articles on SagePub. The conclusion of our extensive research attempt led to a total of 10 scholarly papers. Amongst these carefully chosen papers, a systematic selection criterion was applied, resulting in the inclusion of 5 research articles.

Rong-He, J et al (2023) have recently illustrated in their latest research, as also underscored by He et al. (2023), the remarkable correlation that exists between maternal genitourinary tract infection during the period of pregnancy and the manifestation of childhood leukemia among a cohort comprising approximately 2.2 million children. If this result is being validated through a further study, it has a potential to be a CL preventable cause. In their recent publication, Rong-He, J et al (2022) have explained comprehensive research where they have effectively revealed the correlation between urinary tract infections and respiratory tract infections that manifest during the gestational period, and the increased tendency for the development of childhood leukemia. However, it is crucial to highlight that the actual risk due to this association remains relatively uncertain. Consequently, there exists a demanding requirement to undertake additional investigations with the aim of validating the findings defined in the study.

Table 1. Literature included in this study

Author	Origin	Method	Sample Size	Result
Rong-He, J *et al*., 2023(He et al., 2023)	Sweden	Cohort study	2 222 797 children	The study involved 2,222,797 children, with 51.3% being boys. Over an average follow-up period of around 27 million person-years of follow up (mean [SD], 12.0 [4.6] years per individual), 1,307 children were diagnosed with leukemia (including 1,050 with ALL, 165 with AML,

Author	Origin	Method	Sample Size	Result
				and 92 with other types). Children of mothers infected in pregnancy had 35% higher leukemia risk (adjusted hazard ratio [HR], 1.35 [95% CI, 1.04-1.77]) compared to those born to uninfected mothers. Maternal infections increase childhood leukemia risk: genital infections by 142%, urinary tract infections by 65%. No link with respiratory, digestive infections. Sibling analysis findings align with overall cohort findings. Consistent association patterns observed in ALL and AML. Absence of correlation identified with brain tumors, lymphoma, or other pediatric cancers.
Rong-He, J *et al*., 2022(He et al., 2022)	Sweden	Cohort study	312879 children	Over a mean period of 13.6 years, 312,879 children were monitored, leading to the detection of 167 cases of leukemia, with 129 cases are ALL and 33 cases are AML. Maternal UTI has been found to have a greater likelihood of leukemia development [HR (95% CI) 1.68 (1.10–2.58)], specifically ALL [1.49 (0.87–2.56)] and AML [2.70 ([0.93–7.86)], but not with any other malignancies. Respiratory tract infection increased the risk of leukemia [1.57 (1.06–2.34)], ALL [1.43 (0.94–2.19)], AML [2.37 (1.10–5.12)], and any cancer [1.33 (1.09–1.63)].

Author	Origin	Method	Sample Size	Result
				Influenza-like illness demonstrated a similar pattern with less precise estimates. No association was found between other infections and outcomes.
Bonaventure, A *et al*., 2023 (Bonaventure et al., 2023)	United Kingdom	Case control study	4148 participants	Mothers of 1,624 cases and 2,524 controls were surveyed 6 years after giving birth. Underreporting of drugs and infections was common. Antibiotic prescriptions in general practitioner records tripled, infections increased by over 40% (80% sensitivity among controls). Odds ratios for drug/disease categories were different between self-reported and medical records. Reporting discrepancies were not consistent between mothers of cases and controls.
Hjorth, S *et al*., 2022(Hjorth et al., 2022)	Denmark	Cohort study	44091 children	4,091 children exposed to nitrofurantoin and 247,306 exposed to pivmecillinam were studied prenatally. Children were observed for an average of 9.3 years, with a standard deviation of 4.1. 161 cases of childhood leukemia were identified. The weighted IRR for nitrofurantoin exposure compared to pivmecillinam was 1.34 (95% CI 0.88, 2.06), with an IRD of 15 per million person-years. Higher estimates were found for first- and third-trimester exposure. No dose-response relationship was observed.

Author	Origin	Method	Sample Size	Result
Kumar, A *et al.*, 2014(Kumar et al., 2014)	India	Case control study	132 children	Significant associations exist between childhood leukemia risk and mother's education (p=0.001), occupation (p=0.0005), and exposure to pesticides (p=0.005) during pregnancy. Maternal age (p=0.090), history of fetal loss (p=0.85), radiography during pregnancy (p=0.400), drug intake (p=0.689), and infection (p=0.696) during pregnancy do not show significant links.

Bonaventure, A et al (2023) found that in interviews, there were more reports of influenza and urinary tract infections compared to GP records due to inadequate self-reporting. Sensitivity was low, with 82.5% of women not disclosing influenza diagnosis (17.5% sensitivity) and 64% not disclosing urinary tract infection (35.7% sensitivity). Mothers' recall of their infections during pregnancy is less accurate than their recall of their child's infections, despite sensitivities of over 65% for any infant infection.

Prenatal nitrofurantoin exposure and childhood leukemia association was not significant according to Hjorth, S *et al* (2022), although a slightly higher IRR was detected, the confidence intervals contained the null, indicating a small absolute risk. There is no dose-response relationship or clear biological mechanism to explain findings, indicating no causal association.(Hjorth et al., 2022)

Kumar, A *et al* (2014) demonstrated that mothers' history of fetal loss did not significantly differ between cases and controls (p=0.071). Exposure to pesticides during pregnancy was significantly associated with higher leukemia risk in children. The use of chloramphenicol in pregnancy was higher in cases but not statistically significant. No significant associations were found between maternal history of radiography (p=0.400), infection during pregnancy (p=0.696), and childhood leukemia risk.

DISCUSSION

Leukemia comprises a spectrum of diseases with potentially diverse etiologies. Some experts hypothesize that leukemia arises from an interaction of genetic predispositions and environmental influences. While the etiology of most childhood leukemia remains unknown, certain prenatal and postnatal risk factors, including hereditary conditions have been proposed as contributors to increased susceptibility. Acute Lymphoblastic Leukemia (ALL) represents the predominant childhood malignancy globally, with an annual incidence ranging from 30 to 50 cases per million children.(Flores-Lujano et al., 2009)

The correlation between the incidence of childhood leukemia and maternal exposure to various potential risk factors, such as environmental, genetic, and infectious agents, has been subjected to comprehensive research. Certain maternal prenatal risk factors correlate with higher childhood leukemia risk. An elevated risk of childhood leukemia is associated with maternal exposure to ionizing radiation, pesticides, and pharmaceuticals during gestation.(Kumar et al., 2014b)

A study found strong evidence of Childhood Leukemia clustering at diagnosis for children aged 0-5 years, especially at peak incidence (2-4 years). Similar results were seen for acute lymphoblastic leukemia, possibly

due to "mini-epidemics" causing local clusters over time. No clustering was observed for children aged 5-15 years, with weak evidence for lymphoma and CNS tumors. However, this review focused on specific methodology, and some other studies, like in Germany, did not show clustering. Studies on population mixing suggest a higher leukemia risk in extreme mixing scenarios. Overall, evidence of clustering exists, but the extent and conditions are not fully understood. Complications can arise in pregnancy from different types of infections. Pregnant women may be more susceptible to infections due to physiological changes. TORCH pathogens like Toxoplasma gondii, syphilis, varicella-zoster, Rubella, CMV, and Herpes simplex virus can lead to pregnancy issues. These issues include congenital infections, abortion, and fetal growth restrictions. In addition to common infections related to birth defects, ZIKA, a new TORCH pathogen, raised public concern due to severe pregnancy complications from 2015-2017. TORCH pathogens generally cause mild to moderate illness but can lead to serious fetal outcomes if limited during pregnancy due to various factors.

This systematic review highlighting the potential link between maternal infection during pregnancy and the increased risk of childhood leukemia clarified on a crucial aspect of pediatric health. Maternal infections have long been recognized as a significant risk factor for various adverse outcomes, including obstetric complications, low birth weight neonates, intrauterine death, and severe childhood diseases such as leukemia. The findings emphasize the importance of understanding the impact of maternal infections on the developing fetus and the long-term health implications for the child. By identifying maternal infection as a potential preventable risk factor in childhood leukemia, healthcare professionals and researchers can now focus on implementing preventive measures to mitigate this risk. The relationship between pregnancy maternal infection and childhood leukemia represents a critical area for further investigation and intervention. The systematic review results show that there are many types of infections that related to childhood leukemia, such as genital infections, urinary tract infections, and respiratory tract infections.

Preventing maternal infections during pregnancy through early detection, appropriate treatment, and preventive strategies could potentially reduce the incidence of childhood leukemia. This emphasizes the need for comprehensive prenatal care that includes monitoring and managing maternal infections to safeguard the health of both the mother and the child. Moreover, these systematic review results highlight the importance of raising awareness among healthcare providers and expectant mothers about the potential consequences of maternal infections on the offspring's health. By educating and empowering individuals with knowledge about the risks associated with maternal infections during pregnancy, steps can be taken to minimize these risks and improve overall health outcomes for children.

This review excludes postnatal infections but emphasizes the importance of differentiating infection timing and leukemia risk. The delayed infection or hygiene hypothesis suggests that a lack of early-life infections could raise the risk of childhood leukemia. We studied the period of pregnancy and found a link between maternal infections during pregnancy and childhood leukemia. Maternal infection can change fetal immune system development, this alteration could appear in childhood if there is no correction from early exposure to infection. We couldn't explore the possibility due to limited evidence. Additional studies are required to comprehend important infection periods and the impact of infection timing on understanding changing risk factors and the mechanism of leukemia development.

CONCLUSION

Maternal infection during pregnancy is considered a potential risk factor for childhood leukemia. Transfer of oncogenic infectious agents from mother to fetus can cause genomic instability.

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