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Research Article

The Innate Propensity for Childhood Leukemia Conditioned by Seasonally-Bound Preovulatory Overripeness Ovopathy

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Abstract

Objectives: An intrauterine origin of childhood leukemia has been presumed. The association with specific maternal and child characteristics, such as chromosomal aberrations and monozygotic twinning, compel us to look for aberrant conditions around conception. To study an *ab ovo* origin, the month of birth was analysed according to the predictions of the seasonally bound preovulatory overripeness ovopathy (SPrOO), hypothesis.

Materials and methods: The birth distributions of leukemia patients diagnosed under age 15 in three consecutive datasets from the Netherlands (N=233, born 1965-1979; N=1565, born 1958-1986; and N=1962, born 1973-2003), were graphically compared with the corresponding total birth distributions. In addition, patients born in the SPrOO hypothesis-based high-risk months (January/February and June/July), were compared to patients born in low-risk periods (March/April/May), by conventional chi-square analyses with one-sided p-values and by relative risks (RRs), with 95% confidence intervals (95%,CI).

Results: In the three datasets we found excesses of births during the indicated high-risk months versus deficits during the low-risk months: RR=1.24 (CI 0.87, 1.76), p=0.12; RR=1.14 (CI 0.99, 1.30), p=0.03 and RR=1.13 (CI 1.00, 1.27), p=0.02, respectively. Similar trends were present for the leukemia subtypes ALL and ANLL and for gender. The results appeared to be more pronounced in patients of 0-4 years old, and were waning in the older age groups.

Conclusions: Seasonally-bound overripeness Ovopathy and causally related aberrant DNA expression by hypo- or hypermethylation may be regarded as initiating causal factor in the etiological pathway of childhood leukemia. It remains unclear whether overripeness ovopathy is sufficient to generate innate susceptibility to agents with leukemogenic potential, or whether it acts as a mediator of subsequent disease which needs an additional environmental "second hit". This concept elucidates several controversies related to determinants of childhood leukemia, such as maternal and paternal age, socio-economic status and particularly to an allegedly protective effect of some MTHFR polymorphisms.

ABBREVIATIONS

Optro: Optimally Ripened Oocytes; Soptro: Seasonally-Bound Optimally Ripened Oocytes; Proo: Preovulatory Overripeness Ovopathy; Sproo: Seasonallly-Bound Preovulatory Overripeness Ovopathy; DCLSG: Dutch Childhood Leukaemia Study Group; NCR: Netherlands Cancer Registration; ALL: Acute Lymphoblastic Leukemia; ANLL: Acute Non-Lymphoblastic Leukemia

INTRODUCTION

In all geographical areas in Europe, the incidence of childhood cancer is increasing with an average increase of 0.6% per year, especially the leukemic subtypes of ALL and ANLL [1-3]. The etiology of childhood leukemia, the most common childhood malignancy, is poorly understood. Studies addressing seasonality at time of diagnosis, maternal influenza during gestation, or seropositivity for common infections remain inconclusive [4-6]. A role for environmental agents is apparent among children resident in the radioactively contaminated territories of the Chernobyl accident [7], and after occupational use of pesticides during pregnancy or infancy [8]. However, it remains uncertain whether these mutagenic or environmental factors are either sufficient or necessary for the occurrence of disease.

The association of childhood leukemia with a wide range of congenital anomalies suggests prenatal and intrauterine causal factors [9-11]. The preponderance of males and the high prevalence of this disease in one or both members of monozygotic twins and Down syndrome [12], as well as the many gene rearrangements, non-specific random chromosomal aberrations [13,14], indicate an initiating causal agent *ab ovo: "The major determinants of childhood leukaemia, and possibly of the solid tumors as well, operate before the time of cleavage. They operate either in the early zygote or its component germ cells"* [15,16]. Abnormal splitting of the fertilized oocyte and non-specific chromosomal aberrations are in line with the overripeness ovopathy concept which is based on animal experiments [17-20], and human observations [21-25]:*"The persistence of an embryonic*

appearance of the cells, designated as aplasia or progressive failure of cells to differentiate, is the most constant effect produced by overripeness (of the egg); if combined with considerable growth, it leads to the formation of neoplasms" [17].

The association of childhood leukemia with specific maternal characteristics and fertility problems, e.g., longer time to pregnancy (> 5years), hormonal treatment, very young and advanced reproductive age, increased rate of miscarriage (often prior to the index pregnancy), threatened abortion and complications during the index pregnancy, and congenital anomalies in siblings or maternal family [12,26-30], are all in line with the overripeness ovopathy concept. The association with epigenetic DNA damage [31,32], raises particular interest, as it occurs during the preovulatory maturation of the oocyte [33]. In this study, it will be argued that seasonality of birth in childhood leukemia [34-36], also accounts for an *ab ovo* origin related to inadequate maturation of the oocyte.

The pre-ovulatory and post-ovulatory ovopathy concept

The ovopathy concept is based on the principle that optimal maturation of the oocyte and optimal liquefaction of the cervical mucus by which sperm permits to penetrate the cervix uteri, are modulated by estrogens. Optimal estrogen concentration appears to be associated with achieving clinical pregnancy; intermediate levels are correlated with early pregnancy loss; still lower levels with non-conception cycles [37]. Meiotic progression and developmental competence of the oocytes as well as epigenetic information are acquired during the highly critical period of follicle formation and maturation. The molecular, biochemical, and physiological processes in the oocyte determine the pleiotropic consequences for both nuclear and cytoplasm constituents.

Optimal estrogen concentrations coincide with prime reproductive maternal age, optimal nutritional state, adequate post-pregnancy restoration of the ovulatory pattern, and in particular with seasonally-bound ovulation peaks [21-23,38]. Prime time ovulations in mammals, including humans, involving optimally ripened oocytes (OptRO), which guarantee good embryo quality, equal sex proportions, favourable downstream effects on later life events, and promising life expectancy.

Non-optimal estrogen concentrations cause deficient maturation of the oocyte before ovulation, i.e., preovulatory overripeness ovopathy (PrOO), and deficient liquefaction of the cervical mucus, resulting in inefficient sperm migration through the uterine cervix and fertilization of non-optimally matured oocytes [38]. Inefficient estrogen levels coincide with the transitional stages of reproductive life in which the ovulatory pattern is at stake, e.g., at very young and advanced maternal age, during undernutrition, in very short and (unintended) long pregnancy intervals, and particularly during the seasonally-bound restoration (breakthrough) and inhibition (breakdown) [21-23,38]. The consequences, such as male preponderance, multiple ovulation, abnormal splitting of the zygote, deficient implantation, prenatal loss, transitory retardation, and developmental anomalies in various tissue systems threatening constitutional health, are compatible with the many determinants of childhood leukemia, as will be discussed later.

Seasonally-bound preovulatory overripeness ovopathy (SPrOO) versus seasonally-bound optimally ripened oocytes (SOptRO)

In feral animals seasonally-bound estrus and ovulatory seasons are associated with the transitional breakthrough and breakdown stages characterized by intermediate or low estrogen and progesterone levels. In domesticated animals they are dampened. Seasonal fluctuations in human births were more obvious in earlier centuries, but even present day still detectable at population level, as illustrated by Figure 1 and 2 a. b. and c.: a major birth peak in winter and a minor one in summer, alternated by two birth troughs. The increase in fecundability suggests higher rates of optimally matured oocytes at both the *zeniths* of the 'ovulatory seasons', and lower rates at the transitional stages, or deficits at the *nadir* [39,40].

The SOptRO- and SPrOO-hypotheses are based on this biological phenomenon in animals and humans: high-quality oocytes (SOptRO), coincide with the prime time and early summer ovulations, which are related to higher neonatal weight and sound development of infants and adults, life expectancy of individuals born at the two birth peaks. By contrast, the poor quality oocytes (SPrOO), are concentrated during the transitional stages, i.e., at the ascending and descending slopes [41,42]. They create a so-called 'double-hump surge' of poor quality conceptions intersected by a dip related to optimal conceptions, superimposed on the slopes of the major winter birth peak and to a lesser extent on the minor summer birth peak. Excessive oocyte attrition and inherent embryonal and fetal loss occurs at the conjunction of the descending and ascending slopes, i.e., at the troughs corresponding with the 'anovulatory' seasons, often resulting in a dose-response fallacy [38-42].

MATERIALS AND METHODS

Definition of SOptRO and SPrOO months

The distribution of total births at population level in the Netherlands is visualized in Figures 1a-c, representing three consecutive time spans (data from the Central Bureau of Statistics). This is in line with other populations in Europe [43,44]. The month April together with the two adjacent months March and May during the sixties and seventies can be determined as the obvious major birth peak being the most favourable season of birth (Figures 1a and 1b) . The minor peak in September was flanked by a slightly ascending slope in August and followed by a steep descending slope in October. Since the eighthies (Figure 1c), the major birth peak is less obvious in European countries and has moved to later months [45]. Considering the risk of misclassification of conception date by pre- and postterm births particularly related to childhood leukemia [46,47]. We decided to avoid the latter part of the year, where the peak covers only a short time period, and to concentrate the analyses on the period from January through July. This part of the year encompasses four high-risk or SPrOO months (January/ February and June/ July), which correspond with the transitional stages and three low-risk or SOptRO months (March/ April/ May), corresponding with the prime ovulatory season.

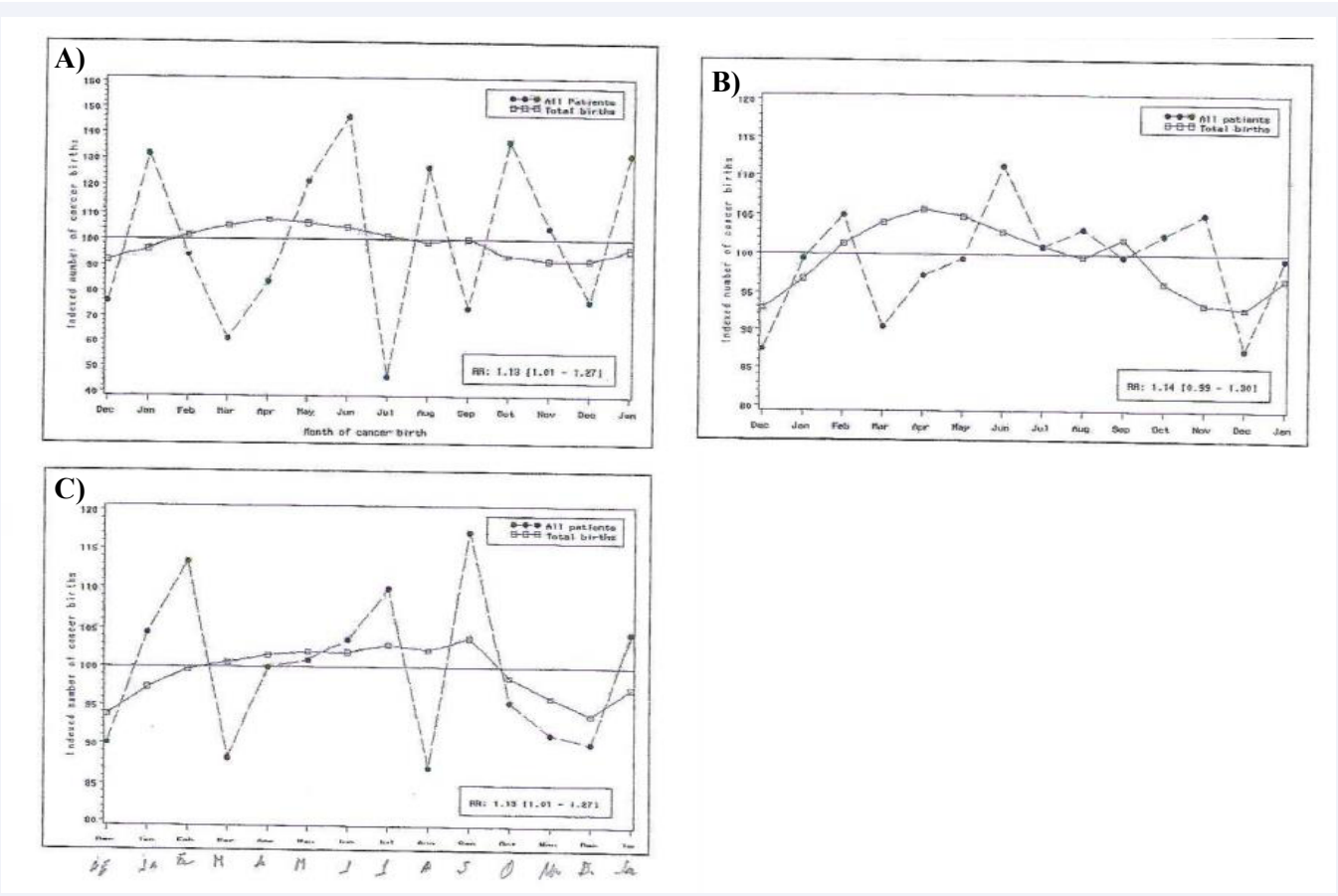

Figure 1 Observed number of births per month in three samples (a) N=233 (ALL only, born 1965-1979), (b) N=1565 (born 1958-1986), and (c) N=1962 (born 1973-2003) of children < 15 years of age with childhood leukemia compared with the total birth distribution during the corresponding years in the Netherlands.

Study populations

The month of birth of the leukemia patients under 15 years of age was compared with the month of birth of the total population retrieved from the Central Bureau of Statistics in the Netherlands. Three datasets were used as listed in Table 1. They were derived from:

A. The Dutch Childhood Leukaemia Study Group (DCLSG): 233 childhood ALL cases collected by collaborating pediatricians covering the western part of the Netherlands (North Holland, South Holland, and Utrecht), born in the period 1965-1979 and diagnosed in 1973-1979 (see Figure 1a) [data published by van Steensel-Moll *et al* in 1983] [48].

B. An extended register of the DCLSG: 1565 childhood leukemia cases identified from registration forms collected by attending pediatricians or specially trained registration assistants covering the whole country of the Netherlands, born in the period 1958-1986 and diagnosed in 1973-1986 (see Figure 1b) [data published by Coebergh *et al* in 1989] [49].

C. Netherlands Cancer Registry (NCR): 1962 childhood leukemia cases, covering the whole country of the Netherlands, born in the period 1973-2003 and diagnosed in 1989-2003 (see Figure 1c) [data not published].

Statistical analysis

The number of births of the childhood leukemia cases and the corresponding total populations were classified per month, corrected for length of month (average = 30.431 days), and indexed to an average of 100 births per month. These numbers were graphically visualised in Figures 1 and 2 in order to recognize the 'double hump surge' hallmark and compared under the assumption that the risk of developing childhood leukemia is the same in each month (null hypothesis). The expected numbers were calculated using the following formula: *expected number of patients in month i = number of births in month i x (total number of patients/total number of births)*. We used conventional chi-square statistics to compare observed and expected numbers during the 4 high-risk and the 3 low-risk months as defined above, using one-tailed tests as a directional hypothesis. In addition, we estimated the risk for children to get leukemia during the determined time periods by relative risks (RRs), with 95% confidence intervals (95%CI), for patients born in the 4 high-risk months versus those born in the 3 low-risk months. These procedures were used to analyse the three total data sets, as well as the subtypes of ALL and ANLL, gender groups, and age categories separately.

RESULTS

The predicted configurations of SPrOO double-hump surges

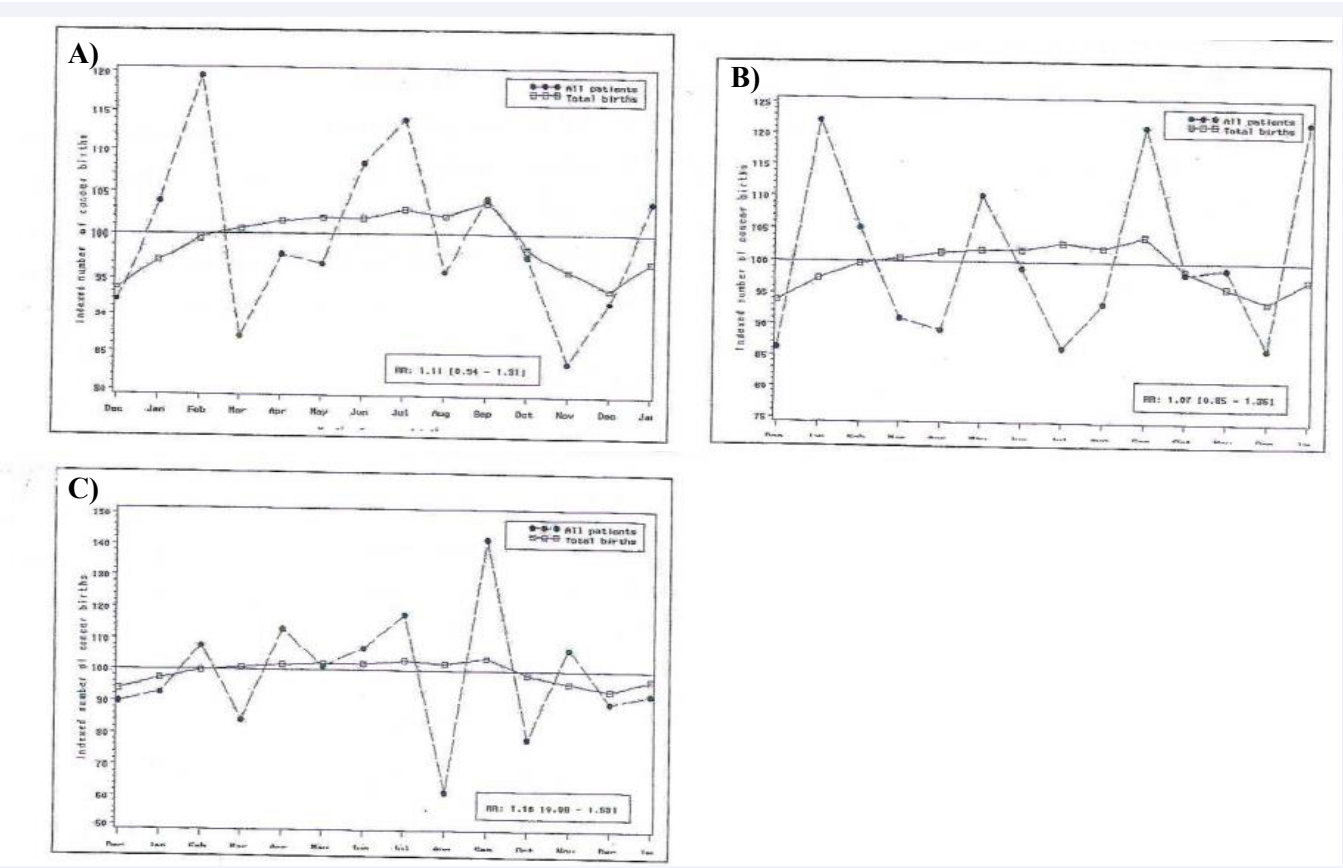

Figure 2 Observed number of births per month per age category at diagnosis in the NCR data set: (a) 0-4 years of age, N=1050; (b) 5-9 years, N=492; and (c) 10-14 years, N=354, compared with the total birth distribution during the corresponding years in the Netherlands.

Table 1: The number of infants in the three childhood leukemia datasets, divided by the subtypes ALL and ANLL and by ender.

Source	Region	Total number ≤ 15yr	Year of Birth	Year of diagnosis	ALL	ANLL	Not specified	Male	Female	Sex Ratio
1DCLSG Steensel-Moll et al 1983	western part of the Netherlands	233	1965-1979	1973-1979	233			133	100	133:100
DCLSG Coebergh et al 1989	the Netherlands	1565	1958-1986	1973-1986	1264	200	101	866	699	124:100
NCR	the Netherlands	1962	1973-2003	1989-2003	1510	336	116	1154	808	143:100

of leukemia cases in January/ February and June/July at the transitional stages of the major birth peak intersected by SOptRO births in March/April/May corresponding with prime time ovulations are illustrated in the graphical representation in Figures 1a-c. The double-hump surges are similar in the three consecutive (Figures 1a-c and Figures 2 a-c), data sets A, B, and C. The same is more or less true for the subtypes ALL and ANLL, in the gender-specific subsamples (not shown), and in the different age categories (Figures 2a-c). The graphical double-hump surges appear to be more pronounced in the 0-4 years age category (Figure 2a), less among the 5-9 years olds (Figure 2b), and are more or less dampened in the age category of 10-14 years old (Figure 2c). Table 2 shows the numbers of observed and expected leukemia cases in the high-risk and low- risk months in the three total data sets A, B, and C. The chi-square tests (with one-sided p-values), indicate that cases were more often born in the high-risk months (p=0.12, p=0.03, and p=0.02, respectively). The same holds true for the relative risks: RR=1.24 (CI: 0.87, 1.76), RR=1.14 (CI: 0.99, 1.30), and RR=1.13 (CI: 1.00, 1.27), respectively. When the leukemia subtypes ALL and ANLL are considered (Table 3), the relative risks appear to be higher for ANLL, but none of these RRs reach statistical significance. Although a male preponderance is present in every data set (Table 1), girls seem to be born preferentially in high-risk months in the DCLSG dataset (RR=1.21 (CI: 1.00, 1.48) and RR=1.04 (CI: 0.87,1.25) for girls and boys, respectively). In the NRC data set , no differences were observed for gender. For the different age categories the RRs are, in principle, all in keeping with the predictions of the SPrOO and SOptRO hypotheses, but confidence intervals are too wide to draw firm conclusions (Table 3).

Table 2: The observed and expected number, p-values and relative risks for childhood leukemia patients born during the low risk SQptRO-Months (March, April and May) compared with those In the high risk SPrOO Months (January, February, June, July).

Period	Observed	Expected	Chi-square	P-value (one-sided)	Total number of births in the Netherlands	Risk of childhood leukemia	Relative Risk CI-Limits
First Dataset (DCLSG) N=223; born in 1965-1979							
4 High-risk months	80	73	0.66		1046122	$7.65.10^{-5}$	
3 Low-risk months	52	59	0.81		843370	$6.17.10^{-5}$	
			1.47	0.12			1.24
							0.87-1.76
Second Dataset (DCLSG) N=1665; born in 1958-1986	536	508	1.59		2016091	$2.52.10^{-4}$	
	377	405	1.59		1610362	$2.34.10^{-4}$	
			3.58	0.03			1.14
							0.99-1.30
Third Dataset (NCR) N=1962; born in 1973-2003	696	662	1.79		1797168	$3.87.10^{-4}$	
	476	510	2.33		1386773	$3.43.10^{-4}$	
			4.12	0.02			1.13
							1.00-1.27

Table 3: Risk Ratio and CI-Limits of childhood leukaemia by high risk month vs.low-risk month of birth.

	Dataset DCLSG 1973-1986	Dataset NCR 1989-2003
ALL	1.08 (0.94-1.25)	1.12 (0.98-1.28)
ANLL	1.28 (0.97-1.69)	1.25 (0.95-1.64)
Boys	1.04 (0.87-1.25)	1.13 (0.97-1.31)
Girls	1.21 (1.00-1.48)	1.13 (0.94-1.36)
0-4 yr	1.10 (0.92-1.32)	1.11 (0.94-1.31)
5-9 yr	1.16 (0.91-1.48)	1.07 (0.85-1.36)
10-14 yr	1.22 (0.90-1.66)	1.16 (0.88-1.53)

DISCUSSION

The current study in three consecutive datasets may be considered representative for the Netherlands and shows that the month of birth distribution of childhood leukemia patients differs from the corresponding total birth pattern. In a population-based data set of 0-4 year old patients in Denmark an identical 'double-hump surge' configuration was present, superimposed on the total major birth peak [36] This configuration is illustrative for pathological progeny caused by SPrOO, as observed for increased sex ratio at birth [38], and in different examples of constitutional diseases in infancy and adulthood [21,23,39-42,50-53]. That means that children conceived from optimally matured oocytes (SOptRO**),** during the prime ovulatory season(s) are less prone to childhood leukemia or more resistant to agents with leukemogenic potential. In contrast, those conceived during the transitional stages are more prone or susceptible to get leukemia because of seasonally bound overripeness ovopathy (SPrOO). Associations with seasonally-bound effects on primary brain tumours in children have also been mentioned [54,55]. The well-known male preponderance in childhood leukemia is also present in our samples. The same male preponderance exists in overall childhood morbidity, mortality and congenital anomalies, always characterised by the same SPrOO-seasonality of birth [38].

Survival and life expectancy are recognized to be connected with seasonality of birth (SOptRO) [42,56]. Therefore the very early onset of the disease (0-4 years), in more than half of the patients and the age-specific waning effect (Figure 2a,b,c), underscore the intriguing relations between overall childhood mortality and development of clinically overt leukemia. These seasonally-bound associations are perhaps insufficient to establish causality, but they provide circumstantial evidence for an etiology *ab ovo*, which is in line with the particular maternal and child characteristics as mentioned in the introduction [9-16,26-30]. The 11-fold increased risk of ANLL associated with cytogenetically cloned abnormalities and chromosomal aberrations after maternal use of marijuana, just prior to (or during) the index pregnancy [57], is in line with ovopathy as initiating agent. Mind-altering drugs in fact influence the hypothalamo-pituitary-ovarian axis while hormonal treatments related to infertility and superovulation produce oocytes without correct primary imprint [33,58], and have even been associated with childhood leukemia [28].

Aberrant DNA methylation, selective remethylation, and silencing of tumour suppressor genes are also associated with leukemia [31,32]. This epigenetic 'danse macabre' comes about during preovulatory maturation of the oocyte and immediately after fertilization.

LIMITATIONS OF OUR STUDY

First, determination of low-risk (SOptRO), and high-risk (SPrOO), months is arbitrarily based on *a priori* knowledge of

the monthly distribution of conceptions in mammals, including humans, and on the total birth curve as a proxy of seasonally alternating ovulation rates nine months earlier. In fact, optimal and non-optimal ovulations and conceptions may occur in every month throughout the year and are not restricted either to the defined SOptRO months (March/ April/ May), or the SPrOO months (January/ February and June/July). This may have diluted our results.

Second, time of birth instead of conception implies serious risks of misclassification due to preterm and post-term delivery. Indeed, 3.7% of the cases (particularly in the major subtype ALL), are born before the 36th week, 6.7% after 36-37 weeks, 32% after 38-39 weeks and 9.7% after 42 weeks [46,47]. *Third*, ovopathy independent of season (e.g., due to stress, post partum conditions, etc.), and unknown causal factors for childhood leukemia acting during pregnancy or in the neonatal period may have confounded the results. However, mimicry of the double-hump surge superimposed on total births, i.e. the SPrOO hallmark, by alternative causes seems very unlikely.

Finally, the continuous shift of the major winter peak to the summer months during the last decades due to family planning in European countries [45], might be a problem. The fact that the 'double hump surge' hallmark in favour of the summer months is not detracted (Figures 1c and 2c) might suggest that behavioural factors do not weigh down the underlying biological background.

EPIDEMIOLOGICAL CONTROVERSIES IN CHILDHOOD LEUKEMIA CLARIFIED BY OVERRIPENESS OVOPATHY

1. Advanced maternal age has been related to childhood leukemia connected with increasing age of the reproductive population in recent decades [2]. In addition, case-control studies - not suffering from participation bias - show that both the youngest (15-19 yr) as well as the oldest maternal age categories (> 35 yr) are associated with high risk factors for ALL and ANLL [29]. That means that aggregation of all age categories conceals this U-shaped relationship in line with ovulatory disturbances at both extremes of reproductive age [23].

2. Increased paternal age (> 35 years) has also been advanced as determinant [59], but does not seem to have an independent effect as it is highly correlated with age of the mother.[2] Moreover, parental age is linked to decreased coition frequency and thus to delayed fertilization and thus to possibility of post-ovulatory overripeness ovopathy (PoOO) [19]. Cotinine also depresses sexual urge and may account for an increased incidence of childhood leukemia, related to preconceptional smoking by the father [60].

3. A third inconsistency regards the associations with socio-economic status [61,62]. These reviewers commented 47 studies in which the older studies differ from the more recent ones, in which interview components and individual family income were included. The lower incidence of childhood leukemia was related to higher parental education or socio-economic status. This again is in line with the overripeness ovopathy concept, which predicts more ovopathy in lower income strata where low standards of nutrition are aggregated: high and low body mass index, less use of safe methods of contraception, more use of drugs and smoking and distorted menstrual cycles [57,63,64].

4. A so-called protective effect of MTHFR polymorphisms for childhood leukemia also is controversial. A positive association between some polymorphisms of the 5,10-methylenetetrahydrfolate reductase (MTHFR) gene, in particular C677T, and several types of adult breast-, colon- and gastric cancer differs from a negative one in childhood leukemia [65]. The inherent increased homocysteine levels would promote 'increased fidelity' of DNA synthesis or the so-called 'protective effect' for childhood ALL.homocysteine levels would promote 'increased fidelity' of DNA synthesis or the so-called 'protective effect for childhood' ALL. This C677T allel is present in approximately 10-15% of Caucasian and Asian populations and has gained great interest because of tightly connected reasons [66]. It reduces the bioavailability of folate and folate metabolites in carriers, which 'mimics' low dietary folate intake at the expense of nucleotide synthesis and epigenetically aberrant DNA methylation. Depressed folate serum levels in fact generate lower concentrations of estradiol and progesteron and slow down the replication of granulosa cells in the maturing follicle. These are markers for retardation of embryonic growth and malformations [67]. Low levels of folate metabolites are shown to be detrimental for embryo quality [68], and to be associated with increased risk of chromosomally aberrant spontaneous abortions [69].

The association with this MTHFR allele may explain why schizophrenia and type 2 diabetes also demonstrate the characteristic seasonally-bound 'double-hump surge' related to SPrOO [21,50,51]. It appears not only that the stronger oocyte attrition, the stronger premature loss during pregnancy or before development of disease, and thus the more negative this association. In contrast, the weaker attrition, the lesser preterm death, but the more positive this association. Therefore, an alledgedly 'protective effect' of C677T polymorphism in childhood leukemia in fact is spurious.

CONCLUSION

The (S)PrOO or season-of-birth effect appears to agree with the known epidemiological determinants for childhood leukemia and particularly with its *ab ovo* origin. If the relations between this disease and the disturbances of ovulation/fertilization are replicated, the associated epigenetic aberrations may be reconciled with this periconceptional causation. It remains unclear whether ovopathy is sufficient to generate the disease or to innate susceptiblity to agents with leukemogenic potential. This may act as a mediator of subsequent disease or need an additional environmental 'second hit'.

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REFERENCES

1. Dobson R. Incidence of childhood cancer rises. BMJ. 2006; 333: 462.
2. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. Int J Epidemiol. 2006; 35: 1495-1503.
3. Coebergh JWW, Reedijk AMJ, de Vries E, Martos C, Jacob Z, Steliarova E, et al. Leukaemia incidence and survival in children and adolescents

in Europe during 1978-1997. Report from the Automated Childhood Cancer Information System Project. Int J Cancer. 2007; 42: 2019-2036.

4. Goa F, Nordin P, Krantz I, Chia KS, Machin D. Variation in the seasonal diagnosis of acute lymphoblastic leukemia: Evidence from Singapore, the United States, and Sweden. Am J Epidemiol. 2005; 162: 753-763.

5. Kroll ME, Draper GJ, Stiller CA, Murphy MFG. Childhood leukemia incidence in Britain, 1974-2000: Time trends and possible relation to influenza epidemics. J Natl Cancer Inst. 2006; 98: 417-420.

6. Pombo-de-Oliveira MS, Koifman S, Brazilian Collaborative Study Group of infant acute leukemia. Infant acute leukemia and parental exposures during pregnancy. Cancer Epidemiol Biomarkers Prev. 2006; 15: 2336-2341.

7. Noshchenko AG, Moysich K, Bondar A, Zamostyan PV, Drosdova VD, Michalek AM. Patterns of acute leukemia occurrence among children in the Chernobyl region. Int J Epidemiol. 2001; 30: 125-129.

8. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology. 1999; 10: 481-487.

9. Wertelecki W, Plato CC, Fraumeni JF, Niswander JD. Dermatoglyphics in leukemia. Pediatr Res. 1973; 7: 620-626.

10. Oorthuys AM, De Vaan GAM, Behrendt H, Caris JA, Lion S, Helsper WM. Dermatoglyphics in childhood leukemia. Birth Defects Orig Artic Series. 1979; 16: 721-735.

11. Mertens A, Wen W, Davies SM, Steinbuch M, Buckley J, Potter L, Robison L. Congenital abnormalities in children with acute leukemia: A report from the Childrens' Cancer Group. J Pediatr. 1988; 133: 617-623.

12. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. Am J Epidemiol. 2002; 155: 603-613.

13. Ludwig WD, Bartram CR, Harbott J, Köller U, Haas OA, Hansen-Hagge T, et al.. Phenotypic and genotypic heterogeneity in infant acute leukemia I. Acute lymphoblastic leukemia. Leukemia. 1989; 3: 431-439.

14. Sreekantaiah C, Han T, Baer MR, Sandberg AA. Acute nonlymphocytic leukemia in a patient with constitutional inv(4). Cancer Genet Cytogenet.1989; 39: 119-123.

15. 15 Knox EG, Marshall T, Barling R. Leukaemia and childhood cancer in twins. J Epidemiol Comm Health, 1984; 38: 12-16.

16. Felix CA. Evidence of early start for common acute lymphoblastic leukaemia. Lancet, 1999; 354: 1486-1486.

17. Witschi E. Overripeness of the egg as a cause of twinning and teratogenesis: A review Canc Res. 1952; 342: 594-598.

18. Mikamo K. Intrafollicular overripeness and teratologic development. Cytogenetics. 1968; 7: 212-233.

19. Butcher RL In: Iffy L and Kaminetzky HA. (eds) Experimentally induced gametopathies. Principles and Practice of Obstetrics & Perinatology. J Wiley & Sons, Ltd, New York. 1981; 339-349.

20. Tarín JJ, Pérez-Albalá S, Cano A. Consequences on offspring of abnormal function in ageing gametes. Hum Reprod. 2000; 6: 532-549.

21. Jongbloet PH. The effects of preovulatory overripeness of human eggs on development. In: Blandau RJ (ed): Aging gametes. Their biology and pathology. International Symposium, Seattle, 1973. Karger, Basel. 1975; 300-329.

22. Jongbloet PH. The ageing gamete in relation to birth control failures and Down syndrome. Eur J Pediatr. 1985; 144: 343-347.

23. Jongbloet PH. Prepregnancy care: Background biological effects. Prepregnancy Care: A Manual for Practice. Chamberlain G, Lumley J (eds) J Wiley & Sons, Ltd. New York: 1986; 31-52.

24. Bomsel-Helmreich O, Gougeon A, Thebault A, Salterelli D, Milgrom E, Frydman R, et al. Healthy and atretic human follicles in the preovulatory phase: Differences in evolution of follicular morphology and steroid content of follicular fluid. J Clin Endocrin Metab. 1979; 48: 686-694.

25. Son WY, Lee SY, Lim JH. Fertilization, cleavage and blastocyst development according to the maturation timing of oocytes in *in vitro* maturation cycles. Hum Reprod. 2005; 20: 3204-3207.

26. van Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, van Zanen GE. Are maternal fertility problems related to childhood leukaemia? Int J Epidemiol. 1985; 14: 555-559.

27. Kaye SA, Robinson LL, Smithson WA, Gunderson P, King FL, Neglia JP. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer. 1991; 68: 1351-1355.

28. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. Int J Epidemiol. 1999; 28: 631-639.

29. Stiller CA. Epidemiology and genetics of childhood cancer. Oncogen. 2004; 23: 6429-6444.

30. Infante-Rivard C, Amre DK. Congenital anomalies in children with acute lymphoblastic leukaemia and their family. Int J Epidemiol. 2001; 30: 350-352.

31. Stams WA, Den Boer ML, Beverloo HB, Meijerink JP, Van Wering ER, Janka-Schaub GE, et al. Expression levels of Tel, AML_1, and the fusion products TEL-AML_1 and AML_1-TEL versus drug sensitivity and clinical outcome in T(12;21)-positive pediatric acute lymphoblastic leukemia. Clin Cancer Res. 2005; 11: 2974-2980.

32. Cheng Q, Cheng C, Crews KR, Ribeiro RC, Pui C-H, Relling MV, et al. Epigenetic regulation of human γ-glutamyl hydrolase activity in acute lymphoblastic leukemia cells. Am J Hum Genet. 2006; 79: 264-274.

33. Wieczorek D, Ludwig M, Boehringer S, Jongbloet PH, Gillissen-Kaesbach G, Horsthemke B. Reproduction abnormalities and twin pregnancies in parents of sporadic patients with oculo-auriculo-vertebral spectrum / Goldenhar syndrome. Eur J Hum Genet. 2007; 121: 369-376.

34. Vianna JV, Polan AK. Childhood lymphatic leukemia: Prenatal seasonality and possible association with congenital varicella. Am J Epidemiol. 1976; 103: 321-332.

35. Meltzer AA, Spitz MR, Johnson CC, Culbert SJ. Season-of-birth and acute leukemia of infancy. Chronobiol Intern. 1989; 6: 285-289.

36. Sørensen HT, Pedersen L, Olsen JH, Rothman KJ. Seasonal variation in month of birth and diagnosis of early childhood acute lymphoblastic leukemia. JAMA. 2001; 285: 168-169.

37. Venners SA, Liu X, Perry MJ, Korrick SA, Li Z, Yang F, et al. Urinary estrogen and progesterone metabolite concentrations in menstrual cycles of fertile women with non-conception, early pregnancy loss or clinical pregnancy. Hum Reprod. 2006; 21: 2272-2280.

38. Jongbloet PH. Over-ripeness ovopathy - A challenging hypothesis for sex ratio modulation. Hum Reprod. 2004; 19: 769-774.

39. Stolwijk AM, Straatman H, Zielhuis GA. Jongbloet PH. Seasonal variation in the time to pregnancy: Avoiding bias by using the date of onset. Epidemiology. 1996; 7: 156-160.

40. Smits LJ, Zielhuis GA, Jongbloet PH, Straatman H. Seasonal variation in human fecundability. Hum Reprod. 1998; 13: 3520-3524.

41. Jongbloet PH, Groenewoud HMM, Roeleveld N. Month of birth related

to fecundity and childlessness among contemporary women. Hum Biol. 2007; 79: 479-490.

42. Jongbloet PH. Seasonal fluctuation of pathological and optimum conceptions, maternal subfecundity, gender dimorphism and survival. Colleg Antropol. 1992; 16: 99-107.

43. RoennebergT, Aschoff J. Annual rhythm of human reproduction: II. Environmental Effects. J Biol Rhythms. 1990; 5: 217-239.

44. Lam DA, Miron JA. Global patterns of seasonal variation in human fertility. Ann N Y Sc. 1994; 709: 9-28.

45. Haandrikman K, van Wissen LJ. Effects of the fertility transition in birth seasonality in the Netherlands. J Biosoc. 2008; 40: 655-672.

46. Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H, Engels EA. Birth weight as a risk factor for childhood leukemia: A meta-analysis of 18 epidemiological studies. Am J Epidemiol. 2003; 158: 724-735.

47. Hjalgrim LL, Rostgaard K, Hjalgrim H, Westergaard T, Thomassen H, Forestier E, et al. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. J Natl Cancer Inst. 2004; 96: 1549-1565.

48. van Steensel-Moll HA, Valkenburg HA, Vandenbroucke JP, van Zanen GE. Time space distribution of childhood leukaemia in the Netherlands. J Epidemiol Comm Health. 1983; 37: 145-148.

49. Coebergh JWW, van der Does-van den Berg A, van Wering ER, van Steensel-Moll, Valkenburg HA, van 't Veer MB, et al. Childhood leukaemia in the Netherlands, 1973-1986: Temporary variation of the incidence of acute lymphocytic leukaemia in young children. Br J Cancer. 1989; 59: 100-105.

50. Pallast EMG, Jongbloet PH, Straatman HM, Zielhuis GA. Excess seasonality of births among patients with schizophrenia and seasonal ovopathy. Schiz Bullet. 1994; 20: 269-227.

51. Jongbloet PH, van Soestbergen, M, van der Veen EA. Month-of-birth distribution of diabetics and ovopathy: A new aetiological view. Diab Res. 1988; 9: 51-58.

52. Jongbloet PH, Kersemaekers WM, Zielhuis GA, Verbeek ALM. Menstrual disorders and month of birth. Ann Hum Biol. 1994; 21: 511-518.

53. Jongbloet PH, Groenewoud HMM, Roeleveld N. Seasonally bound ovopathy versus "temperature at conception" as cause for anorexia nervosa and other eating disorders. Int J Eat Disord. 2005; 38: 236-243.

54. Heuch JM, Heuch I, Akslen LA, Kvåle G. Risk of primary childhood brain tumors related to birth characterics: A Norwegian prospective study. Int J Cancer. 1998; 77: 498-503.

55. McNally RJQ, Cairns DP, Eden OB, Alexander FE, Taylor GM, Kelsey AM, et al. An infectious aetiology for childhood brain tumours? Evidence from space-time clusteering and seasonality analyses. Br J Cancer. 2002; 86: 1070-1077.

56. Doblhammer G, Vaupel JW. Lifespan depends on month of birth. Proc Nat Ac Sc. 2001; 98: 2934-2939.

57. Robison LL, Buckley JD, Daigle AE, Wells R, Benjamn D, Arthur DC, Hammond GD. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. Cancer, 1989; 63: 1904-1911.

58. Sato A, Otsu F, Negishi H, Utsunomlya T, Arima T. Aberrant DNA methylation of imprinted loci in superovulated oocytes. Hum Reprod. 2007; 22: 26-35.

59. Murray L, McCarron P, Bailie K, Middleton R, Davey Smith G, Dempsey S, McCarthy A, et al. Association of early life factors and acute lymphoblastic leukaemia in childhood: historical cohort study. Br J Cancer, 2002; 86: 356-361.

60. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am J Epidemiol. 2006; 163: 1091-1100.

61. Poole C, Greenland S, Luetters C, Kelsey JL, Mezei G. Socioeconomic status and childhood leukaemia: A review. Int J Epidemiol. 2006; 35: 370-384.

62. Kuehni CE, Zwahlen M. Commentary: Numerous, heterogenous, and often poor –– the studies on childhood leukaemia and socioeconomic status. Int J Epidemiol. 2006; 35: 384-385.

63. Münster K, Schmidt L, Helm P. Length and variation in the menstrual cycle – A cross-sectional study from a Danish county. Br J Obstet Gynaecol. 1992; 99: 422-429.

64. Power C, Matthews S. Origins of health inequalities in a national population sample. Lancet. 1997; 350: 262-277.

65. Zintzaras E, Koufalis T, Ziakas PD, Rodopoulou P, Giannouli S, Voulgarelis M. A meta-analysis of genotypes and haplotypes of methylenetetrahydrofolate reductase gene polymorphisms in acute lymphoblastic leukemia. Eur J Epidemiol, 2006; 21: 501-510.

66. Jongbloet PH, Verbeek ALM, den Heijer,M, Roeleveld N. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms resulting in suboptimal oocyte maturation: a discussion of folate status, neural tube defects, schizophrenia, and vasculopathy. J Exp & Clin Ass Reprod. 2008; 5: 5-13.

67. Wynn M, Wynn A. No nation can rise above the level of women: New thoughts on maternal nutrition. The Caline Walker Lecture. London: CarolineWalker Trust. 1993: 1-30.

68. Ebisch IMW, Peters WHM, Thomas CMG, Wetzels AMM, Peer PGM, Steegers-Theunissen RPM. Homocysteine, glutathione and related thiols affect fertility parameters in the (sub)fertile couple. Hum Reprod. 2006; 21: 1725-1733.

69. George L, Mills JL, Johansson ALV, Nordmark A Olander B, Granath F, Cnattingius S. Plasma folate levels and risk of spontaneous abortion. JAMA. 2002; 288: 1867-1873.

70. Ren A, Wang J. Methylenetetrahydrofolate reductase C677T polymorphism and the risk of unexplained recuurent pregnancy loss: A meta-analysis. Fertil Steril. 2006; 86: 1716-1722.

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