The Impact of Congenital Malformations and Mendelian Diseases on Infant Mortality in Israel

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Abstract

Background: Infant mortality in Israel is twofold higher among non-Jews than Jews.

Objectives: To determine the impact of congenital malformations and Mendelian diseases on infant mortality.

Methods: We compared the causes of infant mortality in a 4 year period among Jewish and non-Jewish Israeli citizens. Classification was done by analyzing all the death reports according to whether or not the child had any known major malformation, Mendelian disease and/or a syndrome, irrespective of the immediate cause of death.

Results: The infant mortality among non-Jews was double that among Jews (9 versus 4.4 per 1,000 live births). The rate of children with malformations/genetic syndromes was 3.1 times higher among non-Jews than among Jews (2.94 vs. 1.25 per 1,000 live births). The most significant difference was in the rate of Mendelian diseases, which were 8.3 times more frequent in non-Jewish children (0.16 vs. 1.33 per 1,000 live births respectively). A Mendelian disease was diagnosed in almost 15% of the non-Jewish infants and in less than 5% of the Jewish infants.

Conclusions: The most striking difference between the Jewish and non-Jewish infants was the incidence of congenital malformations and Mendelian diseases parallel to the differences in the consanguinity rates between the two populations.

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Since the creation of the State of Israel in 1948 there has been a very impressive reduction in the infant mortality rates among both Jews and non-Jews; however, a consistent almost twofold difference has occurred since then [1]. In the 4 years between 1993 and 1997, the infant mortality rates were 5.5 per 1,000 live births among Jews and 10.3 per 1,000 live births among non-Jews [1,2]. In 1998, the largest groups of Israeli citizens were Jews (4,743,400), Muslims (883,900), Christians (127,400) and Druze (97,080) [1]. These religious communities differ in various aspects, one of which is consanguinity rates. Among Jews, while consanguinity rates were very high in some communities before their emigration to Israel, in the last decades consanguineous mating has become very rare in most communities [Cohen T, in preparation]. In contrast, in the non-Jewish population the consanguinity rates are high among Muslims and Druze (40–45%) who live mainly in rural settlements, and among Christian Arabs (20–25%) who live mostly in urban settlements [3]. Since, in parallel to the consanguinity rates, infant mortality rates were higher among Muslims (11.2 per 1,000 live births in 1993–1997) and Druze (9.6/1,000) than among Christian Arabs (7.9/1,000) or Jews (5.5/1,000) [2], we undertook to determine the impact of genetic factors on these differences.

The most significant differences in infant mortality rates between Jews and non-Jews were reported to be those of infants with major malformations [2]. However, while the category of "congenital malformations" includes some Mendelian conditions, in most cases genetic diseases are classified in other etiologic categories. In order to better understand the role of genetic factors in infant mortality rates, we analyzed the data, taking into account genetic criteria.

Materials and Methods

The data were collected from the death certificates of infants who died during the 4 year period, 1 January 1996 to 31 December 1999. In Israel, certificates that include the cause of death are completed by the physician who determined the death. We analyzed all the reports; when there were insufficient medical details to make a diagnosis an inquiry was conducted through the respective health district. In almost all the cases the final diagnosis was made on clinical and laboratory grounds; very few were based on post-mortem examinations.

Since the aim of the study was to determine the impact of congenital malformations and/or Mendelian diseases, the immediate cause of death and whether or not the child was premature were not taken into account. The classification was done according to whether or not the child had any known major malformation, a Mendelian disease and/or a syndrome. A disease was classified as monogenic when a definite diagnosis had been made during life, or when such a diagnosis was highly probable according to the geneticist who examined the data. The other categories for this study were those used by the Central Bureau of Statistics: prematurity, infectious disorders, sudden infant death, congenital malformations, perinatal cause, other, external causes, and unknown [2].

The infants were divided into two major groups only – Jews and non-Jews – since it was not possible to make an analysis according to each of the religious subgroups.

Results

A similar trend was observed in each of the 4 years studied, and therefore the data presented here are from a summary of those years. The infant mortality was twofold higher among non-Jews than among Jews (9 versus 4.4 per 1,000 live births). A higher infant mortality among non-Jews was found in each of the etiologic categories, with the smallest differences being for prematurity and perinatal causes [Tables 1 and 2].

The rate of children with malformations/genetic syndromes was 3.1 times higher among non-Jews than among Jews (3.94 vs. 1.25 per

Table 1. Malformations and Mendelian diseases in dead infants (1996–1999)

	Jews*	Non-Jews*
Live births	348,032	159,689
Infant deaths	1,535 (4.4)	1,442 (9)
Malformations	378 (1.09)	423 (2.65)
Cardiovascular	113 (0.32)	136 (0.85)
Chromosomal (total)	56 (0.16)	43 (0.27)
Down syndrome	[25 (0.07)]	[23 (0.14)]
Central nervous system (total)	47 (0.14)	95 (0.59)
Open neural tube defects	[30 (0.09)]	[61 (0.38)]
Gastrointestinal	24 (0.07)	23 (0.14)
Renal	32 (0.09)	35 (0.22)
Respiratory	11	20 (0.12)
Multiple malformations	52 (0.15)	50 (0.31)
Other	43	21
Mendelian diseases	56 (0.16)	213 (1.33)
Spinal muscular atrophy	5	16
Epidermolysis bullosa	–	14
Malformations or Mendelian	434 (1.25)	630 (3.94)
Percent of total infant deaths	28.3%	43.6%

* Rates per 1,000 live births

The number of children with Down syndrome and those with open neural tube defects are in square brackets since they are a part of the total number of children with chromosomal aberrations and nervous system malformations respectively.

Table 2. Rates of infant mortality according to the frequency of the different etiologic categories (per 1,000 live births)

Non-Jews		Jews	
Malformations	2.65	Prematurity	2.07
Prematurity	2.38	Malformations	1.09
Mendelian diseases	1.33	Perinatal	0.41
Infectious	0.69	Infectious	0.24
Perinatal	0.59	Other	0.2
Sudden infant death	0.44	Unknown	0.15
Other	0.38	Mendelian diseases	0.16
Unknown	0.39	Sudden infant death	0.1

Table 3. Mendelian disorders diagnosed in more than 2 cases

Disorder	Ethnic group
Spinal muscular atrophy	Jews and non-Jews
Epidermolysis bullosa	Non-Jews
Arthrogryposis, autosomal recessive lethal form	Non-Jews
Non-ketotic hyperglycinemia	Non-Jews
Congenital nephrotic syndrome	Non-Jews
Maple syrup urine disease	Non-Jews
Methyl gluconic aciduria	Non-Jews
Molybdenum co-factor deficiency	Non-Jews
Meckel syndrome	Non-Jews
Osteopetrosis	Non-Jews

1,000 live births). The most significant difference was in the rate of Mendelian diseases, which were 8.3 times more frequent in non-Jewish children (1.33 vs. 0.16 per 1,000 live births respectively). The major Mendelian diseases are shown in Table 3.

Discussion

Together with the improvement in the quality of healthcare and the increasing effectiveness of prevention policies, infant mortality decreased significantly in the last decades in developed countries. In a study on the international variations and time trends of infant mortality attributable to congenital malformations from 1950 to 1994, Rosano et al. [4] demonstrated that the proportion of mortality attributable to congenital anomalies was higher than in poorer countries and their proportion of all infant deaths was lower than in healthier countries. In Israel, the infant mortality is relatively low among Jews and non-Jews, as compared to other countries; and, as expected in a developed country, congenital malformations represent a major category in infant mortality (24.7% vs. 29.3% respectively).

The introduction of Mendelian diseases as an etiologic category emphasized their relative importance in the non-Jewish population. Infants with congenital malformations represented the largest group among non-Jews (29.3%), and those with Mendelian diseases ranked third (14.7%) after infants born prematurely (26.3%). Among non-Jews, Mendelian diseases were present 8 times more often than among Jewish infants [Table 2]. In total, almost 60% of the difference between the two populations was secondary to the differences in the mortality rate in infants with malformations and/or Mendelian diseases.

During the 4 years of this study, almost all the Mendelian diseases diagnosed among non-Jewish infants were autosomal recessive. The two most common were spinal muscular atrophy (1/10,000 live births) and epidermolysis bullosa (1/11,000 live births), however several other diseases known to be relatively frequent among non-Jews in Israel were also diagnosed among dead infants [Table 3]. While we included in this category only disorders in which a Mendelian inheritance was definite or had a high probability, it may be assumed that, in addition, some of the malformations are manifestations of Mendelian syndromes. For instance, several monogenic syndromes such as Meckel or Warburg syndromes and isolated recessive hydrocephalus, which are relatively frequent among Muslim Arabs, may present at birth as an isolated major malformation of the nervous system [5]. On the other hand, among the dead Jewish infants, Mendelian disorders were one of the minor etiologic categories, representing less than 5% of the total. The most frequent single Mendelian disorder among Jews was spinal muscular atrophy (1/70,000 live births), but with a much lower incidence than among non-Jews.

For many of the severe malformations, the incidence at birth does not represent their true rate since the rate of therapeutic abortions and stillbirths are not taken into account. In addition, differences in the type of treatment available after birth may also lead to differences in mortality. Since 1994, all Israeli citizens are entitled by law to medical insurance including prenatal examination, at least theoretically; therefore the availability of treatment should be similar for the whole population.

Differences in the availability and the utilization of prenatal diagnosis as well as the rate of termination of pregnancies may lead to differences of incidence of malformations at birth. Many of the severe congenital malformations and some of the Mendelian

diseases may be diagnosed during pregnancy with the possibility of pregnancy termination. According to Jewish law (*Halakha*), abortion is forbidden after 40 days of conception, whereas Islamic law prohibits elective abortions after 120 days when it is believed that the soul has emerged. However, since most of the Jewish population in Israel is secular, termination of pregnancy because of severe fetal malformations is well accepted. On the other hand, among Israeli Arabs, the Muslim population, which represents 80% of the non-Jews, is mostly religious or traditional; and interruption after the 17th week of pregnancy, when most of the malformations are diagnosed, is often not an option for the couple.

The numbers of therapeutic abortions for malformed fetuses are available form the Central Bureau of Statistics, however they include cases with diagnosed malformations as well as cases in which the fetus was at high risk for a malformation. Specific and complete data on pregnancies with Down syndrome are available from the National Registry, and almost complete data are available for neural tube defects. In the case of Down syndrome, because of a higher proportion of older pregnant women, the incidence during pregnancy is higher among Jews than among non-Jews. Almost 60% of the Jewish women with a fetus affected with Down syndrome opt for an abortion, as compared to less than 20% of the non-Jewish women [6, and unpublished data]. This difference is responsible for a higher incidence of Down syndrome among non-Jewish live-borns, and partially explains the higher proportion of dead infants with Down syndrome among non-Jews. Open neural tube defects are twice as frequent among non-Jews as among Jews during pregnancy, but due to the lower rate of terminations among non-Jews, at birth the ratio rises almost to 4, which explains the differences in infant mortality secondary to these malformations [7].

In conclusion, the differences in infant mortality rates between Jews and non-Jews are secondary to various factors. The infant mortality rate among non-Jews is higher for each of the classical etiologic categories such as prematurity or perinatal causes, but the most striking differences between the two populations are found in the rates of malformations and/or Mendelian diseases, which are responsible for a significant portion of the higher infant mortality rates among non-Jews. The differences in infant mortality are only a partial reflection of the impact of malformations and Mendelian diseases. With the increasing availability of supporting treatment, most of the severe genetic disorders are becoming chronic; and, if they remain lethal the death often occurs after infancy. Therefore, studies based on differences in childhood mortality and morbidity may help to better delineate medical problems that are caused by the differences between the two populations.

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