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Parental Consanguinity and Birth Defects in Lebanon: The National Collaborative Perinatal Neonatal Network (NCPNN)

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Abstract

Objective: To determine the prevalence of birth defects (BD) and its correlation with parental consanguinity in a representative population of Lebanon.

Methods: Secondary data analysis of the National Collaborative Perinatal Neonatal Network (NCPNN), reporting on neonates between September 2003 and December 2007.

Results: Among 50,396 live births, 1,637 were diagnosed with one or more birth defects for an overall prevalence of 32.5‰. The most prevalent defects were cardiovascular, urogenital and musculoskeletal with 15.1‰, 6.3‰ and 5.7‰, respectively. Approximately 40% of affected newborns had multiple defects involving one or more organs. Syndromes were suspected in 128 neonates of whom 77.3% were diagnosed with chromosomal aneuploidies (mostly Down syndrome). Consanguinity was reported among 15.73% of parents, and the odds of BD were found to be significantly increased among first-cousins consanguineous couples (OR 1.6; 95% CI: 1.2-1.7).

Conclusion: Findings of this study estimated for the first time the overall prevalence of BD in Lebanon, with congenital heart anomalies being most common. They further established a significant association between parental consanguinity and the odds of BD in offsprings.

Keywords

Birth defects; Consanguinity; Syndromes; Developing countries; Prevalence; Cardiovascular; Lebanon

Introduction

Birth defects (BD) are defined as any structural and/or functional anomalies that occur during intrauterine fetal life. Prevention, surveillance and management of BD have been the subject of much interest by public health professionals since the global call for action launched at the 63rd World Health Assembly in 2010. After the Millennium Development Goals, the United Nations set a new plan, the Sustainable Development Goals (SDGs), which targets the reduction of preventable newborn deaths to 12 neonatal deaths per 1,000 live births by 2030 [1]. Worldwide data estimate that among 7.9 million children born yearly with major and/or minor BD, approximately 3.2 million of them die before reaching the age of five years [2]. A systematic analysis showed that BD contributed to 0.276 million neonatal deaths (4.4%) during 2013 [3]. According to the CDC 2015 Infant Mortality Statistics, deformations and chromosomal abnormalities were also found to be the leading cause of infant death in the US during 2013 [4]. On the other hand, BD may be a major cause of lifelong disabilities imposing significant financial and psychosocial burden to the individual, society and the healthcare system [5].

Unfortunately, the etiology of BD remains undetermined in about 50 to 70 % of the cases. More defined etiologies may be either inherited or sporadic caused by either genetic or environmental insults[2]. Although evidence based data suggest that at least some BD may be preventable prenatally, the prevalence of these anomalies are still on the rise in many under-developed countries of the Middle East and North Africa (MENA) [2].

The reported prevalence of BD have been highly variable amongst different populations, and have ranged from 5% in western Australia [6], 3.9% in Canada [7], 2.6% in European countries [8], [6,7], 1.1% in Saudi Arabia [9], 0.8 % in India [10], and 0.2% in Turkey [9,11]. The absence in developing countries of compulsory national surveillance systems with reliance solely on hospital-based studies could have introduced a significant sampling bias causing an under-representation of the affected population and an underestimate of the risk in these communities.

Known risk factors accounting for population disparities in reporting prevalence may also include consanguineous marriages, suboptimal pre-pregnancy and pregnancy health status and extreme-age pregnancies [12,13]. Consanguineous marriages are culturally favored in many communities including the Middle East. Some studies have suggested higher rates of BD in infants born to consanguineous marriages compared with the general population [14]. Findings from a large multiethnic birth cohort in the UK showed that BD were highly observed within the Pakistani community, of which 31% could be attributed to consanguinity. The study concluded that consanguineous parents were twice more likely to give birth to an offspring with a BD (multivariate RR=2, 19, 95‰ CI:1,67–2,85) [15]. A study conducted in 2006 in Beirut reported that first-cousin consanguinity was a significant risk factor for congenital heart defects in newborns [16]. Another study reporting on the same population suggested that defects such as spina bifida, hydrocephalus and cleft lip or palate were also more common in offsprings of consanguineous parents [17]. The objectives of this study were to:

Estimate the prevalence of BD in the Lebanese population and evaluate the distribution patterns of specific defects.

Assess whether parental consanguinity is a significant risk factor for some BD in particular.

Materials and Methods

Data from the National Collaborative Perinatal Neonatal Network (NCPNN) were analyzed between September 1, 2003 and December 31, 2007. The NCPNN is a hospital-based surveillance network covering to date approximately 30% of the national birth toll in

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Lebanon, and which goal is to identify statistical patterns for the purpose of improving maternal and neonatal health. All live born neonates admitted to the normal nursery (NN) and/or neonatal intensive care unit (NICU) of contributing hospitals during the study period were included. The contributing hospitals comprised tertiary referral centers in addition to centers from different regions in Lebanon, all of which accept admissions of patients from different socioeconomic, geographic and religious backgrounds. Demographic characteristics and health information on mothers and neonates were collected from medical records and from a questionnaire filled during a personal face-to-face interview with the delivering mother (Table 1).

Collected data were categorized into major and minor defects according to ICD-10 coding. Major defects were defined as any structural or functional abnormality of an organ causing physical or mental disability, or even death; whereas minor defects were those anomalies with no significant health consequences [18]. Data reporting on unconfirmed or unspecified BD diagnosis were excluded. Preterm births with evidence of Patent Ductus Arteriosus (PDA) as the only defect were re-coded as unaffected and were kept in the sample. Recorded defects were revised for each case by a certified geneticist who classified them into isolated or multiple, while identifying sequences, syndromes and associations.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Version 20 (IBM). Analyses included frequency distributions and percentages of BD and consanguinity. Crude odds ratios and 95% confidence intervals were calculated to assess the risk of first- and second-cousins consanguinity on the occurrence of BD using multinomial logistic regression. Significance level was set at 5 percent.

This study was approved by the institutional review board (IRB) of the American University of Beirut to perform data collection from medical records and interviewing mothers at the time of delivery. All women provided informed consent as per approved IRB protocol prior to data collection.

Results

During the study period, a total of 54,248 live born neonates were collected from the NCPNN. After excluding cases with unconfirmed defects (n=98), unspecified anomalies (n=21) and cases with missing data entries (n=3,733), a total of 50,396 live births were analyzed. Sixty-six preterm births with Patent Ductus Arteriosus (PDA) as the only detectable malformation were included in the unaffected study population.

A total of 1,637 affected neonates were reported, bringing the overall BD prevalence in the study population to 3.25%. The majority of affected cases had single defects (specific prevalence of 2.65%), while only 680 had multiples anomalies. Approximately half of these multiple defects occurred in a single organ system (331/680). The overall rate of consanguinity among parents was 15.73% of whom 58% were first- cousins (4,631 /7,928) (Table 2).

The most common BD were cardiovascular anomalies with a prevalence of 15.1‰, accounting for nearly half of all malformations. This was followed by urogenital (6.3‰) and musculoskeletal defects (5.6‰) (Table 3). Prevalence of defects classified as Isolated, Syndromes, Sequences, Associations or Multiple are shown in Table 4. Syndromes were detected in 128 neonates (2.5 ‰), among whom 96 cases of chromosomal aneuploidies were detected (75.0%) with Down's syndrome accounting for 90% (86/96) (Appendix 1). Spina

Table 1: Demographic characteristics and health information.

Socio-Demographics
Place of residence
Area of origin
Religion
Contact information Mother's current age Mother's age at marriage Mother's age at first pregnancy(irrespective of outcome)
Father's Current Age
Mother's education
Father's education
Mother's work status during pregnancy
Father's current work status
Father's main occupation
Parental consanguinity: If yes, specify if: 1. First degree cousins (Mother and Father are cousins) 2. Second degree cousins (Parents are cousins) 3. More (related, but to a lesser extent)
Mother's Parental consanguinity: If yes, specify if: 1. First degree cousins (Mother and Father are cousins) 2. Second degree cousins (Parents are cousins) 3. More (related, but to a lesser extent)
Father's Parental consanguinity: If yes, specify if: 1. First degree cousins (Mother and Father are cousins) 2. Second degree cousins (Parents are cousins) 3. More (related, but to a lesser extent)
Maternal Obstetric History
Gravidity (total number of pregnancies)
Parity (total number of previous live births)
Abortion (Previous)
Living children (total)
Previous neonatal deaths within first 28 days of life
Previous infant deaths within first year of life, including neonatal deaths
Previous stillbirths
Previous infants with congenital malformations. If yes, Specify malformation(s)
Previous C-sections
Maternal Anthropometrics
Maternal Height
Maternal weight (before pregnancy)
Maternal weight (at delivery)
Maternal Lifestyle Characteristics
Before pregnancy (cigarettes, arghile, alcohol)
During pregnancy (cigarettes, arghile, alcohol)
Prenatal Care
Earliest physician visit
Total number of visits during pregnancy
Ultrasound abnormalities. If yes, specify.
Maternal Morbidities
Chronic conditions
Family history of congenital malformations
Pregnancy related complications
Mode of Delivery
Anesthesia & Other Medications
Medications during pregnancy
Medications during delivery
Household socioeconomic characteristics
Total number of people (excluding infant) living in your house
Rooms (excluding kitchen &bathrooms) in your house
Household monthly income

bifida was the most common identified sequence with a specific prevalence of 0.5‰. Monogenic, contiguous gene deletion and those of unknown etiology syndromes occurred in 0.4 ‰, of which Di-Georges, Meckel Gruber, and Charge syndromes were the most common (Appendix 2). Among neonates with cardiac malformations, 13 had hypoplastic left heart syndrome (0.3‰), 6 had hypoplastic right heart syndrome (0.1‰) and only one had Scimitar syndrome. Among neurological malformations, Dandy walker syndrome was reported in 5 newborns (0.1 ‰) (Appendix 1).

The association between the degree of consanguinity and the occurrence of BD by organ system is displayed in Table 5. The overall odds of giving birth to an affected offspring was increased by 50% (95% CI: 1.2-1.7) and 60% (95% CI: 1.3-2.0) in first- and second-cousins consanguineous parents, respectively. First- cousins consanguinity was found to be significantly associated with approximately two-fold increase in the odds of musculoskeletal, gastrointestinal, neurological, eye, ear, face and neck defects. No such association was found with chromosomal aneuploidies (95% CI: 0.5-2.2), orofacial clefts defects (95% CI: 0.5-2.8) and respiratory malformations (95% CI: 0.6-3.4). Second-cousins consanguinity was also a significant risk factor for cardiovascular defects (OR: 1.6 [95% CI: 1.3-2.0]), musculoskeletal malformations (OR: 2.1, [95% CI: 1.2-3.4]) and respiratory anomalies (OR: 3.2 [95% CI: 1.2-8.1]).

Table 2: Rate of single versus multiple birth defects and consanguinity.y.

	N	‰
Any reported birth defects		
No	48,693	966.2
Yes	1,637	32.5
Single birth defects	957	19.0
Minor	415	8.2
Major	542	10.7
Multiple birth defects	680	13.5
Multiple birth defects involving single system	331	6.6
Syndromes	113	2.2
Sequences	31	0.6
Multiple birth defects involving other multiple systems	205	4.1
Parental Consanguinity		
Not related	39,475	783.3
Consanguineous	7,928	157.3
First cousins	4,631	91.9
Second-cousins	1,724	34.2
More distant	1,307	25.9
Missing	2,993	59.4
Total	50,396	1000.0

Table 3: Overall rates of birth defects by organ system.

	N	‰
Any birth defects	**1,637**	**32.5**
Cardiovascular	763	15.1
Urogenital	319	6.3
Musculoskeletal	285	5.6
Gastrointestinal	179	3.5
Neurological	115	2.3
Chromosomal	99	2.0
Eye, ear, face and neck	71	1.4
Cleft lip/palate	59	1.2
Respiratory	58	1.1
Other birth defects	58	1.1

Table 4: Rate of detailed birth defects classified into syndromes and sequences.

	Total	
	N	‰
Any reported birth defects		
No	48,759	967.5
Yes	1,637	32.5
Isolated birth defects	1,336	26.5
Cardiac	610	12.1
Clefts	40	0.8
Digestive	101	2.0
Neurologic	55	1.1
Respiratory	30	0.6
Musculoskeletal	190	3.8
Urogenital	250	5.0
Eye, ear, face, and neck	28	0.5
Other	32	0.6
Syndromes	128	2.5
Chromosomal	97	1.9
Microdeletions	2	0.0
Skeletal dysplasias	8	0.1
Features suggestive of syndromes	21	0.4
Sequences	31	0.6
Prune belly	3	0.0
Pierre robin	2	0.0
Spina bifida	24	0.5
Renal aplasia	1	0.0
Diaphragmatic hernia	1	0.0
Features suggestive of associations (Vater)	3	0.0
Other multiple system birth defects	139	2.8
Multiple systems birth defects, unrelated/not in a syndrome	57	1.1
Multiple system all minor birth defects	12	0.2
Unspecified multiple system birth defects	2	0.0
Unclassified multiple system birth defects*	68	1.3
Total	50,396	1000.0

*Available data not enough to classify into any of the above categories

Although consanguinity has been reported to be related to low educational and socioeconomic status as compared to non-consanguineous couples [17], this however was not supported in our data. Moreover, parameters including parental ages, maternal weight, smoking, chronic diseases and folate intake were recorded and no significant difference was documented between consanguineous and non-consanguineous couples.

Discussion

The prevalence of BD in middle- and low-income countries is generally underestimated mainly as a result of deficiencies in diagnostic capabilities as well as lack of population-based studies [2].

Our findings show an overall BD prevalence of 3.25% among Lebanese neonates. Interestingly, this figure is almost half the originally estimated rate published by the March of Dimes global report for the same population (6.3%) [2]. Nonetheless, data reported in the current study are comparable to those reported from Iran (3.7%), Bahrain (2.7 %) and Oman (2.4%); but higher than those reported from other developing countries such as UAE (0.8%). [19,20]

The distribution pattern of BD affecting specific organ systems has been shown to differ between countries. In Turkey, the most

Table 5: Crude odds ratios of parental consanguinity by birth defects.

Parental consanguinity	Birth defect	No defect	
	N (%)	N (%)	OR [95% CI]
	Any birth defects		
Not related & distant	1,140 (81.2)	39,642 (86.7)	Referent
First cousins	188 (13.4)	4,443 (9.7)	1.5 [1.2-1.7]
Second cousins	76 (5.4)	1,648 (3.6)	1.6 [1.3-2.0]
	Cardiovascular		
Not related & distant	497 (80.3)	40,285 (86.6)	Referent
First cousins	83 (13.4)	4,548 (9.8)	1.5 [1.2-1.9]
Second cousins	39 (6.3)	1,685 (3.6)	1.9 [1.3-2.6]
	Urogenital		
Not related & distant	234 (82.1)	40,548 (86.5)	Referent
First cousins	38 (13.3)	4,593 (9.8)	1.4 [1.0-2.0]
Second cousins	13 (4.6)	1,711 (3.7)	1.3 [0.7-2.3]
	Musculoskeletal		
Not related & distant	197 (76.1)	40,585 (86.6)	Referent
First cousins	45 (17.4)	4,586 (9.8)	2.0 [1.5-2.8]
Second cousins	17 (6.6)	1,707 (3.6)	2.1 [1.2-3.4]
	Gastrointestinal		
Not related & distant	111 (74.5)	40,671 (86.6)	Referent
First cousins	30 (20.1)	4,601 (9.8)	2.4 [1.6-3.6]
Second cousins	8 (5.4)	1,716 (3.7)	1.7 [0.8-3.5]
	Neurological		
Not related & distant	78 (77.2)	40,704 (86.5)	Referent
First cousins	17 (16.8)	4,614 (9.8)	1.9 [1.1-3.2]
Second cousins	6 (5.9)	1,718 (3.7)	1.8 [0.8-4.2]
	Chromosomal		
Not related & distant	73 (84.9)	40,709 (86.5)	Referent
First cousins	9 (10.5)	4,622 (9.8)	1.1 [0.5-2.2]
Second cousins	4 (4.7)	1,720 (3.7)	1.3 [0.5-3.5]
	Eye, ear, face and neck		
Not related & distant	48 (75.0)	40,734 (86.5)	Referent
First cousins	11 (17.2)	4,620 (9.8)	2.0 [1.1-3.9]
Second cousins	5 (7.8)	1,719 (3.7)	2.5 [0.9-6.2]
	Cleft lip/palate		
Not related & distant	44 (83.0)	40,738 (86.5)	Referent
First cousins	6 (11.3)	4,625 (9.8)	1.2 [0.5-2.8]
Second cousins	3 (5.7)	1,721 (3.7)	1.6 [0.5-5.2]
	Respiratory		
Not related & distant	37 (77.1)	40,745 (86.5)	Referent
First cousins	6 (12.5)	4,625 (9.8)	1.4 [0.6-3.4]
Second cousins	5 (10.4)	1,719 (3.7)	3.2 [1.2-8.1]
	Other birth defects		
Not related & distant	34 (70.8)	40,748 (86.5)	Referent
First cousins	11 (22.9)	4,620 (9.8)	2.8 [1.4-5.6]
Second cousins	3 (6.3)	1,721 (3.7)	2.1 [0.6-6.8]

prevalent BD were those affecting the nervous system, accounting for 31.1% of all BD reported in the country. In contrast, the most common single system anomalies were found to involve the gastrointestinal system (30%) in Oman and the cardiovascular system (25.9%) in Saudi Arabia [11,21,22]. Our findings suggest that cardiac anomalies are most common in the Lebanese population studied, reaching 46.6% of all diagnosed BD. Another study from the same country found congenital cardiovascular and limb anomalies to have the highest pattern distribution in the study population [23]. In a study from our group conducted in the province of Beirut, ventricular septal defects were the most frequently diagnosed (26.6%) type of congenital heart anomalies [16].

When considering the distribution pattern of chromosomal abnormalities, comparable rates were reported from neighboring countries. While the specific prevalence for aneuploidies was 2‰ in our study, rates reported from Mediterranean countries ranged from 2.2 ‰ in UAE to 3.2 ‰ in Oman [21,22]. The most commonly encountered chromosomal anomaly was Down's syndrome, with a prevalence of 1.7 ‰. Other chromosomal abnormalities may be underestimated because of under diagnosis or under reporting from worldwide

surveillance data. Chromosomal microdeletions represent only 2‰ of all suspected syndromes, lower than what is reported in the EUROCAT registries 2003–2007 (0.55/1,000 births) [23]. Similarly, skeletal dysplasias represent only 6.2% of the reported syndromes [24].

Associations between parental consanguinity and higher odds of BD have been previously reported in countries with elevated consanguinity rates [17,25] These associations have also been clearly demonstrated in our study in which the odds of cardiovascular anomalies in neonates were increased by approximately 50% in consanguineous marriages compared with the general population. However in our study, no well-defined relationship between the odds ratio of BD and extend of cousinship of parents could be established. In the study of Tayebi et al. [20] , although the prevalence of anomalies was higher in consanguineous marriages, no significant difference was found between the inbreeding coefficient and the prevalence of anomalies. Kushki et al. [26] also failed to show a significant relationship between malformations and extend of cousinship of the parents, despite high consanguinity in malformed patients. In a study by Bromiker and Baruch [27] no statistically significant difference was found in the incidence of congenital malformation with extend of cousinship of parents' relation.

One possible explanation is that the odds ratio is a good measure of associations, but may represent an inaccurate tool for classifying or predicting risk for individual subjects [28]. Strong statistical associations between birth defects and extend of cousinship therefore may not necessarily predict individual risks accurately. This important point is not widely appreciated and may explain to some extent the disappointing performance of many markers when used to predict outcome.

A low prevalence for monogenic and unknown etiology syndromes (0.42 ‰) was encountered in this study. These numbers while comparable to reports from western countries such as Great Britain (0.51 ‰), may be construed as very low considering the consanguinity profile of a country like Lebanon [29]. In fact, single gene disorders are known to be common in the Middle East with a perpetual occurrence of rare genetic disorders due to the practice of inbreeding. Underestimated figures may be explained on the basis of suboptimal clinical evaluation, inadequate case assessment and under reporting. Indeed, the limited number of specialized care centers besides academic institutions in Lebanon significantly limits the opportunity for early and proper diagnosis.

This is the first study to evaluate a total of 50,396 live born neonates from different provinces of Lebanon, estimate the overall prevalence of BD and determine the distribution pattern of particular defects in this country. The study also characterized the association between parental consanguinity and specific patterns of birth defects. This database offers a platform to study maternal exposures and risk behaviors in relation to patterns of birth defects, offering opportunities for antenatal and prenatal counseling and prevention.

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