A prospective study of congenital malformations among live born neonates at a University Hospital in Western Saudi Arabia

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ABSTRACT

Objective: To estimate the incidence of major and minor congenital malformations among liveborn infants at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Estimation of risk factors were also evaluated.

Methods: Between March 2004 and May 2005, a total of 5356 babies born at King Abdulaziz University Hospital, were enrolled in this study for malformations. Details of cases were recorded after parents' interviews, clinical, radiological, and laboratory evaluations.

Results: One hundred and forty-seven (27.06/1000 livebirth) and 13 (2.39/1000 birth) stillbirth had congenital anomalies. In all livebirth, incidences of major anomalies were 93.9% and minor were 6.1%. Mothers of 95.9% with congenital malformation were healthy, 3.4% were diabetic and 0.7% had cardiac malfomation. In 38.8% of cases parents were consanguineous. Among the liveborn births, the most common system involved was cardiovascular (7.1/1000), followed by musculoskeletal/limb (4.1/1000), external genitalia (2.8/1000), urinary (2.6/1000), multiple chromosomal (2.2/1000), orofacial (1.9/1000), central nervous system (1.9/1000), skin (1.7/1000), multiple single gene (1.3/1000), multiple sequence (0.75/1000), eyes (0.56/1000), unclassified (0.19/1000), musculoskeletal/abdominal (0.19/1000), endocrine (0.19/1000).

Conclusion: High incidence of major malformation in Jeddah. Importance of Genetic Counseling is revealed in our study since more than three quarters of mothers were under 36 years, and may well plan future pregnancies.

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Congenital malformation was defined as "a permanent change produced by an intrinsic abnormality of development in a body structure during prenatal life".[1] It was reported that congenital anomalies occur in 3% of all infants.[2] Congenital anomalies including structural malformations, chromosomal abnormalities and metabolic disorders are becoming the most important cause of perinatal mortality (about a quarter of all perinatal deaths) in the countries of Europe and, after prematurity, the second cause of infant morbidity.[3] Beyond the direct impact on affected children and their families, they impose a tremendous financial burden on medical treatment, educational and support services.[4] Currently, there are no adequate services for the prevention of congenital abnormalities and many women continue to give birth after the age of 40 years. There is also a lack of awareness by both families and the health authorities of the importance of genetic counseling in the prevention of congenital malformations. Primary or true prevention is at present limited, for example folic acid can prevent only a small proportion of congenital anomalies.[5] Tertiary prevention (corrective surgery or medical treatment of anomalies) is successful and curative for some malformations.[6] The pattern and prevalence of congenital anomalies may vary over time or geographical location, thereby reflecting a complex interaction of known and unknown genetic and environmental factors including sociocultural, racial and ethnic variables.[7] The causes of congenital malformations are varied and few studies have evaluated the etiology of malformations in newborns.[8] Malformations can be divided into broad categories such as those of simple genic origin (monogenic); those held to be

because of interactions between multiple genetic and non-genetic, usually undefined factors (multifactorial); those associated with chromosomal abnormalities; those attributed to discrete environmental factors as the major cause; and all others with no recognized cause.[9] Accurate quantification of congenital anomalies within a given population is essential for estimating their burden and documenting the need for prevention. The data collected from the monitoring system may then be used for identifying prevalence trends, for conducting research on potential risk factors, for public health policy development, for planning and implementation of services needed by children with malformations and for evaluating the effects of preventive measures and treatment services.[7] The population of the Saudi Arabia is a mixture of different ethnic groups, the majority being Arab Muslims. Currently, there are no adequate services for the prevention of congenital abnormalities and many women continue to give birth after the age of 40 years. There is also a lack of awareness by both families and the health authorities of the importance of genetic counseling in the prevention of congenital malformations. The aim of the present study was to estimate the prevalence of congenital malformations among all live births at King Abdulaziz University Hospital, Jeddah, Saudi Arabia over a period of 14 months. Estimation of importance of risk factors such as maternal age and diseases as well as consanguinity for occurrence of malformations were also evaluated.

Methods. King Abdulaziz University Hospital is the main teaching hospital in Jeddah, Saudi Arabia. A study of 5432 consecutive live (n=5356) and stillbirths (n=76) was carried out at this hospital during a 14-month period from March 2004 to May 2005. After full approval of all procedures had been obtained from the Departmental and Hospital Ethical Committee, the numbers of congenital anomalies were 13 out of 76 among still birth and 147 out of 5356 livebirth. Malformations were subdivided into major and minor malformations following guidelines set out by the European Registers of Congenital Anomalies and Twins (EUROCAT).[10] All cases of major and minor congenital malformations either suspected or diagnosed within the first few days (up to 1 week after birth) were prospectively recorded. Only babies born at or after 24 week gestation, or with a birth weight of >500 g were included in the survey. Stillborn babies were examined immediately after delivery and liveborn babies were routinely examined within 48 hours of birth. Stillbirths referred to all fetal deaths of 24 completed week's gestation and this is the definition used in this study.[11] Major malformations were defined as birth defects that result in fetal mortality, require major surgical intervention, or have a significant long-term effect on the newborn physical and/or mental functions.[12] As expected, in many instances more than one system was involved. However, for the purpose of this study the anomalies were classified only once, according to the affected major system.

Cytogenetic analysis. Blood samples were collected from children with congenital anomaly for chromosomal analysis and karyotyping. Perform chromosomal karyotyping for the samples received through different stages according to the Genomic Medicine Unit (GMU) protocols (The ACT Cytogenetic Laboratory Manual) such as: cell culturing, harvesting and hypotonic treatment, fixation, slide making, G-banding and microscopic analysis using META-system as software. The slides were made from phytohemagglutinin (PHA) stimulated lymphocytes cultured for 48-72 hours before thymidine addition to synchronize the cell proliferation. The chromosome length was 400-550 bands. Chromosomal karyotypes were described according to an International System for Human Cytogenetic Nomenclature (ISCN).

Statistical analysis. We used Statistical Package for Social Sciences Version 10.0 (SPSS Inc, Chicago, IL, USA) software package for data entry. Analyses included frequency distributions and percentages. The chi-squared test was used to compare differences between groups. Statistical significance was accepted at $p<0.05$ level.

Results. Among 5432 total births, 5356 babies were live birth and 76 were stillbirth. During a 14-month period, the prevalence of congenital malformation in the total births were 160 babies (29.46/1000 births), 27.06/1000 births were livebirths and 2.39/1000 births were stillbirths. The diagnosis of congenital malformations was based on the clinical examination by the Geneticist. Appropriate investigations such as chromosome analysis, echocardiography, metabolic screening, sonography, skeletal surveys, radiography and clinical photography and a review of standard dysmorphology texts[13] and dysmorphology databases[14] were assisted in making an accurate diagnosis. In Saudi Arabia, autopsy is not permitted. For each case, a detailed antenatal history including history of exposure to teratogens and family history, including the level of consanguinity, were carefully obtained by reviewing the maternal and labor ward records and by interviewing the parents. Background maternal and infant data (gestational age, birth weights, height, head circumference, gender, singleton or multiple) were collected from the Medical Records. Among the live born births, frequencies of major and minor congenital anomalies between studied congenital malformed

babies were 93.9% and 6.1% with prevalence rate of 25.77/1000 and 1.68/1000, with a highest incidence of major congenital malformation. The prevalence of congenital malformation were non-significantly elevated in males than females (15.30/1000 versus 12.14/1000, $p>0.05$) and in Saudi than in non-Saudi children (14.75/1000 versus 12.70/1000, $p>0.05$) (**Table 1**).

The range of the body weight of malformed babies, length, and head circumference was shown in **Table 2**. The range of the Apgar score at one minute was 2-9, 7.77±1.89 and at 5 minutes was 5-10, 9.35±1.20.

Table 2 shows the characteristics of malformed children and their mothers. The prevalence of affected body system between malformed children are shown in **Table 3** and **Figure 1.** Regarding consanguinity, 38.8% of parents with congenital anomalies had consanguineous marriage. The rates of consanguinity were 27.2% in Saudi and 11.6% in non-Saudi.

Discussion. Differences in reported birth prevalence rates of congenital malformations over time and among countries, or even within the same country among regions, may be attributed to one or more factors such as design of the study (hospital-based or population-based, prospective or retrospective), definitions, classifications and inclusion criteria used, type of surveillance system, etiological heterogeneity of malformations, accuracy of diagnosis, gestational age at which these are included in monitoring reports and extent to which these terminations are notified.[15-17] These make comparison of rates among studies difficult and probably not very informative.[17] The true incidence of congenital malformation can only be determined if all livebirths, fetal deaths and spontaneous, and induced abortions are examined. However, in this study, fetal deaths and spontaneous abortions were not studied. The overall incidence of

Table 1 - Types of anomalies, nationality and gender of malformed children and their mothers.

Variables	Number and prevalence	Percentage
Types of congenital anomalies		
Major	138 (25.77/1000)	93.9
Minor	9 (1.68/1000)	6.1
Nationality		
Saudi	82 (15.30/1000)	55.8
Non-Saudi	65 (12.14/1000)	44.2
Gender		
Male	79 (14.75/1000)	53.7
Female	68 (12.70/1000)	44.2

Table 2 - Characteristics of malformed children and their mothers.

Variables	Mean±SD	Range
Babies		
Body weight (kg)	2.97±0.70	1.11 - 5.20
Length (cm)	50.30±5.36	31.0 - 59.0
Head circumference (cm)	34.22±2.46	23.5 - 44.0
APGAR (1 min)	7.77±1.89	2.0 - 9.0
APGAR (5 min)	9.35±1.20	5.0 - 10.0
Mother		
Mother age (years)	29.30±7.00	16.0 - 48.0
Gravid	3.77±2.69	1.0 - 14.0
Para	2.75±2.68	0 - 13.0

Table 3 - Frequency of congenital anomalies in malformed newborns according to the affected major body system (n=147).

Type of anomalies	No. of cases	Prevalence to total live births	Percentage to total anomalies
Cardiovascular system	38	7.1/1000	25.9
Muscloskeletal/limb	22	4.1/1000	15.0
External genitalia	15	2.8/1000	10.2
Urinary system	14	2.6/1000	9.5
Multiple chromosomal	12	2.2/1000	8.2
Orofacial	10	1.9/1000	6.8
Central nervous system	10	1.9/1000	6.8
Skin	9	1.7/1000	6.1
Multiple single gene	7	1.3/1000	4.8
Multiple sequence	4	0.75/1000	2.7
Eyes	3	0.56/1000	2.0
Unclassified	1	0.19/1000	0.7
Musculoskeletal/abdominal	1	0.19/1000	0.7
Endocrine	1	0.19/1000	0.7
Total	**147**	**27.48/1000**	**100.0**

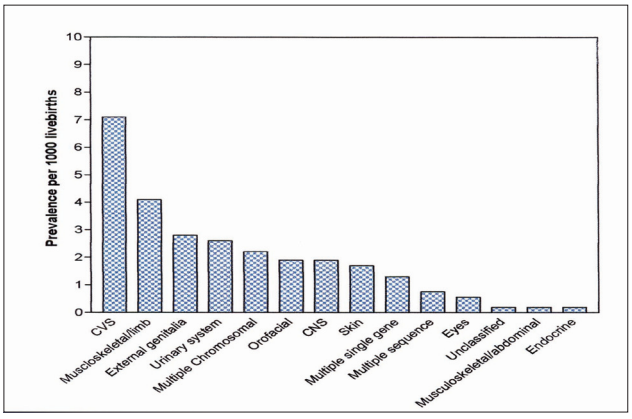

Figure 1 - Frequencies of congenital anomalies in relation to main body system afftected.

congenital malformations in this study was 29.46/1000 birth, 27.07/1000 in livebirths and 2.39/1000 in stillbirth. In livebirths, the frequency of major anomaly was 93.9% (25.77/1000) and minor was 6.1% (1.65/1000). This incidence was higher than that reported in other parts of Saudi Arabia and neighboring Arab countries. It had been reported that incidence of congenital anomalies in Al-Khobar, Eastern Saudi Arabia was 17/1000 with 74.4% major and 25.6% minor anomalies.[18] The prevalence of major congenital anomalies reported in this study in consistence with 24.6/1000 births as reported from Oman,[19] but higher than 0.89/1000 birth as reported from Al-Qassim,[20] 17.4/1000 birth as reported from Hafuf,[21] 16/1000 birth as reported from Jeddah,[22] Saudi Arabia, 12.9/1000 births as reported by Al-Jawad et al[23] and 16.6/1000 births reported by Al-Talabani et al[24] from Abu-Dhabi, 10.5/1000 births reported from Al-Ain,[25] United Arab Emirate (UAE). The incidence of major congenital anomalies reported in this study was also significantly higher than that recorded in 1990s in Europe, which could be contributed to low rate of consanguineous marriage.[26] Also, termination of these pregnancies in Europe may have a definite impact on the prevalence at birth of lethal and congenital anomalies with a low survival rate by reducing their number dramatically.[27] In Saudi Arabia, apart from exceptional cases which are absolutely incompatible with life such as anencephaly, and termination of pregnancy is illegal. The observed low prevalence rate, in a study from Al-Qassim is explained by attrition due to death of subjects with severe anomalies over a 20-year-period that represented target population of that study.[20] One of the reasons of the high incidence of major congenital anomalies obtain by this study could be that some degree of selection bias was probably in effect because study was conducted in a major tertiary hospital in the region, which receives high-risk pregnancies. Importance of genetic counseling becomes evident, considering that most of mothers of malformed babies in our study were younger than 36-years-old and plan to have future pregnancies. In this study, 3.4% of mothers of malformed babies were suffering from diabetes mellitus and 0.7% from rheumatic heart. In Al-Kobar, Al-Jama[18] reported that the incidence of malformed babies in diabetic mothers was 7.8%. Meanwhile, other studies found that maternal age (>25 years) and chronic medical diseases, most importantly diabetes, were significantly correlated with congenital malformation.[20] The incidence of congenital anomalies in this study was not significantly elevated in males compared to females. In this respect, other investigators[28,20] found different congenital malformations were significantly related to male gender. This finding raised some speculations; for instance, either females were afflicted relatively more by fatal congenital anomalies or alternatively, they survived with more minor anomalies as found by some investigators.[20,28] It is evident from the literature that there are large reported variations in pattern of congenital malformations involving different body systems. In this study, congenital anomalies among all livebirths were mostly observed in the cardiovascular system (CVS), followed by musculoskeletal/limb, external genitalia, urinary system, multiple chromosomal, orofacial, central nervous system (CNS), skin, multiple single gene, multiple sequence, eyes, followed by unclassified, musculoskeletal/abdominal and endocrine. On contrary, other investigators[28-30] found that CNS was most common affected system by congenital malformations. The major congenital anomalies observed in Jeddah by Nasrat[12] was CNS, followed by CVS and then by chromosomal anomalies. In Al-Khobar, anatomical organs most commonly affected were CNS (48.8%), with hydrocephalus, anencephaly and meningocele being predominant lesions followed by musculoskeletal, renal defects, gastrointestinal tract and chromosomal defects respectively. Meanwhile, multiple anomalies were present in 16.7% infants.[18] Congenital heart disease is a diverse group of malformations with an apparent heterogeneous etiology.[31] In this study, congenital heart diseases were the most common major malformation (25.9%), most commonly due to atrial septal defect (ASD), followed by ventricular septal defect (VSD), patent ductal arteriosus (PDA), teratology of Fallot (TOF), mitral regurge (MR), tricuspid regurge (TR), and ventricular hypertrophy. Our results with partial similarity to those obtained by Becker et al,[32] where they found a relatively higher proportion of ASD's and TOF's than reported in other large epidemiological studies of more heterogeneous populations.[33] A high proportion of ASD cases had been reported at another center in Saudi Arabia[34] and in India[35] with inbreed populations, suggesting that there may be a recessive component of ASD. Congenital cardiac malformations are frequently associated with non-cardiac malformations and chromosomal anomalies. In this study many syndromes were reported associated with congenital cardiac malformation mostly with Down's and Edward's syndromes. In Malta, during 1990-1994, the birth prevalence of congenital heart disease was 8.8/1000. Of these, 21 (9%) had recognized chromosomal anomalies (0.80 /1000), 2% had recognized non-chromosomal syndromes and 6% had other major non-cardiac malformations (0.69/1000). Down syndrome accounted for 95% of all syndromic congenital heart disease, with a birth prevalence of

0.73/1000.[36] Although, role of intermarriage has been established in some uncommon autosomal recessive disorders,[37] consanguinity may play a part in structural defects, including congenital heart lesions.[38] The CNS anomalies reported in this study was 6.8% from total cases (4.1/1000). The major abnormalities observed in this study were hydrocephalus, then encephalocele, meningeomyelocele, hyperplexia, microcephaly. Among CNS anomalies associated with chromosomal abnormalities cases of Down's syndrome, Edward's syndrome, Arnold Chiarre syndrome, congenital muscle dystrophy, Dandy Walker syndrome were reported in this study. There has been a large variation in the incidence of central nervous system defects in different parts of world and at different periods.[39] The incidence of hydrocephalus was 1.6/1,000 from Al-Madinah Al-Munawarah, Saudi Arabia,[40] 0.41/1000 in Al-Ain, UAE.[41] In Hegazy et al,[25] study the percentage of Trisomy-21 among the neurologically impaired was 25.99%. Only 4 cases (0.75/1000) (2 cases encephalocele and 2 cases meningomyelocele) with neural tube defects (NTD) was reported in this study which is lower than that reported by other investigators. The incidence of neural tube defect were 0.82 to 1.6/1000 in Saudi Arabia,[28,42,43] 0.78/1000 births in Asir region, Saudi Arabia,[44] 1.14/1000 in Al-Ain, UAE,[41] 1.3/1000 in Kuwait,[45] 1.507/1000 in Bahrain[46] and 1.6/1000 in Shiraz- Iran.[47] The etiology of NTD has been proven to be closely related to folic acid deficiency.[39] In the Western countries, NTD form a large but diminishing proportion of all major congenital malformations.[39] Folic acid supplementation is therefore a well-recognized preventive measure against NTD, with a dramatic decline in the incidence of NTD noted in many parts of the world.[48] Abnormalities caused by a multiple single gene defect were found in 1.3/1000 (4.8%) of congenital malformed babies, which is lower than 7% reported by van Regemorter et al,[49] 27% reported by Al-Gazali et al,[25] from UAE and 15.3% reported by Sawardekar[19] from Oman. Kalter and Warkany[9] opined that approximately 7.5% of all congenital malformations have a monogenic (Mendelian) basis for the populations in north-western Europe and north-eastern USA. Many mutant genes cause congenital malformations and further research needs to be conducted in populations of the eastern Mediterranean region.[19] The birth prevalence of chromosomal abnormalities was 2.2/1000 (8.2%) in this study which is almost lower than (12.9%) that reported by Sawardekar[19] and van Regemorter et al.[49] The birth prevalence of chromosomal abnormalities reported in this study was higher than 1.7/1000 reported by Al-Gazali et al[25] and 2.13/1000 by Al-Jawad et al[23] in the neighboring UAE and lower than 3.2/1000 by Sawardekar[19] in Oman. The incidence of congenital anomalies in consanguineous parents were 38.8%, which was higher in Saudi compared to non-Saudi (27.2% versus 11.6%). This is probably related to the high rate of consanguineous marriages in Saudi Arabia. Several studies have reported an association between parental consanguinity and higher rates of congenital anomalies.[50] Jaber et al[51] reported that children born to first-cousin parents have 2.4 to 2.7 times higher risk of having congenital anomalies as compared to children of non-consanguineous parents. Saudi Arabia has a long tradition of consanguineous marriages which have a socio-cultural importance in the region and are preferred because of several reasons including family stability and socio-economic advantages.[16] A family-oriented approach has been recommended to identify families at increased risk and provide them with risk information and counseling.[52] However, further research needs to be conducted to evaluate the potential of this approach.[16] The high incidence of major congenital malformations reported in this hospital-based study indicates that there is a need for surveillance and development of a congenital anomaly monitoring system both at the national and regional levels in Saudi Arabia. As the collection of data is the cornerstone of any surveillance system, it is necessary to obtain more information on prevalence rates and types of congenital anomalies and their possible causes from all regions in Saudi Arabia. At present there are no adequate services for genetic disorders and congenital anomalies in Saudi Arabia. The Eurocat working group for Europe recommend that genetic counseling supported by the availability of antenatal diagnostic procedures and screening should considered an essential part of a genetics surveillance program. Coordination of medical, social and educational services including raising awareness among health professionals as well as the general public about birth defects, developing culturally appropriate educational material and involving community and religious leaders should also form an integral part of the program. Emphasis would be initially on primary prevention measures, which can be incorporated into the existing primary health-care system in the country, such as avoidance of known teratogenic agents, appropriate management of maternal conditions such as obesity and diabetes, advice related to maternal nutrition, family planning and advanced maternal age and premarital and preconception counseling.

Significant scientific and technological advances in the field of genetic medicine and the high prevalence of congenital malformations as shown by this study, emphasize the urgent need for translating the knowledge and research into intensive preventive activities for congenital anomalies to reduce their impact on Saudi society.

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