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Maternal pregestational diabetes and risk of acute lymphoblastic leukemia in the offspring: A population-based study in Northern Italy

Lucia Borsari[a], Carlotta Malagoli[a], Fiammetta Della Torre[b], Monica Cellini[c], Rossella Rodolfi[d], Andrea Pession[b], Marco Vinceti[a,e,*]

[a] Environmental, Genetic and Nutritional Epidemiology Research Centre (CREAGEN), Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Giuseppe Campi, 287, 41125 Modena, Italy
[b] Department of Paediatrics, Sant'Orsola Hospital, University of Bologna, Via Giuseppe Massarenti, 9, 40138 Bologna, Italy
[c] Division of Paediatric Oncology-Haematology, Policlinico Hospital, Largo del Pozzo, 71, 41125 Modena, Italy
[d] Local Health Authority of Reggio Emilia, Via Giovanni Amendola, 2, 42122 Reggio Emilia, Italy
[e] Department of Epidemiology, Boston University School of Public Health, 715 Albany St, Boston, MA 02118, United States

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ABSTRACT

Introduction: This population-based study aims to evaluate the association between maternal pregestational diabetes and risk of acute lymphoblastic leukemia (ALL) in the offspring.
Methods: All 241,958 children born in three Northern Italy provinces 1998–2010 were followed from birth until first cancer diagnosis (National Childhood Cancer Register), age 15 years, or 31 December 2017. We computed hazard ratio (HR) and 95% CI of ALL in relation to the presence of maternal diabetes through Cox proportional regression models.
Results: We observed 145 cases of ALL, with a higher incidence in children born to women with pregestational diabetes compared to the others (12.4 vs 4.6). Adjusted hazard ratio of ALL was 2.6 (CI, 0.6–10.5) for maternal diabetes.
Discussion: We estimated higher risks of ALL in the offspring of women with pregestational diabetes. These results are consistent with previous findings and compatible with a role of prenatal glycaemic environment in childhood cancer aetiology.

1. Introduction

Childhood acute lymphoblastic leukemia (ALL) accounts for approximately 25% of cancer diagnoses in children younger than 15 years in most world regions, except in sub-Saharan Africa where it is rarely recorded [1]. In Italy, ALL occurs at an annual rate of approximately 43 cases per million people aged 0 to 14 years, with about 400 newly diagnosed children every year [2], similar to the annual incidence rate of 42 cases per million reported in the United States [1]. Although risk factors for ALL still remain largely unknown, the peak of incidence in the 1-4-year age group (81 cases per million in Italy) [2] suggests that prenatal factors, combined with postnatal events, may be involved [3]. The association with some genetic syndromes has already been demonstrated. However, these factors appear to explain only a limited percentage of cases, while the literature on other prenatal factors is still contradictory [4]. Among several suggested risk factors, a number of studies have suggested that high birth weight is associated with ALL, encouraging research on the various factors that can influence birth weight, mainly including maternal diabetes [5,6]. More recently, few population-based studies assessing the association between maternal diabetes and risk of ALL in the offspring have been performed, with risks ranging from 1.4 to 2.9 [7–9]. These studies have been performed in Northern Europe and California, but no data are available from Mediterranean countries. In this study, we aim to evaluate the association between maternal pregestational diabetes and risk of ALL in the offspring of an Italian population for the first time. Thus, we provide data from a cohort of children and mothers with genetic, environmental exposure, anthropometric and lifestyles characteristics that may be substantially different from the three cohorts studied so far.

* Corresponding author at: Environmental, Genetic and Nutritional Epidemiology Research Centre (CREAGEN), Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Giuseppe Campi, 287, 41125 Modena, Italy.
E-mail addresses: lucia.borsari@unimore.it (L. Borsari), carlotta.malagoli@unimore.it (C. Malagoli), dellatorrefiammetta@gmail.com (F. Della Torre), cellini.monica@policlinico.mo.it (M. Cellini), rossella.rodolfi@ausl.re.it (R. Rodolfi), andrea.pession@unibo.it (A. Pession), marco.vinceti@unimore.it (M. Vinceti).

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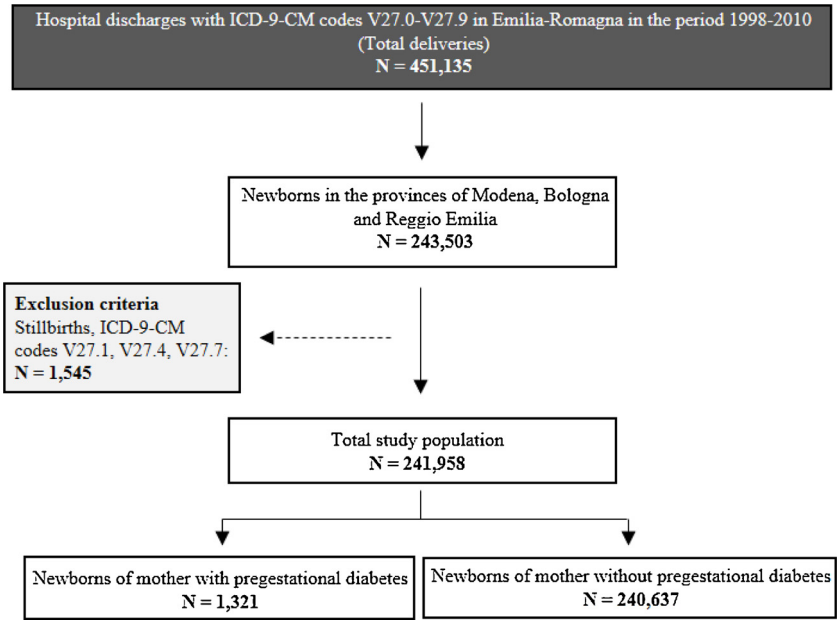

Fig. 1. Flow-chart of the study population.

2. Methods

We carried out a population-based longitudinal study, including all children born in three provinces of Northern Italy (Bologna, Modena and Reggio Emilia) in the period 1998–2010. Stillbirths were excluded from the analysis. In total, the population included 241,958 newborns (Fig. 1).

Of these, 1321 (0.5%) were born to mothers with pregestational diabetes and 240,637 to mothers without the disease. We followed all children from birth until the age of 15, 31 December 2017, or first cancer diagnosis (whatever of these occurred first). We used hospital discharge (HD) records to collect information on maternal diabetes. This information was retrieved through the presence of the ICD-9-CM codes 250.xx or 648.0x listed anywhere in the HD records, date and place of birth, maternal age at delivery, maternal nationality. We identified children affected by ALL from the National Childhood Cancer Register of the Italian association of paediatric haematology and oncology (AIEOP, *Associazione Italiana di Ematologia ed Oncologia Pediatrica*). Since 1989, all malignant tumours diagnosed and treated in the participating centres have been collected in this hospital-based registry, in order to provide epidemiological data and to evaluate and compare compliance with official diagnostic-therapeutic protocols. To date, the AIEOP network treats more than 90% of cancer cases in children from 0 to 15 years [10]. According to the International Classification of Childhood Cancer (ICCC-3), we considered all childhood ALL (code 011) in our study [11].

We calculated the annual incidence rate of ALL per 100,000 person-year in our cohort, stratifying by maternal age at delivery, nationality and diabetes status. We computed hazard ratio (HR) and 95% CI of ALL in relation to the presence of maternal diabetes through Cox proportional hazard regression models, adjusting the results according to maternal demographic characteristics. Children born to mothers without diabetes were the reference group. The study was approved by the Modena Ethics Committee (Protocol note n° 16284/2018).

3. Results

Of the 241,958 children born in Bologna, Modena or Reggio Emilia during the study period, 145 developed ALL. Of these 74 were females (51%), and 71 were aged ≤ 4 years (49%). ALL incidence was 4.7 (95% CI 4.0–5.5) per 100,000 person-years. In Table 1, incidence rates (per 100,000 person-years) and hazard ratio of ALL are shown according to maternal age of delivery, nationality and diabetes status.

The incidence was substantially lower in children born to immigrant women from Africa, even though we did not identify an increased risk specifically associated to maternal nationality. Older maternal age was associated with higher ALL risk, with the children of mothers aged > 40 years at delivery doubling the risk of developing ALL (HR = 2.1, 95% CI 1.1–4.5), compared with the children of mothers aged < = 30 years old.

ALL incidence was higher in children born to women with pregestational diabetes compared to the other women (incidence rate 12.4 vs 4.6, respectively). In the Cox regression analysis, children born to diabetic women had an ALL hazard ratio of 2.6 (CI 95%, 0.6–10.5) in the unadjusted model and 2.7 in the multivariable model, adjusted for maternal age at delivery and maternal nationality (95% CI. 0.7–11.1).

4. Discussion

In this population-based study, we followed a cohort of over 200,000 children born in Italy, for a total of over 3 million person-years. We found an excess risk of developing ALL before the age of 15 in children of mothers with pregestational diabetes, compared to the others. Long-term effects of foetus exposure to maternal diabetes have been only recently assessed in the literature. To the best of our knowledge, this is the first study providing results on the risk of childhood ALL associated to maternal pregestational diabetes from an Italian population. In the multivariable analysis adjusted for maternal demographic characteristics, we found that the risk of childhood ALL in children born to women affected by pregestational diabetes was almost 3-fold increased. In our opinion, inclusion of maternal demographic characteristics in the analysis is very important, considering the long recognized excess risk associated to ethnicity and old maternal age [12,13]. Consistent with previous studies, we found a lower ALL incidence in children born to mothers from Africa compared with those born to Italian mothers, and a higher incidence in children born to mothers aged > 40 years at delivery time than those of mothers aged < = 30 years old.

An association between maternal antecedent diabetes and childhood ALL has been suggested by some recent studies performed in Northern Europe and in California [7–9]. These register-based studies were performed at a national level, and included much larger cohorts of

Table 1
Hazard ratio of acute lymphoblastic leukemia incidence (cases per 100,000 person-years), according to maternal ethnicity, maternal age at delivery and maternal pregestational diabetes in a cohort of children born in Modena, Bologna or Reggio Emilia in the period 1998–2010 and followed up to 31 December 2017.

			Acute lymphoblastic leukemia				
	N	Person-year at risk	N	Incidence	95% CI	Hazard ratio	95% CI
Maternal ethnicity							
Italy	194,958	2,543,188	124	4.9	4.08-5.81	Ref.	
Europe, other than Italy	13,432	148,385	5	3.4	1.4-8.1	0.6	0.3-1.5
Africa	20,196	238,779	7	2.9	1.4-6.1	0.6	0.3-1.2
Asia/Oceania	11,244	131,354	7	5.3	2.5-11.2	1.0	0.5-2.2
America	2,128	25,477	2	7.8	2.0-31.4	1.5	0.4-6.2
Maternal age							
< = 30	103,908	1,360,164	59	4.3	3.4-5.6	Ref.	
31-35	87,148	1,110,960	59	5.3	4.1-6.8	1.2	0.8-1.7
36-40	43,967	535,023	19	3.6	2.3-5.6	0.8	0.5-1.3
> 40	6,935	81,034	8	9.9	4.9-19.7	2.1	1.1-4.5
Maternal pregestational diabetes							
No	240,637	3,071,090	143	4.6	4.0-5.5	Ref.	
Yes	1,321	16,093	2	12.4	3.1-49.7	2.6	0.6-10.5
Total	**241,958**	**3,087,184**	**145**	**4.7**	**4.0-5.5**		

children compared with our study. The two investigations carried out in Northern Europe had study designs and follow-up times similar to our study, including 1,187,482 children in Denmark and 4,239,965 in Sweden. The Danish study reported a hazard ratio of ALL of 2.9 (CI 95% 1.3–6.5), adjusting for maternal age at delivery and ethnicity as in our study, but also for birth order, maternal smoking and birth cohort [8]. In the Swedish study, the very large sample size also allowed for an analysis stratified for type of diabetes. The association with leukemia and ALL was most pronounced for maternal type 1 diabetes, yielding an HR = 2.1 (CI 95% 1.3–3.2), compared to HR = 1.3 (CI 95% 0.6–2.7) for type 2 diabetes. These authors also assessed the association of ALL risk with gestational diabetes, finding a similar risk compared with type 1 diabetes [7].

The biological mechanism potentially underlying the association between maternal diabetes and childhood leukemia is not yet fully understood. However, the results of these studies, along with our findings, support the hypothesis that hyperglycaemia and mainly foetal hyperinsulinemia, in response to maternal hyperglycaemia, could play a role in ALL etiopathogenesis [14]. Foetal hyperinsulinemia may have direct and indirect effects on carcinogenesis, leading to an increase in the bioactivity of insulin-like growth factor-1 (IGF-1). Free IGFs are involved in the regulation of normal and malignant haematopoiesis and have already been implicated in several forms of childhood cancer [15]. Unfortunately, none of the above-mentioned epidemiologic studies provide information about maternal glycaemic control during pregnancy.

The present study has two major strengths, a population-based design and an independent ascertainment of maternal diabetes and ALL in the offspring. We also acknowledge a major limitation inherent in several registry-based studies, i.e. we could not take into account potential confounding factors such as blood glucose levels, concomitant diseases, other relevant environmental exposures and lifestyle factors related to both mothers during pregnancy and children before ALL diagnosis. As an additional limitation, we acknowledge the low number of children with ALL born to diabetic women included in our study, thus decreasing the precision of risk estimates, as reflected by the wide CIs. Despite this limitation, the results of our investigation add to the existing literature and support the hypothesis of a relation between maternal pregestational diabetes and acute lymphoblastic leukemia in the offspring, providing results from a cohort with genetic characteristics and environmental-lifestyles exposures likely differing from those of the cohorts studied so far.

Authorship contribution statement

Lucia Borsari, Carlotta Malagoli and Marco Vinceti conceived and designed the original study, Monica Cellini, Rossella Rodolfi, Fiammetta Della Torre, Andrea Pession contributed to acquiring the study data, Lucia Borsari, Carlotta Malagoli and Marco Vinceti analyzed the data and critically assessed the results, Lucia Borsari draft the manuscript. All coauthors contributed to critically revising the manuscript and approved the final version.

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Declaration of Competing Interest

None.

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