Prevalence of Non-Syndromic Orofacial Clefts among Jews and Arabs, by Type, Site, Gender and Geography: A Multi-Center Study in Israel

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ABSTRACT: **Background:** Orofacial clefts are the most common craniofacial congenital malformations, with significant anatomic, ethnic, racial and gender differences.

Objectives: To investigate the prevalence, distribution and characteristic features of various types of non-syndromic clefts among Israeli Jews and Arabs.

Methods: We conducted a retrospective multi-center survey in 13 major hospitals in Israel for the period 1993–2005. To obtain the true prevalence and detailed clinical characteristics, data on liveborn infants with non-syndromic clefts were obtained from the Ministry of Health's National Birth Defect Registry and completed by chart reviews in the 13 surveyed hospitals.

Results: Of 976,578 liveborn infants, 684 presented unilateral or bilateral clefts, with a prevalence of 7.00/10,000 live births; 479 were Jews and 205 were Arabs. The prevalence was higher among Arabs compared to Jews (11.12 and 6.22 per 10,000 live births in Arabs and Jews, respectively, $P < 0.00001$). Males had higher cleft rates than females (7.69/10,000 and 6.17/10,000 live births, respectively, $P = 0.05$). Males had more cleft lips ($P < 0.05$) and cleft lips with cleft palate ($P < 0.001$). There was left-side predominance. Newborns of younger mothers (age < 20 years) and of older mothers (age ≥ 45 years) had higher cleft rates than those with mothers in the 20–44 year bracket ($P < 0.009$). Children born at or above the 5th birth order had a higher cleft rate ($P < 0.001$).

Conclusions: The prevalence of non-syndromic clefts was 7.00/10,000 live births. The markedly higher rate in Arabs is related to the high rate of consanguinity. Both very young and old maternal age represents a higher risk of clefts in their offspring.

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KEY WORDS: orofacial clefts, cleft lip (CL), cleft palate (CP), cleft lip and palate (CLP), epidemiology, Jews, Arabs

The most common congenital craniofacial anomalies in newborn infants are cleft lip (CL), cleft palate (CP), and cleft lip and palate (CLP). Numerous epidemiological investigations have studied the prevalence of orofacial clefts in various ethnic populations around the world [1-4]. Ethnic and racial differences in the prevalence of clefts have been reported in various groups and in different geographic areas around the world. Orientals have a high prevalence of clefts, Caucasians show intermediate rates, and the lowest prevalence is found in Africans [5-7].

Worldwide epidemiological studies report an increase in the incidence of orofacial clefts over the years due to better neonatal care and improved surgical techniques for clefted children resulting in decreased postnatal mortality. The increased number of surviving clefted children may result in transfer of the defective genes to subsequent generations [8-10]. In addition, registration systems of newborns with congenital defects around the world are expanding and becoming more specific and accurate, resulting in more reports on newborns with orofacial clefts.

in Israel, previous epidemiological reports on CL and CP were limited to regional and small-scale studies [11-13], or national reports on malformations based on the National Birth Defect Registry of the Ministry of Health, with limited epidemiological data and clinical facial cleft characteristics [14,15]. An incidence of 1 in 1837 cases (0.544 per 1000 births) was reported among Jewish children born in six hospitals during the years 1960–1962 [11]. An 11 year study of clefts in both Jewish and Arab populations in the northern region of Israel between 1961 and 1971 revealed a mean incidence of 0.80 per 1000 live births (0.83/1000 and 0.77/1000 among Jewish and Arab live births, respectively) [12].

In a 10 year report on birth malformations in Israel (1991–2000) based on the National Birth Defect Registry, the prevalence of orofacial clefts (CP and cleft lip with or without cleft palate, CL/P) was 5.63 and 8.21 per 10,000 live births among Jews and Muslim Arabs, respectively [15]. Since the actual reporting rate in this Registry is about 60–70% of all congenital malformations, the prevalence of birth defects in this report is an underestimation of the true prevalence.

A comparison of the incidence of orofacial clefts in 41 countries worldwide revealed Israel to have the lowest incidence of CL/P and a relatively low incidence of CL/P in the WHO World Atlas of Birth Defects (WABD). The source of the Israeli data in this report was three major hospitals in central Israel for the years 1993–1998 and included live births and stillbirths, giving a prevalence of 5.1/10,000 for CP and 3.37/10,000 for CL/P [16].

In a recent report on 140 newborns with CL and CP from southern Israel during the years 1996–2006, the prevalence was 1.54/1000 among Bedouins and 0.48/1000 among Jews, with a marked reduction in cleft rates after the year 2000. This report was based on data from the Soroka Medical Center archive and data obtained from the archive of the Division of Obstetrics and Gynecology [17]. However, this report does not specify whether the craniofacial clefts were isolated or included also clefts associated with syndromes or other malformations.

Due to under-reporting of the prevalence of congenital malformations based on National Registries, the true prevalence can be estimated by compiling data from this registry together with a systematic chart review in the hospitals.

We selected 13 medical centers across the country for this study, representing approximately 60% of the total Israeli cohort. In 2005, the last year of the study, there were 86,123 newborns in these hospitals of a total of 143,878 live births in Israel (59.9%). These hospitals were selected on the basis of obtaining an Institutional Review Board (IRB-Helsinki) approval for this survey. These medical centers are quite representative of the Israeli liveborn cohorts across the country during the study period, with slight over-sampling of Jews (79%) compared to Arabs (19%) and others (e.g., Druze) (2%).

The aims of the present report were: a) to study the true prevalence, distribution and characteristics of various types of orofacial clefts in a large sample of Jewish and Arab populations in Israel during a 13 year period (1993–2005), and b) to identify risk factors for CL and CP. To the best of our knowledge this is the largest multi-center investigation of craniofacial clefts ever conducted in Israel, representing the vast majority of the Israeli population.

MATERIAL AND METHODS

The data for this investigation on liveborn infants with non-syndromic orofacial clefts were collected from two sources: the National Birth Defect Registry of the Israel Ministry of Health, and a hospital chart review. The Registry constitutes individual reports on each live birth, with an obligatory list of congenital malformations that includes CL, CP and CL/P. These reports are sent from all hospitals in Israel to the Department of Maternal, Child and Adolescent Health at the Ministry of Health in Jerusalem. The chart review comprises records of newborn children collected directly from 13 major hospitals throughout Israel (north to south) where approximately 60% of all newborns in Israel were born (Central Bureau of Statistics, 2005). Compilation of data obtained from these sources allows a complete and accurate evaluation of the prevalence of orofacial clefts in a large number of newborns in a representative sample in Israel.

Infants with orofacial clefts associated with a genetic craniofacial syndrome were recorded in our study but were not included in the final analysis, since fetuses with clefts associated with syndromes are more likely to be aborted. Also, since the regular follow-up and treatment for clefts is often incomplete, their documentation at the surveyed medical centers might be incomplete. Thus, their inclusion may result in under-reporting of the true incidence.

The participating hospitals were Shaare Zedek, Hadassah Mount Scopus and Hadassah Ein Kerem (in Jerusalem), Padeh Poriya (Tiberias), Rambam (Haifa), Hillel Yaffe (Hadera), Assaf Harofeh (Zerifin), Rabin-Beilinson (Petah Tikva), Kaplan (Rehovot), Sheba-Tel Hashomer (Ramat Gan), Sourasky (Tel Aviv), Barzilai (Ashkelon), and Soroka (Beer Sheva).

Information on each newborn with facial cleft was recorded. This included: cleft type (CL, CP, CLP), location (left, right, bilateral), gender (male, female), ethnic origin (Jewish, Arab), mother's age, birth order, singleton or twin/triplet birth, month of birth, and district of birth.

Statistical analysis was conducted by the computer program SPSS (release 10.0.5, SPSS Inc., Chicago, IL, USA). Chi-square analysis was performed to test the significance of the findings; $P < 0.05$ was considered statistically significant. This investigation was approved by the IRB (Helsinki) Committees of the hospitals that participated in the study.

RESULTS

There were 976,578 live newborn infants in the 13 participating hospitals during the study period 1993–2005. Of these, 684 individuals presented with non-syndromic unilateral or bilateral cleft lip and/or palate (7.00/10,000). An additional 182 liveborns with syndromic orofacial clefts were identified. Thus, the total number of liveborns with orofacial clefts was 866, giving a prevalence of 8.87 per 10,000 live births for all orofacial clefts. However, only those with isolated orofacial clefts underwent detailed analysis.

There were 479 non-syndromic clefts among 769,503 Jewish live newborn infants and 205 among 184,338 Arab live newborn infants. The prevalence of clefts in Arabs was significantly higher than in Jews (11.12 and 6.22/10,000, respectively, $P < 0.00001$). Cleft incidence had fluctuated from year to year but was relatively stable with no significant change ($P = 0.9$).

GENDER

More clefts were found in males (390) than in females (294), namely 7.69 and 6.17 per 10,000 live births, respectively (P

Table 1. Distribution of clefts by type and gender

Type of cleft	Total		Male		Female	
	No.	%	No.	%	No.	%
Cleft lip	235	34	148*	63	87	37
Cleft palate	258	38	121	47	137	53
Cleft lip and palate	191	28	121**	63	70	37
Total	684	100	390*	57	294	43

*The higher prevalence of all clefts in males compared with females was significant ($P < 0.05$)

**The higher prevalence of CL and CL/P in males compared with females was significant ($P < 0.001$)

Figure 1. Rates of clefts according to mother's age

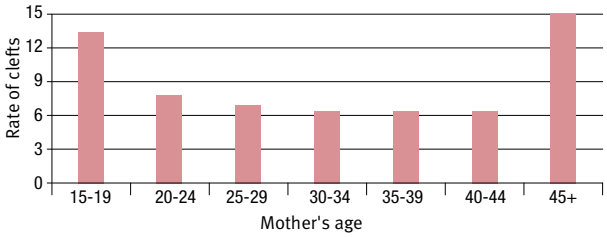
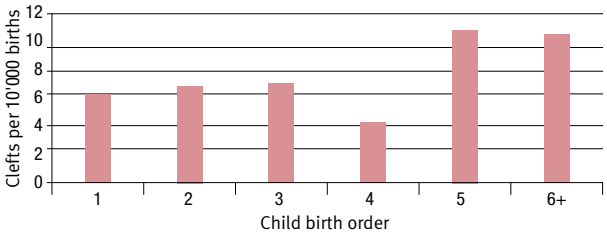


Figure 2. Rates of clefts according to the child's birth order



< 0.05). Males had more cleft lips ($P < 0.005$) and cleft lips with cleft palate (CL/P) ($P < 0.001$), while females had more isolated cleft palates (CP) (not significant) [Table 1].

LOCATION

Left-side clefts were predominant, involving 55% of the cases, right-side clefts involved 26%, and bilateral clefts were found in only 19% of the cases.

MOTHER'S AGE

Young mothers (15–19 years old) and older mothers (age ≥ 45) had a significantly higher rate of children with clefts compared with mothers in the 20–44 age bracket ($P < 0.009$) [Figure 1], while no correlation was found between father's age and the rate of clefts.

CHILD'S BIRTH ORDER

Children born at or above the 5th birth order had a higher cleft rate ($P < 0.001$) [Figure 2].

Table 2. Rates of clefts according to district of birth

District	No. of live births	Clefts	Clefts per 10,000 live births
Jerusalem	200,697	194	9.66
Shaare Zedek	97,042	79	8.14
Hadassah Mt. Scopus	49,200	44	8.94
Hadassah Ein Karem	54,455	71	13.03
Lower Galilee	32,229	29	8.99
Padeh Poriya	32,229	29	8.99
North	108,793	84	7.72
Rambam (in Haifa)	56,415	64	11.34
Hillel Yaffe (in Hadera)	52,378	20	3.81
Center	342,662	182	5.31
Assaf Harofeh (in Zerifin)	72,851	45	6.17
Rabin-Beilinson (in Petah Tikva)	96,093	49	5.09
Kaplan (in Rehovot)	62,792	38	6.05
Sheba-Tel Hashomer (in Ramat Gan)	110,926	50	4.5
Tel Aviv	99,557	56	5.62
Sourasky	99,557	56	5.62
South	192,640	133	6.9
Barzilai (in Ashkelon)	44,372	34	7.88
Soroka (in Beer Sheva)	148,268	98	6.6
Total	976,578	684	7.00

MONTH OF BIRTH

No correlation was found between the month of birth (seasonality) and the appearance of clefts in newborns.

PLACE OF BIRTH

The rates of liveborn infants with clefts according to the hospitals in the districts of birth are presented in Table 2. Significantly higher rates of clefted newborns were found in the districts of Jerusalem, the north and Haifa, while in the Tel Aviv and center district the rates were considerably lower. These differences were statistically significant ($P < 0.001$). In the southern district the rate of clefted newborns was the same as the national rate.

TWIN BIRTH

Among the 684 infants with clefts in the study, 17 (2.5%) were a part of twins. None of the second twins of these infants had clefts.

DISCUSSION

Our investigation presents a prevalence of 7.00 newborns with isolated orofacial clefts per 10,000 live births. With the inclusion of those with syndromic clefts, the total rate of orofacial clefts was 8.86 per 10,000 live births. The rates of isolated orofacial clefts were 6.22 and 11.12 per 10,000 in Jews and Arabs, respectively. Our study population comprises about 60% of the Israeli birth cohorts across the country, including medical centers in the major cities, both in the center of the country and in all other districts, with slight over-sampling of Jews compared to Arabs.

These rates are higher than those reported in a previous National Report in Israel by Zlotogora et al. [15] of 5.63 and 8.21 per 10,000 among Jews and Muslim Arabs, respectively. The higher rates in our study are due to the fact that we compiled data from two sources: reports from the hospitals, and an active search in the archives of 13 hospitals in order to bridge the gap of underestimation due to incomplete reports. Thus, the data from 13 hospitals is the true prevalence in a representative sample covering about 60% of deliveries in Israel.

The prevalence of orofacial clefts in our study is lower than that in most of the 41 countries participating in the WHO WABD for the years 1993–1998 [16]; however, the WABD report included live births and stillbirths, whereas our report includes only non-syndromic clefts in liveborn infants. Of note, many reports on the prevalence of orofacial clefts include also syndromic clefts, or those associated with other congenital anomalies. In most of these reports the syndromic orofacial clefts account for about 10–30% of all cases of infants with clefts [4]. In the 13 medical centers surveyed by us there were an additional 21% of liveborns with syndromic orofacial clefts during the study period.

The higher rates of CL/P in males in our study are in accordance with other reports [2,4,5]. Also, the higher rates of CP in females in our study, although non-significant, was found in previous reports [2,4,5].

In our study, unilateral clefts were found more often than bilateral and had left-side predominance. A possible explanation for the left-side predominance is the anatomy and direction of blood vessels. A greater blood supply arrives to the right side of the face in utero due to higher blood pressure from the right internal carotid artery, which is in a direct line of blood flow, creating a greater blood supply to the right side of the embryo's face compared with the left side [18]. These findings are in close agreement with previous reports on clefts among males and females and the site of cleft involvement [7,18]. The results concerning site of the cleft are similar to international reports.

Several studies have shown that increased maternal age (mothers older than 35–40 years) was associated with increased risk of delivering cleft babies [19,20]. Our study found that both young mothers (age 15–19) and older mothers (age ≥ 45 years) had a significantly higher rate of newborns with clefts. Our findings concur with those of Vallino-Napoli et al. [20] who observed that women > 40 years old have an increased risk of delivering a baby with CL/P and women < 20 years old have an increased risk to have a baby with a CL [20]. However, in the later report [20] about 30% of the cases were associated with syndromes, including chromosomal anomalies which are more likely to occur with advanced maternal age.

We did not find a significant seasonality in children born with clefts. Several studies examined yearly and seasonal fluctuations for cleft lip and palate prevalence that could be influenced by climate changes or environmental factors, but no statistical significant trends were reported [21].

In our study only 2.5% of newborns were born as a part of twins, where one had cleft and the second did not. Previous studies found little evidence of excess risk of oral clefts compared with singletons and did not report statistically significant differences in oral cleft prevalence for twins relative to singletons [20-23].

The present report shows that in the northern, Haifa and Jerusalem districts, the rate of clefts was significantly higher ($P < 0.001$) than in Tel Aviv and the center districts. These findings reflect the fact that there is a significantly larger Arab population in these three districts than in the Tel Aviv and center districts. The higher rate of consanguineous marriages in Arabic populations and their high fertility rate are probably the major risk factors for the higher cleft prevalence [15,24,25].

Higher rates of abortions in the Tel Aviv and center districts could also explain to some degree the lower prevalence. However, since our report excluded orofacial syndromic orofacial clefts, we assume that this could account for only a limited number of cases. Abortions for isolated orofacial clefts were uncommon, particularly in the first years of the study cohort.

The prevalence of isolated orofacial clefts in the southern district in our study (6.9/10,000 and 6.6/10,000 in infants born at the Soroka Medical Center) is lower than those in a recent report from this hospital (10.67/10,000) [17]. However, the latter report probably also included clefts associated with syndromes or other malformations, which are particularly more common in the Bedouin population due to the very high rate of consanguinity, whereas our report included only isolated non-syndromic orofacial clefts.

The main environmental factor associated with orofacial clefts is maternal smoking, which results in an approximately twofold higher rate compared with non-smoking mothers. Several protective factors were reported, including periconceptional folic acid supplementation, maternal weight gain, and higher birth weight. These data were not available in our study population.

CONCLUSIONS

The true prevalence of cleft lip and palate in Israel is lower than the global rate, with a higher cleft rate among Arabs due to the high rate of consanguinity. Data on the prevalence, distribution and risk factors of orofacial clefts in Israel summarized in our report may assist health authorities in organizing and improving comprehensive services needed for children with orofacial clefts. It may also provide a basis for genetic research and counseling and the development of health care programs. Primary prevention of orofacial clefts by reducing consanguineous marriage, refraining from smoking in pregnancy, and periconceptional folic acid supplementation could further reduce the prevalence of these defects.

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