The evidence that folate deficiency is mutagenic.

In a recent contribution to this journal, Oakley [1] discussed specific vitamins on neuroblastoma and some childhood brain tumors. In the United States, it is the most common tumor in infants with an incidence of 9.1 per million children under the age of 15 years. Multivitamin use during conception has already been shown to reduce the risk of several birth defects like neural tube defects and oral clefts. Besides, there is increasing evidence that maternal multivitamin use has a protective effect on childhood brain tumors and childhood leukemias. Olshan et al. performed an epidemiologic study on maternal vitamin use and neuroblastoma as part of a large study to identify risk factors for neuroblastoma.

Cases were children diagnosed with neuroblastoma over the period May 1, 1992, to April 30, 1994, at Children's Cancer Group and Pediatric Oncology Group institutions throughout the United States and Canada. One matched control (by date of birth) was selected using random-digit dialing. Thus households were screened for individuals with dates of birth close to cases. To identify 504 control mothers, almost 30,000 households were screened. Telephone interviews were performed on 538 case and 504 control mothers with questions on the frequency and duration of vitamin use during the year before pregnancy, the month before pregnancy, and during the first, second, and third trimesters of pregnancy. The authors also evaluated the heterogeneity of the effect for child's age at diagnosis (comparing the effects of vitamins in children diagnosed <1 year, 1–3 years, and >3 years) and amplification of the MYCN oncogene. MYCN amplification may identify a genetically distinct subgroup of neuroblastoma that might be relevant to etiology. Furthermore, they performed a set of analyses that restricted vitamin use only to those vitamin preparations with 0.4 mg or more of folic acid.

Women who were daily vitamin users during that entire period had an adjusted odds ratio (OR) of 0.6 (confidence interval, CI = 0.4–1.0) as compared to women who did not use any vitamins. Daily vitamin use in the month before pregnancy as well as in each trimester was associated with a 30–40% reduction in the risk of neuroblastoma. Analysis of the specific periods showed that daily multivitamin use resulted in ORs of 0.7 (CI = 0.5–1.1), 0.7 (CI = 0.5–1.0), 0.6 (CI = 0.4–0.9) and 0.6 (CI = 0.4–0.9) for the month before pregnancy and the first, second, and third trimesters, respectively. No association was found for less often than daily use of multivitamins in the period 2–12 months before pregnancy (OR = 1.1; CI = 0.6–1.8). In the other periods, less often than daily use resulted in ORs of 0.6–1.0, but mostly with nonsignificant CIs, except for the first trimester. Eighty-three percent of cases and 88% of controls reported any use of multivitamins from the month before pregnancy through birth. The authors were unable to isolate the effects of specific vitamins or minerals. For those vitamin preparations with 0.4 mg or more of folic acid, the results were very similar to the general results. Neither age at diagnosis nor MYCN oncogene amplification status materially altered the results.

Comments

Olshan et al. managed to perform a huge telephone study and the results suggest an association between maternal multivitamin use during pregnancy and reduced risk of neuroblastoma. As the study was retrospective, study limitations are potential exposure misclassification, selection bias and recall bias. The questionnaire did not include information on dietary intake of vitamins. In their search for environmental exposures related to the risk of neuroblastoma, they obtained valuable data. There is a high correlation of vitamin use among the various periods, so conclusions on the time period of the protective effect are hard to make. The authors were able to estimate the effect of starting daily vitamin use in the second trimester (OR = 0.7; CI = 0.4–1.4), but no data were available for the effect of using multivitamins during the first or third trimester only. The recommended period for using folic acid to reduce the risk of neural tube defects is 1 month before and 3 months after conception. On the one hand, the data of Olshan et al. suggest that a complementary protective effect of multivitamin use for a longer period than this period can be expected. On the other hand, the data suggest that even starting multivitamin use in the second or third trimester reduces the risk of neuroblastoma. Knowledge about the influence of specific vitamins and minerals would be of great value. Like the authors mentioned, additional research is warranted on the biological effect of specific vitamins on neuroblastoma and some childhood brain tumors. In a recent contribution to this journal, Oakley [1] discussed the evidence that folate deficiency is mutagenic.

Reference

People with Down Syndrome Live Longer

The article describes a study based on a continuous cohort of 1,332 people with Down syndrome in Western Australia. The aim of the study was to provide an update on the life expectancy of individuals with Down syndrome, differentiating by gender, level of intellectual disability, and year of birth, as little is known about Down syndrome patients throughout their life span and especially to advanced age.

In Western Australia, all people who need intellectual disability services have been registered since 1953. These computerized records were linked to four state-based health registers: Mortality registrations (since 1969), the Hospital Morbidity database (since 1970), the Cancer Registry (since 1982), and the Mental Health Register (since 1966). All people with Down syndrome registered for intellectual disability services between 1953 and 2000 and in contact with the intellectual disability services within the past 10 years, or who were recorded in the linked data sets were included (n = 1,332). The age at registration varied between 0 and 61 years with a median registration age of 1 year.

For these 1,332 Down syndrome patients, Kaplan-Meier survival probabilities were calculated. Survival rates were calculated for the whole group, and for gender, level of cognitive impairment and decade of birth, separately. Groups were compared using log rank tests.

The median life expectancy for the cohort studied was 58.6 years. According to the Kaplan-Meier analysis, 75% survived to 50.0 years of age and 25% to 62.9 years of age. Males lived on average 3.3 years longer than females, with median survival probabilities of 61.1 years for males and 57.8 years for females. The median survival probability increased by decade of birth. No significant relation was found for the level of cognitive impairment.

Comments

The increasing life expectancy of Down syndrome patients has several important implications. The information is important for parents and relatives taking care of Down syndrome patients, who may not be able to care for the patients during their entire life. Information given to parents of Down syndrome patients diagnosed prenatally may influence the reproductive choice.

Furthermore, the tendency to have pregnancies at more advanced maternal age, as is the case in many European countries, may result in an increased birth prevalence of Down syndrome in live births, as the use of prenatal diagnosis remains stable. This, in combination with the increasing life expectancy of Down syndrome patients, has important implications for the future health costs of Down syndrome patients, as adult Down syndrome patients show important health problems such as Alzheimer dementia, diabetes mellitus and cancer which result in increased medical costs.

It remains unclear how many Down syndrome patients were not registered for intellectual disability services, and therefore excluded from this study. The mentioned age at registration between 0 and 61 years suggests that not all Down syndrome patients were included, and the younger they died the higher the chance that they were not registered. The number of 1,400 registered Down syndrome patients (the studied cohort of 1,332 patients and the 68 excluded cases) in a 47 years’ registration period seems somewhat low. Assuming 250,000 annual births in Australia, at least 11,750 Down syndrome patients should have been born in a period of 47 years with a birth prevalence of Down syndrome of 1 per 650–1,000 live births. Unfortunately, no data about the number of annual births in Western Australia were given.

In the studied population, approximately 25% of all Down syndrome deaths occurred between 58.6 and 62.9 years of age. More than 75% of the studied population was still below that age, and approximately half of the studied cohort was still below 20 years of age. It would be interesting to know whether the high percentage of deaths around 60 years of age will also occur in the later birth cohort. The increased survival in the first years of life is explained by the improved medical treatment of cardiac anomalies. However, the diseases presenting later in life, may be more difficult to cure and/or treat.

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Countrywide Second-Trimester Down Syndrome Screening in France

Prenatal diagnosis of Down syndrome is based on fetal karyotyping. Because of the costs and risks associated with fetal tissue sampling, it is limited to patients at increased risk. Maternal age, nuchal translucency and maternal serum markers are some of the criteria. In France, a 9-year debate about the ethical aspects of prenatal screening resulted in specific legislation: every pregnant woman is offered prenatal screening for Down syndrome.

For this study, all 60 laboratories accredited in maternal serum marker screening were sent a questionnaire about the method of screening, the number of patients screened, the number of patients identified in the high-risk group, the number of fetuses with Down syndrome detected by prenatal screening, and those diagnosed at birth or later.

All patients that have been screened in France over the years 1997 and 1998 were included in this study. During these years, 854,902 (58.6%) of approximately 1,460,000 pregnant women un-
derwent maternal serum trisomy 21 screening. The used cutoff value was 1 in 250. The positivity rate increased with maternal age: 3.9% for patients under 30 years, 8.2% for patients aged 30–34 years, and 26.8% for patients aged 35–37 years. Of the 837,765 patients under 38 years of age, 54,321 (6.5%) were at an increased risk. Amniocentesis was performed in 95% of the patients at risk. Among these patients, 884 fetuses or children with Down syndrome were found (prevalence: 1 in 950). Of these cases 70.8% were detected by maternal serum screening followed by amniocentesis. To detect one case of trisomy 21, 87 karyotypings were necessary (positive predictive value: 1 in 87). From the 13,891 patients aged 38 years and older, 34% were identified to be at risk. The detection rate was 98.9% with a positive predictive value of 1 in 52. Overall, 72% of the population screened for Down syndrome was also screened for neural tube defects, based on AFP values >2.5 MoM. Of these patients, 1% was screened positive. There were 178 cases identified, indicating a 1 in 52 positive predictive value.

Muller et al. conclude that the strict French rules on prenatal screening are of benefit to patients, practitioners and laboratories, ensuring a high Down syndrome detection rate and a low amniocentesis rate.

Comments

This large second-trimester serum screening study is the only one covering a whole country. The large number of women included provides reliable estimates. This study also provides a relatively high detection rate, which is probably due to the frequent use of ultrasound to determine gestational age.

However, screening involves more than just numbers. For instance, the study does not provide any data on how the results of the screening test were presented to the pregnant women. Whereas we know that the way in which information (e.g. risks) is given to a person, significantly affects how the person perceives that condition or risk [1]. So, in what way were the prenatal tests offered to the pregnant women? In what way were the results of the tests presented to them? In odds, or just ‘increased’ or ‘not increased’?

Of the patients under 38 years of age, 6.5% are ‘at-risk’. Of these women, 95% underwent amniocentesis. However, Muller et al. do not give the number of iatrogenic abortions. When we estimate the miscarriage rate induced by the amniocentesis at 1% [2], approximately 516 (mainly healthy) pregnancies have been terminated by this screening strategy, while still 258 cases of Down syndrome were not detected. So, to detect 626 cases of Down syndrome, 516 ‘normal’ pregnancies have been lost, and 258 cases of Down syndrome still were not detected. The results put into this perspective, raise the following ethical dilemma: is prevention of the live birth of 626 children with Down syndrome, worth the abortion of so many ‘normal’ fetuses? That French obstetricians and midwives indeed face complex ethical problems raised by prenatal screening, prenatal diagnosis, and termination of pregnancy is also the conclusion of Garel et al. [3].

Finally, it can be questioned why these pregnant women are supposed to be patients. The authors consistently use the term ‘patient’. Do they see pregnancy as an illness, as a medical problem, or is this terminology an exponent of the medicalisation of pregnancy?

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References