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Congenital Anomalies in Newborns: Review Article

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ABSTRACT

Introduction: Congenital anomalies (CAs) are a worldwide problem and an important cause of childhood death, chronic illness, and disability. They result from defective embryogenesis or intrinsic abnormalities in the development process and often lead to long-term disability, which may have significant impacts on individuals, families, health-care systems, and societies. The most common, severe congenital anomalies include heart defects, neural tube defects and the Down syndrome. Although congenital anomalies may be the result of one or more genetic, infectious, nutritional or environmental factors, it is often difficult to identify the exact causes. Some congenital anomalies can be prevented; timely vaccination of the mother, adequate intake of folic acid or iodine through fortification of foods or supplementation during pregnancy, and adequate antenatal care are just 3 examples of primary preventive methods. Physicians involved in the provision of health care for children and adolescents, need a basic understanding of how to evaluate and when to refer children and adolescents with congenital anomalies to the respective subspecialty. Therefore, the aim of this article is to review the incidence, and different patterns of birth defect or congenital anomalies in several Eastern Mediterranean developing countries.
Materials and Methods: In this study, the terms Birth Defects, Congenital Anomalies and Congenital Malformations are synonymous and have been used interchangeably throughout this article.
Conclusion: This study provides useful information about the extent and range of congenital malformations diagnosed immediately after birth in infants and highlighted the prevalence and types of congenital malformations. Maternal vaccination, adequate intake of folic acid or iodine through fortification of main foods or supplements during pregnancy, and adequate prenatal care are just three examples of contraceptive methods.

Keywords: Congenital Anomalies; Infants; Congenital Heart Defects.

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Introduction

The WHO defined congenital anomalies (CAs) as structural, functional, or metabolic anomalies that originate during intrauterine life and can interfere with the body function [1]. They result from defective embryogenesis or intrinsic abnormalities in the development process [2]. Various systems have been used to categorize congenital abnormalities: These may be classified according to severity into major and minor anomalies [3].

Alternatively, the International Classification of Diseases, (ICD), has classified CAs according to the affected body system. Congenital anomalies involving the brain are reported to have the highest incidence at 10/ 1000 live birth compared to heart at 8/1000, kidney at 4/1000, limb at 1/1000 while all others have a combined incidence of 6/1000 live birth [4]. CAs can also be categorized into three groups based on their cause: genetic, environmental, and multifactorial although the exact cause of CAs is unknown in about 40-60% of cases. Both genetic and environmental causes have identified in about 25 % of cases, approximately 15% of congenital malformations are caused solely by genetic factors [5].

The precise cause of many malformations that fall under the multi factorial group although unknown is thought to be due to interactions between genetic and environmental factors [6]. Malformation caused by known environmental exposure (e.g., teratogens including maternal infections) are treated separately. Teratogens may cause various alterations during the process of embryogenesis, including chromosomal breakage, gene mutation or enzyme inhibition. These changes are affected by various factors, like the dose of the teratogen, frequency of exposure or the stage of embryo development. Malformations associated with chromosomal disorders are treated as part of the relevant chromosomal syndrome, and malformations associated with single gen disorders, genetic syndrome or parenteral consanguinity are grouped as inherited disorders. These steps leave a large group of congenital malformation with multifactorial or unknown cause [7].

Factors that may increase the risk occurrence of CAs include genetic disorders, socioeconomic and demographic factors like parental consanguinity, maternal infections during pregnancy, drugs abuse, ionizing radiation, and chemical and air pollution. Pregnancy- associated conditions such as insulin-dependent diabetes, and hypertension during pregnancy were also found to be associated with a higher incidence of congenital malformations in the baby [8,9]. Ethnic and environmental factors affect the birth prevalence of some groups of non-syndromic malformations, including neural tube defects and orofacial clefts. The diversity and relatively constant birth prevalence of these unexplained malformations suggest that many are due random accidents during the complex process of embryonic development, a concept that is supported by mathematical consideration [8].

Pregnancy associated conditions such as insulin – dependent diabetes, hypertension during pregnancy such as antepartum hemorrhage, twin pregnancy, oligohydramnios, and polyhydramnios were also found to be associated with more CAs [10, 11]. Oligohydramnios interferes with fetal movement resulting in a cascade of developmental events leading to fetal anomaly. Some congenital anomalies can be prevented by removal of risk factors or establishment of protective factors. Important interventions during the antenatal period include ensuring adequate dietary intake of vitamins and minerals especially folic acid, avoiding harmful substance such as tobacco, and reducing environmental exposure to hazardous substance such as heavy metals and pesticides, teratogens and radiation.

Trisomy 21 is the most common genetic cause of moderate intellectual disability. Different types of chromosome errors lead to Down syndrome. Associated factors that increase the risk of chromosome 21 mal segregation include advanced maternal age and recombination [12]. The incidence of Down syndrome in live births is approximately I in 733; the incidence at conception is more than twice that rate; the difference is accounted by early pregnancy losses. Affected individuals are more prone to congenital heart defects (50%) such as atrioventricular septal defects or endocardial cushion defects, ventricular septal defects, isolated secondum atrial septal defects, patent ductus arteriosus, and tetralogy of Fallot.

Gastrointestinal atresia (duodenal or esophageal atresia) and vertebral abnormalities are also common. Nuchal translucency (NT) is the sonographic appearance of a collection of fluid under the skin behind the fetal neck in the first trimester of pregnancy. To document the incidence of congenital heart defects (CHD) that are detectable echocardiographically in the fetus with trisomy 21, and the relationship with nuchal translucency, fetal sex, and ethnicity, a study was conducted by MograV et al in 2011. They concluded that most fetuses (66–76%) with trisomy 21 have a structurally normal heart on echocardiography. The presence of structural CHD was not associated with increased NT. The increased incidence of atrioventricular septal defect (AVSD) in females was

confirmed in their study, although an ethnic difference could not be confirmed [13].

Discussion

Congenital anomalies (CAs) are a worldwide problem, causing perinatal and infant deaths and postnatal physical disabilities. CAs accounted for 510,400 deaths worldwide in 2010 according to the Global Burden of Disease Study [14]. The following study determined the pattern and associated risk factors of the congenital anomalies in newborns delivered at the Maternity Teaching Hospital, at Erbil city. All the births occurring in the Maternity Teaching Hospital in Erbil city, Kurdistan region, Iraq, between 1st April 2015 and the end of March 2016 were recorded. All babies with congenital anomalies were identified. The rate and common types of congenital anomalies were estimated. Then a case-control study was conducted involving all women who had babies with congenital anomalies and the same number of women whose babies had no congenital anomalies.

Data were collected using a structured questionnaire.

Of the 35,803 recorded births in the Maternity Teaching Hospital, Erbil, 130 women delivered babies with at least one congenital anomaly, giving a rate of 3.63/1000 deliveries. The most common anomalies involved the central nervous system (37.7%) followed by the musculoskeletal (23.1%) and gastrointestinal systems (20.8%). There was a statistically significant association between delivering a child with congenital anomalies, and a maternal history of having a previous child with congenital anomalies, the presence of parental consanguinity, and the history of maternal medical disorders. Maternal occupation and smoking did not have any influence on the incidence of congenital anomalies [15].

This study provides baseline information for future prevention and better management of patients likely to have babies with congenital anomalies. The central nervous system anomalies, which occurred both as single-system and multiple-system malformations were the most common type of anomaly found in this study. The occurrence of this anomaly can be explained by a lack of foods fortified with folic acid. Studies have shown that daily maternal intake of folic acid alone or in the form of multivitamin supplement before conception until the first trimester can help in preventing the occurrence of neural tube defects [16,17].

In a report from Turkey the distribution and demographic characteristics of CAs in a Turkish province, Denizli, were evaluated for five years. The records of 63,159 births between 2000 and 2004 were examined retrospectively. Major CAs were classified according to year, organ system, gender, family relationship, maternal age, mortality rate and method of delivery. There were 183 cases of major birth defects among 63,159 live births, giving a prevalence of 2.9/1000. Consanguineous marriages are believed to have an important contribution to the risk of congenital abnormalities. The risk of a child having a recessively inherited condition is higher among related parents and this risk increases with the closeness of the relationship [18,19].

Anomalies of the central nervous system were the most common defects (31%), followed by cleft palate/lip (19%), musculoskeletal system anomalies (14%), and Chromosomal anomalies (13%). Among the infants with major anomalies, 14% did not survive, 56% delivered vaginally, and 25% were miscarried [20]. Another report from Europe found that lethal congenital anomalies of the central nervous system were present in the still birth group. Cardiovascular and pulmonary defects were more prominent in the neonatal period. Urogenital and minor anomalies (miscellaneous) are more often seen in perinatal deaths without being a contributor to the cause of death [21].

CM accounts for 8-15% of perinatal deaths and 13-16% of neonatal deaths in India [22,23]. A cross-sectional descriptive study was carried out in the neonatal care unit of R.G. Kar Medical College and Hospital during the period of September 2011 to august 2012 in India. All the live born babies born in this hospital during this period were included. The newborns were examined for the presence of congenital anomalies and mothers were interviewed for socio-demographic variables. During the study period 12,896 babies were born, of which 286 had CMs, making a prevalence of 2.22%. Most of the women (55.7%) belonged to the age group between 21 and 30 years. Congenital anomalies were seen more commonly (3.3%) in multiparas in comparison with primiparas (1.8%).

The predominant system involved was the musculoskeletal system (33.2%) followed by gastro-intestinal (GI) system (15%). Talipes equinovarus (17.1%) was the most common malformation in the musculoskeletal group, cleft lip and cleft palate in GI system. CAs was more likely to be associated with low birth weight, prematurity, multiparity, consanguinity and cesarean delivery. They concluded that public awareness about preventable risk factors should be created and early prenatal diagnosis and management of common anomalies is strongly recommended [24]. A retrospective case series and a case -control study was conducted to estimate the frequency, describes the types and identify the possible risk factors of CAs among infants admitted at the Pediatric University Hospital, Alexandria, Egypt. Patient's records for the years 2010-2015 were reviewed and a sample of 200 infants (100 cases and 100 controls) was taken from infants presenting to general pediatrics, pediatric surgery, and genetic clinics of the hospital. Data were collected using a record checklist and a predesigned interviewing questionnaire. The study revealed that Congenital anomalies of the digestive system (38.0%), musculoskeletal system (32.9 %) and circulatory system (11.0%) were the most common types of CAs.

Males were more affected than females (63% versus 37%). The major risk factors for CAs were older parents, complications during pregnancy, prescribed medications, exposure to chemicals, and pesticides during pregnancy [25]. A Study done in AIN Shams University, Cairo in 1995-2009 showed a significant association between mothers' age over 35 years and CAs [26].

In a descriptive study at Rabat, they collected all the cases of congenital malformations diagnosed at the "les Orangers" Maternity and Reproductive Health Hospital in Rabat, from January 1st,2011 to June 31st,2016. Data were recorded on pre-designed sheets and a registry of malformations. Total and specific prevalence's were calculated for each malformation. A principal component analysis was then conducted in order to identify the different association of malformations. They registered 245 cases of congenital malformations out of a total of 43,923 recorded births; a prevalence of 5.58 per thousand births of which 19.2% were FDIU (fetal deaths in utero). A poly malformation syndrome was found in 26.5% of cases which makes a total number of 470 anomalies. The musculoskeletal anomalies predominated with a rate of 33%, followed by neurological abnormalities (18%) of whom 31% were hydrocephalus, 26.2% anencephaly, and 20.24% spina bifida. Malformations of the eye, ear, face and neck were described in 12% of cases, while genetic abnormalities were observed in 8.5 %, Down Syndrome comprised 87.5 of these anomalies. The antenatal diagnosis of congenital malformations was established in 28.6% of cases [27].

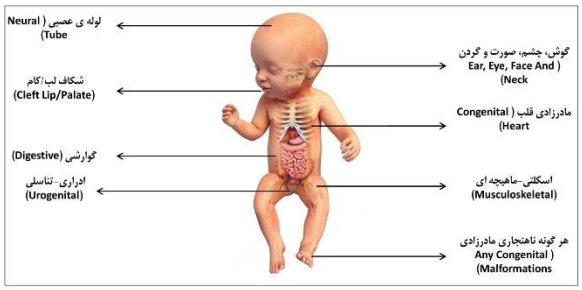

Figure 1: Organs involved in congenital malformations in babies

Musculoskeletal defects top the list of malformations in most series, perhaps because they are extremely visible and hence readily identified at birth. Early intrauterine period (between the 3rd and 8th week of gestation) is the vital period of life for the normal development of organs. Any insult within that period may result in congenital abnormalities [28]. Congenital malformations are present in 3% of all newborns and responsible for nearly 7% of neonatal deaths worldwide [29]. An unmatched case-control study was conducted from February 2018 to January 2019 in the Bale Zone hospitals of Ethiopia. A total of 409 women (136 cases and 273 controls) were selected. Mothers who gave birth with any type of congenital malformation were assigned as cases and those who gave live birth without any congenital abnormalities were assigned as controls. Controls were selected by the lottery method from the labor ward. For each case, two consecutive controls were assigned.

Logistic regression was conducted to analyze the data. Various types of CAs were diagnosed during the study period. Out of 136 congenital malformations, 42(31.0%) of them had anencephaly and 27 (19.8%) suffered from spina bifida. Alarmingly women who had been exposed to pesticides during current pregnancy were two times more prone to give birth to malformed infants than their counterparts.

Additionally, those women who chewed Khat during the periconceptional period were two times more likely to have congenital malformed babies as, compared to women who did not engage in this activity. Khat is a stimulant vegetable drug, which means it speeds up the messages going between brain and the body. Chewing the leaves of the ever - green shrub releases an amphetamine-like stimulant, although it is considered highly addictive. Khat is part of some social tradition in parts of the Middle East such as Saudi Arabia and Yemen and in eastern Africa such as Somalia [30].

During a one-year period (2008 - 2009), 45 opium-addicted mothers and their newborns were enrolled in a case - control study in Niknafs Maternity hospital, in Kerman, Iran. Maternal drug usage was determined via self-reporting by structured interviews. Neonates with in-utero opium exposure were assessed and treated for neonatal abstinence syndrome (NAS). Demographic characteristics and perinatal complications for case and controls were obtained from medical records. All cases were addicted to inhaled opium and none received methadone therapy. None of the cases was a heavy cigarette smoker, consumed alcohol, or had positive serology result for sexually-transmitted diseases. The mean ages were similar in both case and control groups. There was a higher prevalence of opium addiction among spouses of the case group compared with the control group (P = 0.001). The case group had significantly lower education level (P = 0.01) and socioeconomic status (P = 0.001) compared to the control group. Low birth weight (LBW) was more frequent in the opium-exposed neonates compared with the control group neonates (P = 0.001). In the opium-exposed infants, signs of NAS (Neonatal abstinence syndrome) were found in 32 (71%), requiring pharmacotherapy in 25 (55%) cases. Authors concluded that**:** Opium addiction among Iranian pregnant women is associated with an increased frequency of LBW (Low Birth Weight) in newborns. Furthermore, approximately half of the newborns exposed to opium in utero require pharmacotherapy for NAS. These findings support the need for comprehensive multidisciplinary evidence-based interventions in population who are at risk. [31].

The etiology of congenital abnormalities may be genetic (30-40%) or environmental (5-10%). Among genetic causes, chromosomal abnormality makes up

about 6%, single gene disorders about 25%, and multifactorial factor etiology 20-30%. In about 50% of cases, the cause is not known [32]. In a report from south-east Nigeria during the period of Jan 2007 to March 2011, a total of 607 newborns were admitted in the neonatal unit of a tertiary hospital. Seventeen (17) babies were found to have congenital abnormalities of various types giving a prevalence of 2.8%. Common abnormalities seen in these babies were mainly surgical birth defects and included cleft lip/ cleft palate, neural tube defects (occurring either singly or in combination with other abnormalities), limb abnormalities (often in combination with neural tube defect of various types), omphalocoele, umbilical hernia, ano-rectal malformations and dysmorphism associated with multiple congenital abnormalities [33].

In Iran a review study was conducted between 1992 to 2014 by Vatankhah S, et al (2017). The review of studies was performed through searching databases including IranMedex, SID, Magiran, Scopus, and PubMed. Descriptive and cross-sectional studies investigating on the prevalence of congenital anomalies among infants were included into the study. Hand search for some related journals and websites was done. The list of studies' references was reviewed. The data were analyzed using the CMA 2 software. Of 455 studies, 27 studies were included into the meta-analysis study. The overall prevalence of congenital anomalies among infants was estimated to be 2.3%. The overall prevalence rates, in terms of gender, were estimated to be 3% in boys and 2% in girls. The highest prevalence rates were related to musculoskeletal anomalies (27.5%), skin anomalies (19.7%) and genitourinary system anomalies (15.8%). The lowest prevalence rate was related to respiratory system (1.82%). They concluded that the prevalence of congenital anomalies among infants in Iran is high. Preventive strategies such as genetic counseling seem to be appropriate [34].

In another research about congenital anomalies in Iran a case control study was conducted to investigate the risk factors of congenital heart disease (CHD) by Roodpeyma et all (2002). The cases were 346 children with CHD who were admitted to a university hospital in Tehran from 1995 to 2000 and controls (n=346) were randomly selected from children without CHD who were admitted during the same period. The medical records of both cases and controls were reviewed. Ten risk factors were studied and found to be more prevalent among cases than controls (47 % versus 35%, $p<$ 0.005). Extra cardiac malformations (OR, 31.1;CI95, 15.9-60.9; *P<0.001* and choromosomal abnormalities (OR,34.05; CI95, 23.3-49.8; *P<0.001* were significant risk factors for CHD. Dysmorphic syndromes (*P<0.05*) and CHD in siblings (*P*<0.001) were also significant risk factors. Maternal illness and drug use in the first trimester of pregnancy, maternal history of previous abortions and stillbirths, parental consanguinity, and parental cardiac lesions were not significant risk factors for CHD in the offspring. Results suggest that genetic factors are associated with a higher risk for CHD than environmental or reproductive factors [35].

Despite improvements in medical care provided during pregnancy for diabetic mothers, the cardiac complications in their infants are still more frequent than in normal population. Congenital anomalies of the spine and skeletal system, genitourinary, cardiovascular systems, and visceral situs inversus are significantly more frequent among infants of diabetic mothers than. The most specific anomaly is sacral agenesis.

Between July 2010 to June 2011, two-dimensional/M-mode and Doppler echocardiography evaluations were performed in IDMs at the out-patient clinic of the pediatric cardiology ward of a University hospital in Tehran. The primary objective was to explore the spectrum of cardiovascular complications in infants of diabetic mothers (IDMs). The study also aimed at investigating probable relations between infants' heart lesions, the type of maternal diabetes, and the neonatal somatic data. A total of 32 IDMs (18 male and14 female) were studied. Congenital heart disease was found in 6 (18.7%) neonates and 3 of them suffered from conotruncal malformations. Hypertrophic cardiomyopathy[1] (HCM) was observed in 15 (46.9%) cases. Twenty- two infants (68.8%) were large for gestational age (LGA) infants. Gestational diabetes was found in 21 (65.6%) mothers. The researchers did not find a significant relation between the types of maternal diabetes and the frequency of CHD (P= 0.9), and the frequency of HCM in their infants (P= 0.9). Also a significant relation could not be found between LGA and the rate of CHD (P= 0.6) or the rate of HCM (P= 0.4). Data showed a high prevalence of CHD in IDMs in our pediatric cardiology clinic. Neither the types of maternal diabetes nor the somatic findings of newborns were related to the occurrence of cardiac complications [36].

Congenital heart disease is increased up to five –fold among infants of diabetic mothers, compared to the general obstetric population. Conotruncal defects, notably double-outlet right ventricle, transposition of great arteries, and truncus arteriosus are identified as the primary malformations associated with maternal diabetes. There is the possibility that abnormalities of neural crest migration are responsible for the cardiac defects seen in diabetic pregnancies. In another study by Meyer-Witt Kopf M et al (1996) 25-35%of fetuses with heart defects had other ultrasonographically detectable anomalies [37].

[1] Hypertrophic cardiomyopathy

Table 1: Incidence of congenital anomalies as reported in studies from several developing countries

Country	Study	Total number of affected patients	Central nervous system (%)	Gastrointestinal system (including cleft lip/cleft palate) (%)	Musculoskeletal system (%)	Cardiovascular system (%)	Genitourinary system (%)
Turkey	Tomatir et al (2009) [20]	183	31	19	14		
Nigeria	Obu et al (2012) [33]	17	98	2			
India	Sarkar et al (2013) [24]	286	11.2	15	33.2	9.1	10.5
Iraq	Ameen et al (2018) [15]	130	37.7	20.9	23.2		
Egypt	Abdou et al (2019) [25]	200		30	32.9	11	
Morocco	Forci et al (2021) [27]	245	18		33		

Conclusion

This study provides useful information on the magnitude and spectrum of congenital anomalies diagnosed soon after birth among neonates, it also has highlighted the prevalence and types of birth defects. CAs can contribute to long-term disability, which may have significant impacts on individuals, families, health-care system, and societies. The most common, severe CAs are heart defects, neural tube defects and Down syndrome. Although CAs may be the result of one or more genetic, infectious, nutritional or environmental factors, it is often difficult to identify the exact causes. Some CAs can be prevented. Maternal Vaccination, adequate intake of folic acid or iodine through fortification of staple foods or supplementation during pregnancy, and adequate antenatal care are just 3 examples of prevention methods.

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