



Surveillance of Neural Tube Defects in Israel: the Effect of the Recommendation for Periconceptional Folic Acid

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Abstract

Background: Open neural tube defects are among the most common severely disabling birth defects. Secondary prevention by early diagnosis during pregnancy and abortion of affected fetuses lead to a marked reduction of NTD incidence at birth. For primary prevention of these defects, in August 2000 the Israel Ministry of Health issued guidelines recommending a daily 0.4 mg folic acid supplement for all women in their childbearing years with special emphasis on the 3 months preceding conception and the first trimester of pregnancy.

Objectives: To compare the epidemiologic characteristics of NTD in Israel before and after the guidelines for folic acid supplementation.

Methods: A national registry of NTD was begun in 1999. Since the Ministry of Health published the recommendation for folic acid supplementation in mid-2000, the years 1999–2000 represent the status prior to the recommendation and the years 2002–2004 the status after.

Results: A marked decline in the rate of spina bifida was observed in the last 3 years (from 4.9 to 2.7 per 10,000 live births among Jews and 9.5 to 6.2 among Arabs and Druze). There was no apparent reduction for anencephaly.

Conclusions: Following the Ministry of Health guidelines on folic acid supplementation for women in the reproductive age, a marked reduction in the rates of NTD was observed. In light of this apparent success, continuous efforts should be made to increase the percentage of women taking the supplementation and, especially, to introduce folic acid fortification.

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termination of affected pregnancies. The studies of Smithells et al. [2], confirmed by other clinical trials, showed that supplements containing folic acid, when consumed by women before conception, could reduce the rates of neural tube defects. Accordingly, professional organizations and governmental agencies promoted the use of folic acid supplements before and during pregnancy to prevent neural tube defects. In some countries like the United States and Canada, the recommendations of supplementation are integrated with a policy of folic acid food fortification [3]. In Israel, the Public Health services in the Ministry of Health issued a circular in August 2000 containing guidelines with recommendations for 0.4 mg folic acid supplement in the preconceptional period and during pregnancy [4]. The subject was also introduced by a campaign to doctors and nurses in the well-baby clinics run by the Ministry of Health and to the four health management organizations, various professional organizations, and the public via the media [5]. Although most cereals for breakfast in Israel as well as a few types of bread are fortified also with folic acid, fortified foods represent only a small part of the diet of the majority of the population [6].

Data on the total rates of NTD (including those of terminated pregnancies) in Israel have been available since 1999 when a national registry of NTD was initiated [7]. The registry therefore includes data before and after the recommendations on folic acid supplementation, allowing monitoring and evaluating the implementation and outcome of the project.

Subjects and Methods

Reporting newborns with malformations is obligatory in Israel; the registration uses the child's ID number. In 1999 all the medical units involved in the diagnosis of NTD either during pregnancy or at birth were informed of the establishment of a national registry and were asked to participate. The major participants came from the hospitals' ultrasound units, genetic units, triple test laboratories, and departments of pathology. In addition, data were extracted from the National Registry of Malformations for live-born as well as stillborn infants. Many of the cases were reported twice or more to the NTD registry, however the ID numbers prevented multiple entries of cases.

While the registry includes syndromic NTD the data presented

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Open neural tube defects are among the most common severely disabling birth defects [1]. A general declining trend in the incidence of NTD at birth has been observed in many countries because of a primary prevention causing reduction in the total incidence and/or due to secondary prevention by screening and

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NTD = neural tube defects

here refer only to non-syndromic NTD, and were categorized in four groups: anencephaly, spina bifida, encephalocele, and unknown. The cases were classified according to the ethnic religious affiliation of the parents. The major religious groups in the Israeli population are Jews (81%), Muslim Arabs (15%), Christian Arabs (2%), and Druze (2%) [8]. The newborn population in 1999–2000 comprised 69.1% Jews, 26% Muslim Arabs, 2.1% Christians and 2% Druze.

Because the recommendations for preconceptional supplementation with folic acid were issued in mid-2000, the first weeks of the pregnancies that ended in 1999 and 2000 preceded publication of these guidelines. The pregnancies ending in 2002–2004 were after the recommendations. The year 2001 includes pregnancies whose first weeks were both before and after the recommendations and the data for 2001 were therefore not included in the comparisons.

Fluctuations in the rates of NTD are observed in all populations, often without apparent causes. In order to minimize the fluctuation in rates observed from year to year for the analyses, the data were grouped as before the recommendation for supplementation (1999–2000) and after supplementation (2002–2004). In addition, no statistical analysis was performed and the results are presented as pointing to a trend.

Results

The total numbers of NTD were stable in 1999 and 2000 and a decline occurred from 2002 [Table 1]. The mean total number of NTD was 103 for Jews and 93 for non-Jews in 1999–2000, and declined to 81 for Jews and 74 for non-Jews in 2002–2004. During the years the rate of pregnancy terminations for neural tube defects remained in similar ranges for the various ethnic groups: significantly higher for Jews (range 69–79%) than for Arabs and Druze (range 40–56%).

From the analyses of data grouped as before the recommendation for supplementation (1999–2000) and after supplementation (2002–2004) the trend was to a reduction in NTD rates [Table 2]. The NTD rates in the period 2002–2004 declined as compared to 1999–2000 in the two religious groups: from 11.7 to 8.1 per 10,000 live births among Jews (31% decline) and from 22 to 16.7 per 10,000 live births among non-Jews (24% decline). The reduction was from 21.1 to 18 per 10,000 live births among Druze and 16 to 8.8 per 10,000 among Muslims not including the Bedouins. Almost no changes were observed among the Christians, and in the Bedouin subgroup of Muslim Arabs there was even an elevation in the rates from 25 to 28 per 10,000 live births.

The main change observed was a reduction in the rates of spina bifida [Table 3] – from 4.9 to 2.7 per 10,000 live births among Jews (44% decline) and 9.5 to 6.2 per 10,000 live births among Arabs and Druze (34.4% decline). There was almost no change in the rates of anencephaly in both groups: from 5.3 to 4.9 per 10,000 live births among Jews and 8.9 to 8.2 per 10,000 live births among Arabs and Druze.

Discussion

Open neural tube defects are among the most common severely disabling birth defects [1]. In Israel it has been demonstrated

Table 1. Neural tube defects per year among Jews, Arabs and Druze*

	1999	2000	2001	2002	2003	2004
Jews	24/99 (76%)	31/107 (71%)	31/99 (69%)	19/73 (74%)	18/87 (79%)	25/84 (70%)
Arabs and Druze	47/92 (51%)	49/94 (52%)	58/96 (40%)	38/80 (53%)	34/77 (56%)	32/71 (55%)

* For each year, the numbers in the table are the number of children born with NTD (live births + stillbirths)/total numbers of NTD. Stillbirths refer to intrauterine deaths only and do not include late terminations of pregnancies
Numbers in parentheses are the percentages of NTD in which the pregnancy was medically interrupted

Table 2. Rates of NTD* in the different religious groups (per 10,000 live births)

	Jews	Christians	Druze	Muslims**	Bedouins
1999-2000	11.7	12	21.1	16	25
2002-2004	8.1	11	18	8.8	28

* Including all the NTD

** Not including Bedouins

Table 3. Rates of NTD per 10,000 live-births at different time periods

	1958-1968	1999-2000	2002-2004
Jews			
Anencephaly	8.6	5.3	4.9
Spina bifida	6	4.9	2.7
Total*		11.7	8.1
Arabs and Druze			
Anencephaly		8.9	8.2
Spina bifida		9.5	6.2
Total*		22.0	16.7

* Including all the NTD

that the prevalence is particularly high among Muslim Arabs and Druze [7]. The disparities between the different religious groups probably represent a combination of genetic differences with environmental and cultural factors. The living conditions of the Bedouins in the Galilee are close to those of the other Muslims in the region but mostly different from the Bedouins in the Negev Desert. However, a similar high prevalence of NTD is observed among the Bedouins living either in the Galilee or in the Negev.

In Israel most NTD are diagnosed during pregnancy, and between 40% and 79% are terminated [Table 1]. Therefore, while in the past, Israeli surveys of the NTD prevalence were performed at birth, nowadays it is imperative that such surveys include also termination of pregnancies. A comparison of the NTD rates among Jews in 1958–1968 at birth [9] with those from 1999–2000 including termination of pregnancies revealed a 20% decline (from

14.6 to 11.7 per 10,000 live births) [Table 3]. Since complete data were not available for the 30 year period between the two surveys, it is difficult to determine whether the decline was progressive or occurred only in recent years. However, the national registry shows that the number of cases of NTD was very stable for 3 years prior to publication of the new recommendations, i.e., from 1999 to 2001, in Jews as well as Arabs and Druze. A decline in NTD rates was observed beginning in 2002. From 1999–2000 to 2002–2004 the total rates declined by 31% among Jews (11.7 to 8.1 per 10,000 live births). In the same periods a 24% decline was observed among Arabs and Druze (from 22 to 16.7 per 10,000 live births). The reduction in NTD rates occurred in each religious group, except for the Bedouins in the Muslim group (respectively 25 and 28 per 10,000 live births). The observation that the decline in NTD rates occurred in all religious groups supports the assumption that the reduction is not an artifact such as lower reporting in recent years. The decline was noted in both registries – stillbirth and live-born, while the data for each were obtained from independent sources. In addition, a 30% decline in the number of pregnancy terminations due to NTD was observed in recent years (Central Bureau of Statistics, unpublished data). It should be emphasized that reports of pregnancy termination including its indication is obligatory by law; however, since the data are collected anonymously they are not used in our registry. The observation of a significant decline in NTD obtained from several independent sources supports the assumption that the decline in the NTD rates is real.

In parallel to the recommendations for folic acid supplementation, several surveys were conducted on awareness, knowledge and practice of folic acid consumption in pregnant women in Israel, demonstrating significant changes in the habits of the population. In 2000, before the recommendation, only 17.6% of the women knew about the effects of folic acid, and 5.2% took it as recommended; 2 years later the numbers rose to 77.7% and 30.5% respectively [5]. The preliminary results of a similar survey in 2005 indicate a further rise in the preconceptional use of folic acid to 35%. Therefore, the observations of stable rates in the years preceding the recommendation and the progressive decline in NTD rates accompanying both the increased knowledge of women on the importance of folic acid and the increased intake suggest that a direct link exists between the two.

Another observation supporting the effect of folic acid is that the most significant decline (31%) occurred among Jews, who also had the highest consumption of folic acid (34.8%). Among Arabs and Druze there was a 24% decline in NTD and the folic acid consumption was 21.2%. As already mentioned there were no changes in the rates of NTD among the Bedouin. Since data on their folic acid consumption are insufficient it cannot be determined whether this is due to the low intake or to differences in genetic background resulting from consanguineous marriages in the community.

An intriguing observation from other studies as well is that the reduction in NTD rates is more significant for spina bifida than for anencephaly in all religious groups. In the 3 years following the recommendation a 41% reduction occurred among

Jews (from 4.9 to 2.7 per 10,000 live births) and 35% among non-Jews (from 9.5 to 6.2 per 10,000 live births). Changes in the rates of anencephaly were minimal among both Jews (from 5.3 to 4.9 per 10,000 live births) and non-Jews (from 8.9 to 8.2 per 10,000 live births). One possible explanation may be the use in recent years of the nuchal translucency test for Down syndrome screening, whereby anencephaly can be diagnosed very early in pregnancy. Many of these early-affected pregnancies would otherwise have been spontaneously aborted and not diagnosed. This early ultrasonographic diagnosis led to an increase in the total numbers of anencephaly in recent years, masking in part the reduction. However, this explanation accounts for only a small portion of the difference in the decline of rates between anencephaly and spina bifida. Another possible explanation is that higher amounts of folic acid are needed to prevent the more severe defects [10]. A third possibility, namely, that anencephaly is more sensitive than spina bifida to folic acid, may also be raised. Already before the folic acid recommendation a 35% decline in the rates of anencephaly was noted among Jews, while for spina bifida the reduction was only 18%. It may well be that socioeconomic changes in Israel in the period between the two surveys, with concomitant improvement in diet before and during pregnancies led to a drastic reduction in the rates of anencephaly and a moderate reduction in spina bifida. Only with the folic acid supplement did a significant reduction occur in the rates of spina bifida while the reduction in anencephaly was moderate. Similar observations were made in the U.S. [11,12]; however, in Ireland for instance a significant decline occurred in the 15 years preceding the folic acid recommendation both for anencephaly and spina bifida [13]. In Chile, a third type of observation was made – no changes in NTD rates before folic acid supplementation, whereas afterward a decline occurred in both malformations [14]. It is possible that in those populations different nutritional status, socioeconomic conditions as well as genetic background contribute to these diverse observations.

In a recent study covering birth defect registries from various countries and including a total of more than 13 million births, there was no detectable change in NTD rates associated with recommendations to consume folic acid [15]. Either the rates were unchanged or the rate of decline was similar to that observed during the period before the recommendations. The authors attributed this to the fact that the recommendations were not effectively implemented and therefore did not induce a sustained change in behavior in a sufficiently large proportion of women to cause measurable effects. The present study confirms other observations that if the recommendations are accompanied by effective implementation leading to an increase in the intake of folic acid, the supplementation is effective in reducing the NTD rates.

However, to a certain degree, it is very difficult or even impossible to increase the rate of utilization of folic acid supplements [16]. Therefore, the next step should be mandatory food fortification, the success of which has been demonstrated in various countries [17]. The importance of food fortification in Israel has been emphasized and planned in parallel with the effort

to increase folic acid intake [6,18]. However, several unexpected events slowed the process and general folic acid fortification has not yet been implemented.

In light of the apparent success of folic acid in reducing NTD rates in the different communities living in Israel, continuous efforts should be made to increase the percentage of women taking the supplementation and, particularly, to institute folic acid fortification.

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