**Surveillance of Neural Tube Defects in Israel**

Joël Zlotogora MD PhD, Yona Amital MD, Dorit Nitzan Kaluski MD MPH RD and Alex Leventhal MD MPH MPA
Public Health Services, Ministry of Health, Israel

**Key words:** neural tube defect, spina bifida, anencephaly, encephalocele, folic acid

---

**Abstract**

**Background:** Open neural tube defects are among the most common malformations of the fetus. Secondary prevention by early diagnosis during pregnancy and abortion of affected fetuses resulted in a marked reduction of NTD incidence at birth. The dramatic effect of folic acid for primary prevention of these defects led to recommendations for folic acid supplementation in women of reproductive age.

**Objective:** To describe the epidemiologic features of NTD in Israel in 1999–2000.

**Methods:** A national registry of NTD was begun in 1999. During the years 1999–2000, a non-syndromic NTD was diagnosed in at least 394 pregnancies (166 anencephaly, 166 spina bifida, 43 encephalocele, and 19 with other types of NTD). The religious-ethnic affiliation was known in 392 cases (209 Jews and 183 non-Jews).

**Results:** Despite a marked decline in the rate of NTD at birth in the last few decades, the total rates during pregnancy did not change significantly, demonstrating that the changes were secondary to termination of affected pregnancies. At birth, NTD were almost four times more frequent among non-Jews (3.6 per 10,000 live births for anencephaly and 5.9 for spina bifida) than among Jews (anencephaly 1/10,000 live births, spina bifida 1.4/10,000 live births). The complete data of the registry showed an approximately twofold difference in the overall rates during pregnancy between Jews (anencephaly 5.3, spina bifida 4.6, total 11/10,000 live births) and non-Jews (anencephaly 8.8, spina bifida 10.3, total 22.3/10,000 live births). The registry demonstrated that the significant differences in NTD incidence observed at birth between Jews and non-Jews are secondary to a combined effect of a higher frequency of the malformations among non-Jews and a lower proportion of termination of affected pregnancies among non-Jews.

**Conclusions:** The data presented here will serve as a basis for evaluating the impact of the Ministry of Health recommendations for folic acid supplementation on the incidence of NTD.

IMAJ 2002:4:1111–1114

---

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 due to a primary reduction in the total incidence and/or the interruption of affected pregnancies.

In Israel, the rate of NTD at birth declined markedly in the last few decades (Ministry of Health). However, no data are available for the total incidence since the end of the 1980s. With the introduction of a national program for the promotion of folic acid supplementation and fortification, the creation of a national registry for NTD became of utmost importance to determine the basic rates of NTD and the effects of the interventions. In 1999 a national registry of NTD was initiated with the active help of many physicians involved in their diagnosis and/or treatment. The data from the first 2 years are presented here.

**Methods**

At the beginning of 1999 all the medical units involved in the diagnosis of NTD either during pregnancy or at birth were informed about the establishment of a national registry and were asked to participate. The major participants were hospital ultrasound units, genetic units, triple-test laboratories, and pathology departments. In addition, data were extracted from the National Registry of Malformations in liveborn and stillborn. While most of the reports in 1999 were obtained retrospectively at the end of the year, those from 2000 were often reported by means of a questionnaire completed at the time of diagnosis to obtain more information.

The registry includes only open NTD, and those were categorized into four groups: anencephaly, spina bifida, encephalocele, and others. The cases were classified according to the ethnic religious affiliation of the parents. In 1999, the major religious groups in the Israeli population comprised Jews (81%), Moslem Arabs (15%), Christian Arabs (2%), and Druze (2%) [2]. Among the newborns in 1999–2000 with known religious affiliation, 69.1% were Jews, 26% Moslem Arabs, 2.1% Christians, and 2% Druze.

**Results**

In addition to the data from existing national registries, data were obtained from at least one source at each of the hospitals in Israel, resulting in most of the cases being reported twice to the NTD registry, some even more.

During the years 1999–2000, of the 401 NTD cases registered (167 anencephaly, 167 spina bifida, 43 encephalocele, and 19 with other malformations), NTD was part of a syndrome in 7. Anencephaly and open spina bifida were rarely associated with syndromes (one case of anencephaly with frontonasal dysplasia and one case of spina bifida with triploidy), while encephalocele was more often part of a syndrome—Meckel syndrome (two cases), and Warburg syndrome, trisomy 13, and unknown syndrome (one case each). Among the 394 cases of non-syndromic NTD, associated malformations were present in 13 cases (9 with open spina bifida). Most of the malformations were among those considered as midline malformations: cleft lip/palate (n=3), omphalocele (n=2), cloacal exotropia (n=2), heart malformation (n=2), caudal regression (n=1), imperforate anus (n=1), vertebral fusion (n=1), and renal agenesis (n=1). The data presented thereafter refer to the 394 non-syndromic NTD.

NTD = neural tube defects
Gender of those affected
Of the 156 cases in which the gender of the affected was known, 97 were females (ratio males:females 0.4). Females predominated in anencephaly (35/58), spina bifida (35/58) and encephalocoele (9/13).

NTD incidence by type of NTD and patients' origin [Tables 1-3]
The religious affiliation was known in 392 cases (209 Jews and 183 non-Jews). At birth, open NTD rates were almost four times more frequent among non-Jews (3.6 per 10,000 live births for anencephaly and 5.9 for spina bifida) than among Jews (anencephaly 1/10,000 live births, spina bifida 1.4/10,000 live births). The complete data of the registry revealed an approximately twofold difference in the overall rates during pregnancy between Jews (anencephaly 5.3, spina bifida 4.6, total 11/10,000 live births) and non-Jews (anencephaly 8.8, spina bifida 10.3, total 22.3/10,000 live births). When the non-Jewish population was separated according to ethnic religious criteria [Table 3], the highest rates of NTD were observed among Moslem Arabs (anencephaly 9.3, spina bifida 11, total 23.5/10,000 live births) and Druze (anencephaly 11.3, spina bifida 7.6, total 20.8/10,000 live births). Among the Christian Arabs the numbers are small but the rates were lower than those in the Jewish population (anencephaly 1.8, spina bifida 5.3, total 7.3/10,000 live births).

Termination of pregnancies
Pregnancies with anencephaly were terminated more often than pregnancies with spina bifida or encephalocoele. For each of the

Table 4. NTD total rates per 10,000 live-births

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Jews</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anencephaly</td>
<td>8.6</td>
<td>7.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>6</td>
<td>3.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Non-Jews</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anencephaly</td>
<td>12.2</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Spina bifida</td>
<td>8</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>22.3</td>
<td></td>
</tr>
</tbody>
</table>

malformations the rate of pregnancy termination was higher among Jew than among non-Jews. For anencephaly the rates of termination were 90% among Jews and 59% among non-Jews, and for spina bifida 73% and 43% respectively. In the case of encephalocoele, the rates of termination were 75% among Jews and 57% among non-Jews.

Significant differences were observed in the gestational age at the time of termination according to the type of malformations. In approximately 90% of the anencephaly cases and 65% of the spina bifida cases that were aborted, pregnancy termination was performed before the 23rd week of gestation. Of the total number of pregnancies for which data were available, about 37% (48 of 131) were terminated before the 17th week of gestation. The cases of anencephaly were most commonly diagnosed by early ultrasound (35 of 48). Most of the cases interrupted after the 23rd week of gestation were either missed by the maternal serum alphafetoprotein screening or were due to lack of maternal participation in the screening program. Among those cases most were spina bifida (20/26).

NTD and multiple gestations
Among the 394 cases, the pregnancy was multiple in 25 (7 triplets). A significant difference was observed between the two groups: in 21 of 205 cases among Jews the gestation included more than one fetus (10%) as compared to 4 of 181 cases among non-Jews (2.3%); all the triplet gestations were among Jews.

Discussion
Since 1995 all Israeli residents are covered by national health insurance. During pregnancy this includes at least one ultrasound examination and a triple test as well as amniocentesis for women older than 35. Overall, while most of the pregnant women utilize the basic services offered by the general health insurance, a non-negligible group of residents – either foreign workers and their families or Arabs from the Palestinian Authority – do not use these services. In addition, a significant portion of the Israeli population, particularly in the highest socioeconomic groups, utilizes more services during pregnancies, especially early detailed ultrasound screening examinations.

In Israel, the law authorizes abortions for major malformations at all stages of the pregnancy subject to the decision of a hospital committee. However, this option is often not compatible with the patient's religion. For instance, according to Halakha (Jewish Law),

Table 1. NTD among Jews at birth/total

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>10/50</td>
<td>8/46</td>
<td>18/96</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>9/33</td>
<td>16/50</td>
<td>24/83</td>
</tr>
<tr>
<td>Encephalocoele</td>
<td>3/12</td>
<td>4/9</td>
<td>7/21</td>
</tr>
<tr>
<td>Total*</td>
<td>22/101</td>
<td>28/108</td>
<td>49/209</td>
</tr>
</tbody>
</table>

* Including other NTD.

Table 2 NTD among non-Jews at birth/total

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>12/51</td>
<td>17/41</td>
<td>29/72</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>26/66</td>
<td>22/38</td>
<td>48/84</td>
</tr>
<tr>
<td>Encephalocoele</td>
<td>6/12</td>
<td>5/9</td>
<td>11/21</td>
</tr>
<tr>
<td>Total*</td>
<td>44/94</td>
<td>44/89</td>
<td>88/183</td>
</tr>
</tbody>
</table>

* Including other NTD.

Table 3. Rates of NTD in the different religious groups (per 10,000 live births)

<table>
<thead>
<tr>
<th></th>
<th>Jews</th>
<th>Moslems</th>
<th>Druze</th>
<th>Christians</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of live births</td>
<td>181,307</td>
<td>70,140</td>
<td>5,285</td>
<td>5,472</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>53</td>
<td>9.3</td>
<td>11.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>4.6</td>
<td>11</td>
<td>7.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Total*</td>
<td>11</td>
<td>25.5</td>
<td>20.8</td>
<td>7</td>
</tr>
</tbody>
</table>

* Including other NTD.
abortion is allowed only within the first 40 days of pregnancy; thus, among Orthodox Jews, who represent some 40% of the pregnant women in the Jewish sector, this is often not an option. According to Islamic Law, abortions are either not permitted or are allowed only within the first 120 days of gestation if the fetus is diagnosed with a severe disease or malformation [3]. Since most of the Moslem Arab population in Israel is religious or traditional, interruption of the pregnancy after the 17th week is often not an option. The religious/traditional influence on the rate of utilization of prevention programs is evident in women older than 35, who are offered amniocentesis free of charge. In this group, some 65% of the Jewish women and less than 15% of the non-Jewish women underwent prenatal diagnosis when the indication is age only (unpublished observations).

We assume that the registry includes most cases of NTD, since reports were obtained from several independent sources and the numbers were stable during the 2 years of the study. Moreover, the numbers presented here underestimate the real situation. Comparing the data from previous surveys with the data presented here reveals a significant decline in the rate of anencephaly at birth both among Jews (7.9–1/10,000 live births) and non-Jews (12.2–3.6/10,000 live births) [4–6]. A parallel observation was made for spina bifida, although the reduction was less significant (from 3.1 to 1.4 among Jews and 8 to 5.9 among non-Jews). From the complete data of the registry in 1999–2000, it is evident that the major cause for the reduced incidence of malformations at birth was prenatal diagnosis and pregnancy termination. The rates of NTD pregnancy termination were significantly lower in the non-Jewish population (59% for anencephaly, 43% for spina bifida, and 57% for encephalocele). The differences in the utilization of pregnancy termination accentuated the difference in the malformation incidence, and at birth the ratio between Jews and non-Jews was almost 4:1. Furthermore, among Jewish pregnant women, since the estimated proportion of Orthodox and Ultra-Orthodox (who in most cases will not abort a fetus with an open spina bifida or encephalocele) is 25%, the abortion rates for spina bifida (73%) and encephalocele (73%) imply very high detection rates for these malformations during pregnancy. For anencephaly the abortion rates were even higher (90%), which can be attributed to the authorization to abort very severely affected fetuses even among Ultra-Orthodox Jews, in addition to a high diagnostic rate. Such high rates of pregnancy termination, particularly in the Jewish sector, clearly demonstrate that in order to be relevant, any surveillance program for severe malformations must include complete data on abortions.

A significant difference was observed between the incidence of NTD among Jews and non-Jews. The total rates of anencephaly, spina bifida and encephalocele were approximately twice as high among non-Jews as among Jews. While there are many differences between the two communities, including socioeconomic factors, fertility index and others, the introduction of the new health insurance law in 1995 rendered the differences in the availability of health services less significant. A major difference between the Jewish and non-Jewish population in Israel is the rate of consanguinity. In the last few decades consanguineous marriages have become rare in the Jewish population, whereas in the non-Jewish population they are frequent. The rates of consanguineous marriages are highest among the Moslem (42%) and Druze communities (47%), but significantly lower among Christian Arabs (22%) [7]. As a direct consequence, genetic disorders are more frequent in the non-Jewish population, which may partly explain the different NTD rates between the religious communities, with the highest incidence observed in both Moslems and Druze – groups with the highest rates of consanguinity. In addition to genetic syndromes, which explain a few of the cases, the possible genetic factors that may be responsible for the higher frequency of non-syndromic NTD among non-Jews have not been identified. Although some studies have assessed the frequency of the C677T MTHFR mutation, which is relatively frequent among Jews (44% among Ashkenazi) and Moslem Arabs (33%) [8], to our knowledge no studies have yet been undertaken on the allele frequencies in families with NTD.

An additional finding of our study was a very high NTD rate in twin or triplet pregnancies among Jews. While an increased rate of malformations, especially NTD, is well known in twin pregnancies, the differences in the incidence are less marked. In a large study [9], a relative risk of 1.8 of multiple compared to single gestations was observed for anencephalus while the rates for spina bifida were not significantly different. According to our data the relative risk is much higher among Jews, but this is difficult to calculate since information on multiple gestations is obtained only at delivery (2.3% in the year 2000), whereas our registry is based on pregnancies. The most intriguing finding was the difference between the two religious communities – the high rate of NTD in multiple pregnancies – observed only among Jews. We do not yet have any explanation for these findings, which should serve as the basis for a prospective investigation.

We tried to collect data on women's consumption of folic acid before they became pregnant, but in most cases this information was not available. However, recent surveys in Israel have shown that less than 10% of women take folic acid before becoming pregnant and the consumption of folic acid is therefore low [10,11].

The Ministry of Health issued recommendations that, beginning in 2000, all women of reproductive age should take folic acid supplementation, and it instituted a program to introduce folic acid into flour. The data presented here will serve as a basis for the evaluation of the impact of these measures on the incidence of NTD.

Acknowledgments. This study would not have been possible without the help of the many physicians who contributed their observations to the registry.

References
5. Krishman E. Neural tube defects in Israel. MD thesis. Technion Faculty of Medicine, Haifa, 1982.
6. Elon S. Neural tube defects in northern Israel between 1971-1985. MD thesis. Sackler Faculty of Medicine, Tel Aviv University, 1989.

Correspondence: Dr J. Zlotogora, Dept of Community Genetics, Public Health Services, Ministry of Health, Building 67, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-2) 353-8432
Fax: (972-2) 535-5166
email: joelz@cc.huji.ac.il

Whatever women do, they must do twice as well as men to be thought half as good. Luckily, this is not difficult.

Charlotte Whitton, former mayor of Ottawa

---

**Capsule**

**Fatal attraction**

Type 1 diabetes is the outcome of an autoimmune T cell response that destroys the insulin-producing beta cells within the pancreas. The early stage of the disease — known as insulinitis — is marked by infiltration of pancreatic islets by T cells, and Frigerio et al. suggest that beta cells may themselves be partly responsible. Exposure of a beta cell line to a mix of inflammatory cytokines stimulated the production of chemokines, proteins that orchestrate the migration of leukocytes. The same assortment of chemokines was detected in islets from mice with an induced form of insulinitis; in culture, these chemokines stimulated migration of T cells isolated from prediabetic mice. This chemotaxis depended most strongly on the CXCR3 receptor and corresponded with delayed induction of diabetes in CXCR3-deficient mice.

*Nature Med* 2002;8:1414

---

**Capsule**

**Boozing and cardiovascular mortality**

Moderate alcohol consumption is associated with reduced cardiovascular mortality, but binge drinking is thought to be detrimental. Malysutina et al. examined the effects of heavy and binge drinking in a population with high rates of drinking. The authors conducted a prospective cohort study in Novosibirsk, Russia in 6,502 men aged 25-64 at baseline who were examined in WHO MONICA (monitoring trends and determinants in cardiovascular disease surveys) in 1985-1986, 1988-89, and 1994-95, and in a pilot study in 1984. They assessed alcohol intake and drinking pattern by questionnaire. Binge drinking was defined as consumption of 160 g or more of pure alcohol on a typical occasion. Participants were followed for a median of 9.5 years (range 3.1-15.2).

The results revealed 836 deaths in the cohort, 395 of which resulted from cardiovascular diseases. Prevalence of binge drinking at baseline was 16% (n=1,005). Adjusted relative risks for binge drinking at least once a month (compared with consumption of <80 g pure alcohol) were 1.05 for death from all causes, 0.99 (0.66-1.50) for death from cardiovascular disease, 1.27 (0.81-1.99) for death from coronary heart disease, and 2.08 (1.08-3.99) for death from external causes. The risk for total and cardiovascular mortality was higher in a small group of frequent heavy drinkers (5%, 12,641 of all drinkers); for this group, adjusted relative risks were 1.61 (1.04-2.50) for total mortality and 2.05 (1.09-3.86) for death from cardiovascular disease. The authors conclude that risk of death from cardiovascular disease seems to be increased in frequent heavy drinkers, but is not necessarily associated with episodic binge drinking.

*Lancet* 2002;360:1448