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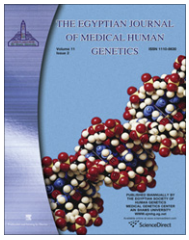

ORIGINAL ARTICLE

Congenital malformations prevalent among Egyptian children and associated risk factors

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KEYWORDS

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Birth weight

Abstract According to the World Health Organization the term congenital anomaly includes any morphological, functional, biochemical or molecular defects that may develop in the embryo and fetus from conception until birth, present at birth, whether detected at that time or not. Based on World Health Organization report, about 3 million fetuses and infants are born each year with major malformations. Several large population based studies place the incidence of major malformations at about 2–3% of all live births. In this study we tried to assess the frequency and nature of congenital malformations (CMs) among Egyptian infants and children as well as the associated maternal, paternal and neonatal risk factors. Patients (13,543) having CMs were detected among 660,280 child aged 0–18 years attending the Pediatric Hospital Ain Shams University during the period of the study (1995–2009), constituting 20/1000. Males were more affected than females (1.8:1). According to ICD-10 classification of congenital malformations the commonest system involved were, nervous system, followed by chromosomal abnormalities, genital organs, urinary system, musculoskeletal, circulatory system, eye, ear, face, and neck, other congenital anomalies, digestive system, cleft lip and palate, and respiratory anomalies. Among the maternal risk factors detected were multiparity, age of the mother at conception, maternal illness, exposure to pollutants, and intake of the drugs in first months. Consanguineous marriage was detected in 45.8% of

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patients. Surveys of CMs must be done in every country to provide prevalence, pattern of occurrence, nature, identify causes, and associated risk factors to prevent or reduce the occurrence of CMs.

1. Introduction

According to the World Health Organization the term congenital anomaly includes any morphological, functional, biochemical or molecular defects that may develop in the embryo and fetus from conception until birth, present at birth, whether detected at that time or not [1,2]. In this study we will concentrate on structural birth defects of prenatal origin that result from defective embryogenesis or an intrinsic abnormality of developmental process. The prevalence and types of congenital malformations (CMs) differ from one country to another and even in the same country from one region to another. This depends on the definition of congenital malformations applied; method of their detection, length of time the population under observation, ethnic and socio-economic characteristics of the population studied [3–5]. Based on World Health Organization report, about 3 million fetuses and infants are born each year with major malformations [5,6]. The impact of the birth defects on the fetus and newborn infant is great as they are responsible for 495,000 deaths world wide [6]. The great majority of these deaths occurred during the first year of life and thus contribute mostly to infant mortality rate. In Egypt, infant mortality rate due to birth defects is about 15% of all infant deaths (22/1000) [7]. Several large population based studies place the incidence of major malformations at about 2–3% of all live births [2,6]. Birth defects account for 15–30% of all pediatric hospitalizations and they exert a proportionately higher health care cost than other hospitalizations i.e. they impact a significant burden to families and society [8]. Children with major congenital malformations (CMs) were more likely to have Bayler Mental Development Index Scores of $\leqslant$70, Psychomotor Developmental Index Scores $\leqslant$70, neurodevelopmental impairment, moderate – to – severe cerebral palsy, length in the $\leqslant$10th percentile, head circumference in $\leqslant$10th, more rehospitalization and higher rate of early intervention use at 18–22 months corrected age [9]. The causes of congenital malformations are divided into four broad categories, genetics, environmental, multifactorial and unknown. A genetic cause is considered to be responsible in as many as 10–30% of all birth defects, environmental factors in 5–10%, multifactorial inheritance in 20–35% and unknown causes were responsible for 30–45% of cases [9]. Most of the CMs therefore are thought to have a multifactorial inheritance resulting from interactions between genes and environmental factors which are mostly unknown, such diseases are called complex diseases. This interplay between genes and environmental factors underlie the etiological heterogeneity of these defects and study of gene–environmental interactions will lead to better understanding of the biological mechanisms and pathological processes that contribute to the development of complex birth defects. It is only through this understanding that more efficient measures will be developed to prevent these severe costly and often deadly defects [10].

Figure 1 Map of Egypt.

2. Demographic features of Egypt

Egypt is about one million kilometers and is located on the north eastern corner of Africa and South Western Asia. Egypt is the most popular country in the Middle East and the third most populous on the African continent, with an estimated 72.50 million people, 37.1 males and 35.4 females. One Egyptian baby is born every 23 s. Almost all the population is concentrated along the banks of the Nile (notably Cairo and Alexandria), in the Delta and near the Suez Canal. Small communities spreading throughout the desert regions of Egypt are clustered around oases and historic trade and transportation routes (Fig. 1) [11].

Cairo population rose to more than 7.8 millions (the highest population density in Egypt). The vast majority (94%) of the population of Egypt consists of ethnic Egyptians. Ethnic minorities in Egypt include the Bedouin Arab tribes of the Sinai Peninsula and the eastern desert, the Berber-speaking community of Siwa Oasis and the Nubian people clustered along the Nile in the southernmost part of Egypt [11]. The average age of marriage is 27 years in males and 25 years in females. There have been an increase overtime in the median age of marriage within all areas of Egypt. Although the average family size is falling from 4.65 people in 1996 to 4.18 in 2006, the family size is still large. Population growth rate is 1.75%. Birth rate 22.12 births/1000 population and death rate 5.23 deaths/1000 population [11]. Birth rate among women over 35 years have been almost twice (65/1000) as often as those occurring among women of the same age in USA (33.7/1000) [12]. The

infant mortality rate improved from 29/1000 in 1996 to 20.1/1000 in 2005. Disabled increased from 0.48 in 1996 to 0.6 in 2006. As regards consanguinity Khayat and Saxena [13] reported a general incidence of 38.9%. It ranged from 25.4% in Lower Egypt urban to 55.2% in Upper Egypt rural. First cousin marriages were the most common. Over the years Egypt has made substantial progress in establishing an extensive network of health facilities and providing easy accessible basic health services to almost the entire population, controlling communicable diseases, achieving high immunization rates and reducing population growth. The vast majority of population has access to safe water and sanitation. However infant mortality and maternal mortality (24.5 and 6.9, respectively, per 1000 live births) are still high as is the prevalence of malnutrition under the age of 5 years especially in Upper Egypt and iron deficiency anemia is widely prevalent. The impact of an on going epidemiological transition with the emergence of non communicable diseases including genetic diseases and risk behavior-related diseases as a major contributor to disease burden started to be recognized [14]. Currently, no nationwide birth defect monitoring system exists in Egypt. Only a small number of reports are available from general and university hospitals which demonstrate the prevalence in the area of the hospital among live births and still births. Also there are no reports from Egypt about prevalence of CMs among children.

3. Aim of the study

In this study we tried to assess the frequency and nature of CMs among Egyptian infants and children (0–18 years) as well as the associated maternal and neonatal risk factors.

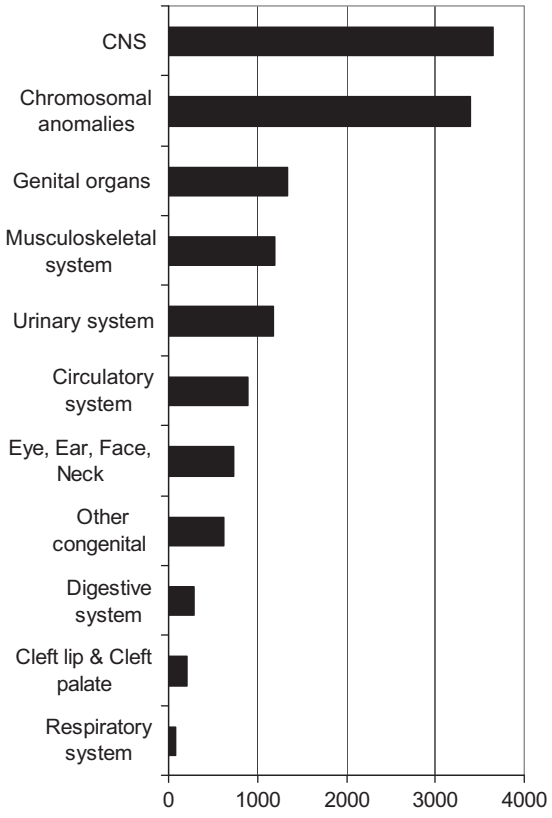

Figure 2 Frequency of congenital malformations prevalent in Egyptian infants and children.

4. Subjects and methods

The geographical area studied is the North East region of Cairo. The sample size studied was 660,280 patients attending the pediatric clinic, Ain Shams University hospital (from birth up to 18 years) during the period of the study from year 1995 up to year 2009. This is considered one of the major Universities in Egypt and it was established in July 1950 under the name of "Ibrahim Pasha University". It includes 15 Faculties and 2 High Institutes. The Educational Hospital of the Faculty of Medicine contain about 3000 beds and serving about 1000,000 patients annually at the outpatient clinics and inpatient departments. These hospitals comprise a distinguished panel of professors of medicine in all specializations, and are also provided with the most up-to-date medical equipment and technology. Thus people come for consultation from all areas of Egypt, so the study population were close to the distribution in the whole Egypt to a great extent. The Genetics Unit is included in Pediatric Department of this hospital and it is the 1st genetic unit to be established (year 1964) in all Arab Countries. Charts of children with congenital malformations (CMs) were extracted (13,582). To determine the associated risk factors and their relation to CMs we studied pedigree charts, degree of consanguinity of parents and family history of similarly affected infants or children. Maternal risk factors including parity, age of the mother at conception, history of maternal illness as diabetes, fever and common cold, exposure to irradiation, pollutants, smoking (passive or active), intake of any drugs, multivitamins and folic acid were also studied. Pregnancy history in the affected child including polyhydramnios, oligohydramnios, breech presentation, vaginal bleeding early in pregnancy, twin pregnancy, period of gestation, antenatal care during pregnancy, mode of delivery, history of previous abortions and still births, paternal factors as age at the time of conception and occupation (professional or not). Newborn factors as sex and birth weight were also studied. Control group included 5000 mothers of infants and children attending the Pediatric Department for consultation for diseases other than CMs for comparison as regards risk factors. Reports of physical examination of infants and children with CMs as regards weight, length, skull circumference, facial features and any congenital malformations were studied. Reports of investigations as echocardiography, abdominal ultrasonography, CT brain, chromosomal studies were also studied. The malformations were classified into major and minor anomalies. Major anomalies are classified by the use of anatomic systems to organize human anomalies according to the International Statistical Classification of Diseases and Related Health Problems, 10th version, for 2007 [15]. There are a list of minor anomalies that are to be excluded unless occurring in combination with major anomalies. Minor anomalies can be of importance especially in cases of suspected dysmorphic syndromes and in relation to environmental effects, but there is as yet little standardization in their definition reporting [16]. A statistical study was done using the data obtained and involving χ^2, odd ratio, and CI 95%.

5. Results

Patients (13,543) having CMs were detected among 660.280 child aged 0–18 years attending the Pediatric Hospital during the period of the study (1995–2009), constituting 20/1000. Males were more affected than females (8831:4712) (1.8:1). According to ICD-10 classification of CMs the systems involved in descending order of frequency were, central nervous system 5.5/1000, chromosomal abnormalities 5.1/1000, genital organs anomalies 2/1000, musculoskeletal 1.8/1000, urinary system anomalies 1.8/1000, circulatory system anomalies 0.13/1000, eye, ear, face and neck anomalies 0.11/1000, other congenital malformations 0.9/1000, digestive system anomalies 0.4/1000, cleft lip and palate 0.3/1000 and respiratory system anomalies 0.1/1000 (Table 1 and Fig. 2). Distribution of maternal, paternal and neonatal characters in comparison with controls, Odd ratio, and CI 95% were summarized in Table 2. Among the maternal risk factors for CMs in Egypt were multiparity (54%), age of the mother above 35 years at conception (59.96%), maternal illness especially diabetes (7.28%), fever and common cold (16.69%), exposure to pollutants (58.57%). Only 31.8% of the mothers received antenatal care and 27.5% received multivitamins and folic acid during pregnancy. 36.32% of mothers received some drugs (not exactly known) in first 3 months of pregnancy. Mothers of children with CMs were more significantly affected ($p < 0.05$) than controls with polyhydramnios (10.8%), oligohydramnios (9.81%), early vaginal bleeding (39.43%) and preeclampsia (39.43%). Twin pregnancy was recorded in 2.94% and breech presentation in 11.32%in this study. Delivery by CS was needed by 23.1%of mothers of patients with CMs. Past history of abortion or stillbirth was detected in 32.39% of mothers of patients with CMs. Fathers above 50 years at time of conception was detected in 29.99% of patients with CMs, and 85.28% of them were non professionals as drivers, peasants, laborers in factories. Birth weight in patients with CMs less than 2.5 kg was detected in 71.04% and 18.89% of them were delivered prematurely. Consanguineous marriage was present in 45.8% of parents of patients and family history of CMs was detected in 16.69% of affected families.

6. Discussion

The frequency of CMs in this study among children aged 0–18 years was 2%. This is the first report about CMs in this age group in Egypt. This figure is lower than the figure reported among Turkish school children aged 6–15 years (6.18%) [17]. However it is higher than the figure reported in India by Sridhar [18] in a community based survey of visible congenital anomalies 1.03%.

Comparing the frequency of CMs in children with that of liveborns in the same locality (2.7%) [19] or in other localities in Egypt, 3.17% in Giza [20], 1.6 in Alexandria [21], 2.3% in Mansoura [22], it was found to be unexpectedly lower. Longitudinal cohort studies with special follow examination provide high incidence figures for congenital anomalies as contrasted to studies based only on birth certificate information because it collects valid information on late manifesting CMs [23]. The higher frequency in live borns in Egypt may be due to either inclusion of all minor anomalies in the study of live borns [19], or inclusion of congenital anomalies in still births in addition to that of live births [20].

The highest frequency of CMs reported in this study involved the nervous system, followed by chromosomal abnormalities, genital organs, urinary system anomalies, musculoskeletal, circulatory system, eye, ear, face and neck, other congenital anomalies, digestive system anomalies, cleft lip and palate, and respiratory anomalies. CNS anomalies are considered the most common anomalies in this study as well as in other studies in live borns and still borns in Egypt as well as in other countries [19,20,24,25]. However the frequency of anomalies in other systems differs in different studies done in Egypt or in other countries [26–29]. It is evident that the prevalence and type of CMs differ from one country to another. Even in the same country it differs from one locality to another. Therefore country and/or region specific studies are necessary to describe types of CMs encountered in the area [25]. Further the geographic variation for some defects may reflect local prevalence rates and risk factors, environmental, genetic and ethnic variations [26].

In this study males were more affected than females (1.8:1). However this difference was not evident in other studies in Egypt among liveborns and stillborns [19,20]. However congenital malformation male excess was also reported in other studies [26,30–33]. Lisi et al. [34] reported that sex distribution varied significantly among registers and it depends on the type of malformation and whether it is isolated, associated or syndromic. Deviation of sex distribution was observed for 24 of 29 groups studied (a male excess in 16, a female excess in 8) and in 8 of such groups these estimates varied significantly across registers. So sex distribution should be studied in every CM separately and not in the whole group. Consanguineous marriages are reported to play a major role in the occurrence of congenital malformations and it is a recognized common practice in Middle East [35]. In the present study consanguineous marriage was significantly increased 45.8% compared to that in the general population 38.9% [13]. The same was also reported in other Arab countries, and in Iran [27,28,35–38]. Zlotogora, also reported increased incidence of CMs in the offsprings of consanguineous couples due to homozygous expression of recessive genes inherited from their common ancestors [39]. Pinto Escalante reported twofold increase in incidence of CMs among the clinical effects of parental consanguinity [40]. Also the mating in consanguinity gives exactly the conditions most likely to enable rare features to show itself [41]. A study done in Egypt on the etiology of CMs, chromosomal anomalies constituted 21.4%, genetic syndromes 31% and 47.6% were due to unknown causes. Most of the genetic syndromes were due to autosomal recessive inheritance and this is due to high degree of consanguinity [42].

Family history of CMs was reported to occur in 16.69% in this study, compared to 5% in the control group ($p < 0.05$). A history of CMs was more common among siblings of consanguineous marriages than non consanguineous marriages [38].

In this study the prevalence of CMs was significantly increased with maternal age above 35 years. So far increasing maternal age is the most important, perhaps the only documented non genetic risk factor for trisomies in humans [43]. This is due to increase in chromosomal meiotic errors that occur with age [44]. Increasing paternal age above 50 years was also a risk factor in this study. Although a paternal age effect is not well established, Zhu et al. demonstrated that the prevalence of malformations of the extremities and syndromes of

Table 1 Frequency of major congenital anomalies by system according to ICD-10 classification among 660.280 infants and children studied.

MCAs by system (ICD-10)	No.	%	% of total MCAs	/1000 population
Q00–Q07 Congenital malformations of the nervous system				
Neural tube defect	1078	29.57		
Microcephaly	777	21.31		
Hydrocephalus	677	18.57		
Cranial cerebrovascular anomalies	430	11.79		
Cranial anomalies	284	7.79		
Cerebral defects	281	7.71		
Neuroectodermal anomalies	119	3.26		
Subtotal	3646	100.00	26.92	5.5
Q10–Q18 Congenital malformations of eye, ear, face and neck				
Eye				
Optic nerve atrophy	130	17.78		
Microphthalmia	117	16.01		
Retinal anomalies	99	13.54		
Lens anomalies	85	11.63		
Anophthalmia	38	5.20		
Corneal anomalies	30	4.10		
Iris anomalies	22	3.01		
Ear anomalies	120	16.42		
Mouth anomalies	34	4.65		
Neck anomalies	30	4.10		
Others	26	3.56		
Subtotal	731	100.00	5.39	0.11
Q20–Q28 Congenital malformations of the circulatory system				
Ventricular septal defect	403	45.43		
Fallot's teratology	180	20.29		
Atrial septal defect	74	8.34		
Vascular anomalies	59	6.65		
Patent ductus arteriosus	35	3.95		
Congenital valvular anomalies	23	2.59		
Dextrocardia	23	2.59		
Cardiomyopathy	19	2.14		
Transposition of great vessels	14	1.58		
Coarctation of aorta	11	1.24		
Endocardial fibroelastosis	9	1.01		
Situs inversus totalizes	7	0.79		
Others	30	3.38		
Subtotal	887	100.00	6.55	0.13
Q30–Q34 Congenital malformations of the respiratory system				
Congenital laryngeal cord anomalies	34	41.98		
Congenital polycystic lung	24	29.63		
Unilateral lung agenesis	15	18.52		
Others	8	9.88		
Subtotal	81	100.00	0.6	0.1
Q35–Q37 Cleft lip and cleft palate	203		1.5	0.3
Q38–Q45 Other congenital malformations of the digestive system				
Congenital umbilical hernia	150	52.26		
Hirshsprungs disease	70	24.39		
Biliary atresia	20	6.97		
Imperforate anus	10	3.48		
Congenital pyloric stenosis	10	3.48		
Others	27	9.41		
Subtotal	287	100.00	2.10	0.4
Q50–Q56 Congenital malformations of genital organs				
Hypospadius	375	28.13		
Mullerian tube defects	250	18.75		
Intersex	220	16.50		
Epispadius	175	13.13		
Ovarian dysgenesis	163	12.23		

Table 1 (*continued*)

MCAs by system (ICD-10)	No.	%	% of total MCAs	/1000 population
Others	150	11.25		
Subtotal	1333	100.00	9.84	2
Q60–Q64 Congenital malformations of the urinary system				
Renal dysplasia	257	21.89		
Renal agenesis	254	21.64		
Polycystis kidney	185	15.76		
Ectopic kidney	131	11.16		
Cysto-uretheral anomalies	126	10.73		
Others	221	18.82		
Subtotal	1174	100.00	8.67	1.8
Q65–Q79 Congenital malformations and deformations of the musculoskeletal system				
Limb anomalies	819	68.54		
Dyschondrodystrophies	182	15.23		
Osteogenesis imperfecta	87	7.28		
Arthrogryposis	33	2.76		
Congenital pelvifemoral anomalies	17	1.42		
Others	57	4.77		
Subtotal	1195	100.00	8.82	1.8
Q80–Q89 Other congenital malformations	619		4.57	0.9
Q90–Q99 Chromosomal abnormalities, not elsewhere classified				
Down syndrome	2523	74.49		
Chromosomal deletions	143	4.22		
Other trisomies	78	2.30		
Others autosomal syndromes	35	1.03		
Fragile X syndrome	248	7.32		
Turner	204	6.02		
Klinefelter syndrome	130	3.84		
Others sex chromosome syndromes	26	0.77		
Subtotal	3387	100.00	25.00	5.1

multiple systems, as well as Down syndrome, increased with increasing paternal age (40 years and above) [45]. More over there is a positive association between advanced paternal age and hypospadias, cleft lip and cleft palate. Also advanced maternal and paternal ages were both independently associated with congenital heart defects [46]. On the other hand a positive association of young maternal and paternal ages were independently associated with gastroschisis. In addition young maternal age carried a higher risk of neural tube defects [47]. So the association between prevalence rate of CMs and maternal age is U shaped with a higher proportion of malformed children among women aged less than 20 years and more than 39 years [48].

68.2% of mothers in this study did not receive antenatal care. The same was also reported in Brazil, where CMs were more statistically associated with maternity hospitals belonging to or outsourced by the unified National Health System and inadequate prenatal care ($\leqslant$3 visits). This high-lights the importance of measures for health promotion and disease prevention in child bearing-age women with special attention to prenatal care and childbirth which can influence neonatal indicators and prevention of birth defects [49].

27.5% of mothers received folic acid or multivitamin which is significantly lower than that in the control group. MTHFR genetic polymorphism (1298A/C) is considered a risk factor in Egyptian mothers with Down syndrome [50]. Medium serum folate concentrations among nonpregnant women of childbearing age was reported to be decreased 16% and RBC folate concentration decreased 8%, and it is recommended that all women of childbearing age who are capable of becoming pregnant should consume 400 μg of folic acid daily to reduce the occurrence of neural tube defects in affected pregnancy [51]. Also folic acid supplementation for 1 year before conception might significantly reduce the risk for preterm delivery, according to an analysis involving more than 38,000 women [52]. Vitamin B_{12} might also confer health benefits, however, such benefits are difficult to ascertain because of the complementary functions of vitamin B_{12} and folic acid. Furthermore, the interactions between the nutritional environment and genotype might have an important influence on vitamin B_{12}, and risk of neural tube defects. However more research, particularly in the area of nutritional genomics, is needed to determine how vitamin B_{12} might augment the benefits of folic acid. So foods have to be fortified with vitamin B_{12} in addition to the current mandatory folic acid fortification of grains [53].

Multiparity was associated with increased prevalence of CMs in this study (54%). Sipila et al. found an increase in frequency of CMs in 4th gravida mothers. The risk of mutations in women with 3rd and higher gravida is higher than in women with primary or secondary gravida [54]. However Perveen and Tyyab found more CMs in newborns of primiparaipara [55]. History of spontaneous abortion or still birth obtained in this

Table 2 Maternal and paternal risk factors associated with CMs.

Maternal and neonatal factors	Cases (n = 13,543)		Control (n = 5000)		Odd ratio	CI 95%	
	N	%	*N*	%	Odd	L	U
Age of mother at conception >35 years	8121	59.96	1500	30.00	3.495*	3.260	3.747
Parity (multipara)	7313	54.00	2000	40.00	1.761*	1.648	1.881
History of abortion or stillbirth	4387	32.39	300	6.00	7.507*	6.643	8.482
Antenatal care during pregnancy	4306	31.80	3000	60.00	0.311*	0.291	0.332
Diabetes	986	7.28	100	2.00	3.848*	3.124	4.739
Fever	2260	16.69	200	4.00	4.807*	4.144	5.577
Pre-eclampsia	5340	39.43	82	1.64	39.043*	31.303	48.696
Polyhydramnios	1462	10.80	44	0.88	13.631*	10.081	18.431
Oligohydramnios	1329	9.81	27	0.54	20.041*	13.672	29.377
Antipartum hge	429	3.17	30	0.60	5.419*	3.738	7.858
Contact with infectious case	3470	25.62	120	2.40	14.009*	11.641	16.859
Maternal smoking active and passive	7508	55.44	1750	35.00	2.310*	2.160	2.471
Intake of multi vitamin and folic acid	3725	27.50	3973	79.46	0.098*	0.091	0.106
Drug intake	4919	36.32	700	14.00	3.504*	3.211	3.823
Contact with pollutants	7932	58.57	1325	26.50	3.921*	3.650	4.212
Twin pregnancy	398	2.94	25	0.50	6.025*	4.017	9.038
Period of gestation	Fullterm	10,985	81.11	4950	99.00	0.043*	0.033
	Preterm	2558	18.89	150	3.00		
Mode of presentation	Breech	1533	11.32	500	10.00	0.870*	0.782
Mode of delivery	CS	3128	23.10	250	5.00	0.175*	0.153
Birth weight	<2.5	9621	71.04	450	9.00	24.803*	22.360
Paternal factors							
Age of father at conception >50 years	4062	29.99	800	16.00	0.445*	0.409	0.484
Father's non professional	11,549	85.28	3000	60.00	0.259*	0.241	0.279

* Significant at p-value < 0.05 for odd ratio with Fisher's exact test (χ^2).

study was 32.39%, might probably be due to birth defects of a severe degree in the conceptuses which was incompatible with life [56].

History of oligohydramnios, and polyhydramnios, were present in high frequency among mothers of patients with CMs in this study. Stoll et al. reported that 55% of cases with polyhydramnios had more than one malformation, 13.4% of them had a chromosomal aberration and 32% had multiple malformations that do not constitute a syndrome [57]. He also reported that the incidence of neonatal congenital anomalies in pregnancies complicated by oligohydramnios was 1.88% with 7.14% of malformed children born after oligohydramnios. The malformations most often associated with oligohydramnios involve the urinary system (15.9%), the digestive system (10.2%), the genital system (5.9%) and the limbs (5.7%), and a chromosomal aberration was present in 5.9% [58].

The frequency of CMs presenting by breech in this study was 11.32%. It is well recognized that a fetus presenting by breech is more likely to have congenital malformations than a fetus with cephalic presentations. The abnormality is approximately threefold [59].

Major and minor malformations are more common in twins than in singletons, with monozygotic twins more commonly affected than dizygotic twins [60,61]. The same was also reported in this study.

In this study a history of common cold and fever (39 °C and above) was reported to occur in 16.69% of mothers, in the first trimester. Zhang and Cai found an elevated risks of birth defects among offspring of women having common cold with or without fever in the first trimester of pregnancy. Increased relative risk was observed for anencephalus, spinabifids, hydrocephalus, cleft lip and undescended testicles [62].

We found a higher frequency of CMs in the offspring of mothers having pre-eclampsia (39.43%) compared to controls (1.64%). Chromosomal abnormalities and structural chromosomal abnormalities are considered pregnancy associated risk factors for preeclampsia [63,64].

An association between antipartum hemorrhage early in pregnancy and CMs reported in this study (3.17%) could be noted in some retrospective and prospective studies [65,66].

The association between maternal glycemic control and the increased risk of major CMs has been well established [67,68]. In this study there were a significant number of diabetic mothers (7.28%). Also in another study done in Egypt [19] on live borns, the incidence of major congenital anomalies in infants of diabetic mothers was 11% (4.6 times higher than the general population and that of minor anomalies 18%). Apeland et al. found that major anomalies occurred in 6.4% of pregnant diabetics [69] and Hod et al. found that minor anomalies ranged between 19.4% and 20.5% [70]. Sehaefer-Graf et al. reported that increasing hyperglycemia at diagnosis in diabetic pregnant females was associated with an increasing risk of anomalies in general and with anomalies involving multiple organ systems without a preferential increase in involvement of specific organ system. Also congenital anomalies in offspring of women with gestational and type 2 diabetes affect the same organ systems that have been described in pregnancies complicated by type 1 diabetes [71].

A high frequency (15.9%) of extrathyroidal congenital anomalies had been reported in Egyptian infants with primary congenital hypothyroidism, detected by neonatal screening, i.e., more than fivefold higher than that reported in liveborn (2.7%). The cardiac and musculoskeletal systems (mostly minor as brachydactly and digitalization of thumb were the most

commonly involved, comprising 9.09% and 47.72% of all anomalies [72]. On the other hand Kumar et al. reported an increased prevalence of congenital renal and urologic anomalies in children with congenital hypothyroidism and suggested further studies of common genes involved in thyroid and kidney development [73]. Also maternal thyroid disease both overactive or underactive or taking medicine to treat thyroid disorders during pregnancy was reported to be a risk factor for craniosynostosis in infants [74].

Maternal obesity although not studied in this work, was usually associated with maternal diabetes and was significantly linked with spinabifida, heart defects, anorectal atresia, hypospadias, limb reductions, diaphragmatic hernias, omphalocele. It also slightly increased the risk of cleft palate and significantly decreased the risk of gastroschisis. Under weight on the other hand was associated with modest increased risk of orofascial clefts [75].

In this study, 36.32% of mothers of patients with CMs had a positive history of drug intake (not definitely identified) in the first trimester of pregnancy. About 2–3% of all birth defects result from the use of drugs other than alcohol. Drugs taken by pregnant women can affect the fetus by acting directly on it, causing damage, abnormal development (leading to birth defects) or death. They can alter the function of the placenta by constricting blood vessels thus reducing the supply of oxygen and nutrients to the fetus from the mother. The result is under weight, under developed and may be abnormal developed baby [76].

55.44% of mothers in this study were cigarette smokers compared to 35% of controls ($p < 0.05$), either actual smokers or passive smokers, i.e., exposed to environmental tobacco smoke. Maternal smoking for one month before conception through the third month of pregnancy (periconceptional period) was linked with birth defects of the heart, cleft lip with or without cleft palate (CLP). A weaker link was found with cleft palate only (CPO). CPO with Pierre Robin sequence was also linked with heavy maternal smoking. The link with smoking is stronger among mothers who did not take folic acid. However there was no link between CLP or CPO and exposure to environmental tobacco smoke alone [77]. These defects are thought to be caused by carbon monoxide and nicotine. Carbon monoxide may reduce the oxygen supply of the body's tissues. Nicotine stimulates release of hormones that constrict the vessels of uterus and placenta so that less oxygen and fewer nutrients reach the fetus.

In this study 58.57% were exposed to pollutants by working or living near industrial factories, or helping their husbands in cultivating the land where pesticides were aggressively used. In Egypt there is no specific regulations regarding the use of pesticides (type, amount) and there is no considerable awareness about possible related health problems including CMs. This point should be studied thoroughly in Egypt. Countries such as Italy, where there is close control of the use of pesticides, there is no epidemiological evidence that pesticides have any effect on the prevalence of CMs [78]. However residential proximity to the regional industrial park was associated with major congenital malformations among Arab-Beduin, but not in Jewish populations. These observations indicate the need for public health protection of a vulnerable society and the relative importance of chemical exposure and health care utilization requires further study [79]. Other chemicals reported to be associated with CMs include hair spray (which contain a chemical phthalates) where women exposed to it are at increased risk of having a boy with genital defects because it suppresses the production of testosterone, a critical agent in penile development [80]. Also some chemicals as Bisphenol A (BPA), which is an ingredient in plastics and epoxy resins that line food cans is found in unsafe levels in canned food and may be linked to birth defects [81].

A high frequency of CMs (71.04%) was observed in children whose birth weight was less than 2.5 kg in this study. A high frequency of birth defects was also reported in other studies among infants with low or very low birth weight as well as in prematures [82,83].

As regards fathers occupation, the professional fathers were significantly decreased (14.72%) in this study compared to 40% in control group with a significant difference. The non professional jobs were mostly farmers, drivers, and hand workers. Most of the mothers were house wives. This denotes a higher incidence of CMs in lower socio-economic groups. These are at higher risk due to environmental or lifestyle factors. In addition their wives lack access to prenatal care, proper balanced nutrition and intake of vitamins or folic acid.

To conclude, congenital anomalies continue to be an important cause of morbidity and mortality in infants and children especially in developing countries including Egypt. Surveys of congenital anomalies must be done in every country and even in different regions of same country to provide prevalence of CMs, pattern of occurrence, nature, identify causes and associated risk factors and ultimately to prevent or reduce the occurrence of MCAs. Variation between population is due to genetic characteristics of ethnicity and geographical location, an important component of environment.

The possible role of genomics in uncovering genetic susceptibilities and helping prevention of these conditions require in depth epidemiological studies and cost/effective analysis [84]. Also understanding the interaction between genetics and the environment in the development of CMs will lead to better understanding of the biological mechanisms and pathological processes that contribute to the development of complex birth defects. It is through such understanding that more efficient measures will be developed to prevent these severe, costly, often deadly defects. This will also support health service planning for prevention as regards prenatal diagnosis and screening programs.

References

[1] Guidelines for the study of genetic effects in human populations. Geneva, World Health Organization; 1985 (Environmental Health Criteria No. 46).
[2] Smith WD. Classification, nomenclature, and naming of morphologic defects. J Pediatr 1975;87(1):162–3.
[3] Christianoon RE, Van Den Berg BJ, Milkovich WF, Oechsli L. Incidence of congenital anomalies among white, black live births with long-term follow-up. J Public Health 1981;71:1333–41.
[4] Christianson & Modell 2004, MOD, 2006, WHO/I GBDMS/Eurocat; 1998.
[5] Aihw NP, Birch MR, Grayson N, Sullivan EA. Recommendations for development of a new Australian birth anomalies system: a review of the congenital malformations & birth defects data collection. AIHW Cat. No. PER 23, Sydney: AIHW National Perinatal statistics Unit (Birth Anomalies Series no.1); 2004.
[6] Eurocat working group. Eurocat Report 7, Scientific institute of Public Health Louis Pasteur, Brussels, 1997;

Kalter H. Five-decade international trends in the relation of perinatal mortality and congenital malformations: Still birth & neonatal death compared. Int J Epidemiol 1991;20:173.
[7] Controlling birth defects: Reducing the hidden toll of Dying and Disabled children in low-income countries. Disease control priorities Project. http://www.dep2.org; Dec. 2008.
[8] Hobbs CA, Cleves MA, Simmons CJ. Genetic epidemiology and congenital malformations. Arch Pediatr Adolesc Med 2002;156:315–20.
[9] Walden RV, Taylor SC, Hanson NI, Kenneth Poole W, Stall BJ, Dianne Abuelo, Vohr BR. Major congenital anomalies place extremely low birth weight infants at higher risk for poor growth and developmental outcome. Pediatrics 2007;120(6):1512–9.
[10] Zhu H, Kartiko S, Finnell RH. Importance of gene – environmental interactions in the etiology of selected birth defects. Clin Genet 2009;75(5):409–23.
[11] The Central Agency for Public Mobilization and Statistics. C.A.P.M.A.S. http://www.capmas.gov.eg; June 2007.
[12] Elzanaty and Associates. Current fertility. Egypt demographic and health survey. Calverton, Maryland, Cairo, Egypt: Egypt Macro-international Inc.; 1998, p. 7.
[13] Khayat RG, Saxena PC. Consanguinity and its effect on infant and child mortality in Egypt. http://ussp2005princeton.edu.
[14] Country cooperation strategy for WHO and Egypt 2005–2009, Executive Summary, p. 7, Document, EM/ARD/011/E/R.
[15] International Statistical Classification of Diseases and Related Health Problems. 10th Revision (ICD-10). Version for 2007. Chapter XVII. Congenital malformation, deformation, and chromosomal abnormalities.
[16] Ingeborg Barisic, EUROCAT Working Group EUROCAT – epidemiological surveillance of congenital anomalies in Europe Zdrav Westn. 2009;78:1-175–9.
[17] Yucesan S, Dindar H, Olcay I, Okur H, Kilicaslan S, Ergoren Y, Tuysuz C, Koca M, Civilo B, Sen I. Prevalence of congenital abnormalities in Turkish school children. Eur J Epidemiol 1993;9(4):373–80.
[18] Sridhar K. A community-based survey of visible congenital anomalies in rural Tamil Nadu. Indian J Plastic Surg 2009;42(Suppl.):184–91.
[19] Shawky RM, Elsedfy HH, Abolouz SK, Labatia GY. Prevalence of congenital malformations in a thousand consecutive Egyptian liveborn. Egypt J Med Hum Genet 2001;2(1):43–53.
[20] Temtamy SA, Abdelmeguid N, Mazen I, Ismail SR, Kassem NS, Bassiouni R. A genetic epidemiological study of malformations at birth in Egypt. East Mediterr Health J 1998;4(2):252–9.
[21] Ansary MK. A genetic study of congenital malformations in a sample of newborns in Shatby University Maternity Hospital, Alexandria (Thesis). Alexandria, Egypt, University of Alexandria; 1995.
[22] Hafez M, Elshabrawy M, Elsalab SH, El Shafei M. Study of congenital malformations in Egypt. Egypt J Pediatr 1985;2:69–93.
[23] Gonzalez AJ, Morales JJ, Luna L, Arteaga J, Mutchinick OM. Beginner's guide to genetics: congenital malformations. BMJ 2004;12:437–80.
[24] Tomatir AG, Demirhan H, Sorkun HC, Köksal A, Ozerdem F, Cilengir N. Major congenital anomalies: a five-year retrospective regional study in Turkey. Genet Mol Res 2009;8(1):19–27.
[25] Singh R, Al-Sudani O. Major congenital anomalies at birth in Benghazi, Libyan Arab Jamahiriya. East Mediterr Health J 2000;6(1):66–75.
[26] Shawky RM, Khazbak M, Kamal AM, Maher A. Epidemiological studies on congenital anomalies among Egyptian children. Egypt J Pediatr 1990;7(3-4):273–86.
[27] Ali A, Zahad S, Masoumeh A, Azar A. Congenital malformations among live births at Arvand Hospital, Ahwaz, Iran – a prospective study. Pak J Med Sci 2008;24(1):33–7.
[28] Al-Ghazali LI, Dawodu AH, Sabarinathan K, Varghese. The profile of major congenital abnormalities in the United Arab Emirates (UAE) population. J Med Genet 1995;32:7–13.
[29] Al Hosani H, Salah M, Abu-zeid H, Farag HM, Saade D. The national congenital anomalies register in the United Arab Emirates. East Mediterr Health J 2005;11(4).
[30] Alshehri MA. Pattern of congenital anomalies in Southwestern Saudi Arabia. Bahrain Med Bull 2005;27(1):2.
[31] Mir NA, Galezek WC, Soni A. Easily identifiable congenital malformations in children: survey of incidence and pattern in 32,232 liveborn neonates. Ann Saudi Med 1992;12:366–71.
[32] Khan SMA, Ahmad GS, Abu-Talib A. Are congenital anomalies more frequent in Saudi Arabia? Ann Saudi Med 1990;10:488–9.
[33] Daly LE, Kirke PN, Molly A, et al. Folate levels and neural tube defects. Implication for prevention. JAMA 1995;274:1698–702.
[34] Lisi A, Botto LD, Rittler M, Castilla E, Bianchi F, Botting B, et al. Sex and congenital malformations: an international perspective. Am J Med Genet 2005;134 A:49–57.
[35] Hudgin L, Cassidy SB. Congenital anomalies. In: Marten RJ, Fanaroff AA, Walsh MC, editors. Neonatal – perinatal medicine. Philadelphia: Mosby – Elsevier; 2006. p. 561–86.
[36] Kanaan ZM, Mahfouz R, Tamim H. The prevalence of consanguineous marriage in an underserved area in Lebanon and its association with congenital anomalies. Genet Test 2008;12(3):367–72.
[37] Madi SA, Al-Naggar RL, Al-Awadi SA, Bastaky LA. Profile of major congenital malformations in neonates in Al-Jahra Region of Kuwait. East Mediterr Health J 2005;11(4):700–6.
[38] Mosayebi Z, Movahedian AH. Pattern of congenital malformations in consanguineous versus nonconsanguineous marriages in Kashan, Islamic Republic of Iran. East Mediterr Health J 2007;13(4):868–75.
[39] Zlotogora J. Genetic disorders among Palestinian Arabs: effects of consanguinity. Am J Med Genet 1997;68:427–35.
[40] Pinto Escalante D, Castillo Zapata I, Ruiz Allec D, Ceballos Quintal JM. Spectrum of congenital malformations observed in neonates of consanguineous parents. An Pediatr (Barc) 2006;64(1):5–10.
[41] Jaouad IC, Elalaoui SC, Sbiti A, Elkerh Belmahi L, Sefiani A. Consanguineous marriages in Morocco and the consequence for the incidence of autosomal recessive disorders. J Biosoc Sci 2009;41(5):575–81.
[42] Shawky RM, El-Baz FM, Elsobky ES, Osman A, Elsayed SM. High resolution cytogenetic study of patients with multiple congenital anomalies, M.D. Thesis, Ainshams University, 2005.
[43] Hassold T, Hunt P. Toerr (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2001;2:280–91.
[44] Yoon P, Freeman S, Sherman L, et al. Advanced maternal age and the risk of Down syndrome, characterized by the meiotic stage of chromosomal error. a population based study. Am J Hum Genet 1991;58(3):628–33.
[45] Zhu JL, Madsen KM, Vestergaard M, Olesen AV, Basso O, Olsen J. Paternal age and congenital malformations. Hum Reprod 2005;20(11):3173–7.
[46] Materna-Kiryluk A, Wisniewska K, Badura-Stronka M, Majnartowicz J, Wieckowska B, Balcar-Boron A, et al. Parental age as a risk factor for isolated congenital malformations in a Polish population. Pediatr Perinat Epidemiol 2009;23(1):29–40.
[47] Creon LA, Shaw GM. Young maternal age and congenital malformations: a population based study. Am J Public Health 1995;85(5):710–3.
[48] Nazer HJ, Cifuentes OL, Aguila RA, Ureta LP, Bello PMP, Correa CF, Melibosky RF. The association between maternal age and congenital malformations. Rev Med Chil 2007;135(11):1463–9.
[49] Costa CM, da Gama SG, Leal Mdlo C. Congenital malformations in Rio de Janeiro, Brazil: prevalence and associated factors. Cad Saude Publ 2006;22(11):2423–31.

[50] Meguid NA, Dardir AA, Khass M, Hossieny LE, Ezzat A, El-Awady MK. MTHFR genetic polymorphism as a risk factor in Egyptian mother with Down syndrome children. Dis Markers 2008;24(1):19–26.
[51] Centers for Disease Control and Prevention. Folate status in women of childbearing age, by race/ethnicity-united states, 1999–2000, 2001–2002, and 2003–2004, MMWR Morb Mortal Wkly Rep 2007;55(51):1377–80.
[52] Beil L, Medscape Medical news. http://www.medscape.com/viewarticle/569590?sssdmh=dm1.334737&src=nldne; Jan 31, 2008.
[53] Rayan-Harshman M, Aldoori W. Vitamin B12 and health. Can Fam Phys 2008;54(4):536–41.
[54] Sipila P, Von Wendt L, Hartikainen-Sorri AL. The grand multipara-still an obstetrical challenge? Arch Gynecol Obstet 1990;247(4):187–95.
[55] Perveen F, Tyyab S. Frequency and pattern of distribution of congenital anomalies in the newborn and associated maternal risk factors. J Coll Physicians Surg Pak 2007;17(6):340–3.
[56] Devi R, Tilak P, Rajangam S. Multiple congenital anomalies – an aetiological evaluation. Bombay Hosp J [Review articles]. http://www.bhj.org/journal/2007.
[57] Stoll CG, Alembik Y, Dott B. Study of 156 cases of polyhydramnios and congenital malformations in a series of 118,265, consecutive births. Am J obst Gynecol 1991;165:586–90.
[58] Stoll CG, Dott B, Alembik Y, Roth MP. An epidemiology study of oligohydramnios associated with congenital malformations. J Gynecol Obstet Biol Reprod Paris 1990;19(8):947–53.
[59] Brenner WE, Bruce RD, Hendricks CH. The characteristics and perils of breech presentation. Am J Obstet Gynecol 1974;118:700–12.
[60] Chen CJ, Wang CJ, Yu MW, Lee TK. Perinatal mortality and prevalence of major congenital malformations of twins in Taipei city. Acta Genet Med Gemellol Roma 1992;41(2–3):1997–2003.
[61] Doyle PE, Beral V, Botting B, Wale CJ. Congenital malformations in Twins in England and Wales. J Epidemiol Comm Health 1991;45(1):43–8.
[62] Zhang J, Cai WW. Association of the common cold in the first trimester of pregnancy with birth defects. Pediatrics 1993;92(4):559–63.
[63] Villar J, Carroli G, Wojdyla D, Abalos E, Giordano P, Ba' aqueel L, Famot U, Bergsj P, Bakketeig L, Lumbiganon P, Campodorico L, Al-Mazron Y, Lindheimer M, Kramer M. Preeclampsia gestational hypertension and intrauterine growth restriction, related or independent conditions. Am J Obstet Gynecol 2006;194(4):921–31.
[64] Wagner LK. Diagnosis and management of preeclampsia. Am Fam Phys 2004.
[65] Ananth CV, Savitz DA. Vaginal bleeding and adverse reproductive outcome: a meta-analysis. Pediatr Perinat Epidemiol 2008;8(1):62–8.
[66] South J, Naldrett J. The effect of vaginal bleeding in early pregnancy on the infant born after the 28th week of pregnancy. Obstet Gynaecol 2005;80(3):236–41.
[67] Becerra JE, Muin JK, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects. A population based case control study. Pediatrics 1990;85(1):1–9.
[68] Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JS, Kitz miller JL. Elevated maternal hemoglobin Alc in early pregnancy and major congenital anomalies in infants of diabetic mothers. N Engl J Med 1981;304(22):1331–4.
[69] Apeland T, Bergrem H, Berget M. Pregnant diabetics: a retrospective study of pregnancy and labour in women with type I diabetes in Sor-Rogaland (1982–90). Tidsskr-Nor-Laegeforen 1992;112(19):2520–3 [Abstract].
[70] Hod M, Merlob P, Friedman S, Rusecki Y, Schoenfeld A, Ovadia J. Prevalence of congenital anomalies and neonatal complications in the offspring of diabetic mothers in Israel. Isr J Med Sci 1991;27(8–10):498–502.
[71] Schafer-Graf UM, Buchanan TA, Xiang A, Songster G, Montoro M, Kjos SL. Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. Am J Obstet Gynecol 2000;182(2):313–20.
[72] Elkholy M, Fahmi ME, Nassar AE, Selim S, Elsedfy HH. Prevalence of minor musculoskeletal anomalies in children with congenital hypothyroidism. Horm Res 2007;68:272–5.
[73] Kumar J, Gordillo R, Kaskel FJ, Druschel CM, Woroniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. J Pediatr 2009;154(2):263–6.
[74] Ras-mussen SA, Yazdy MM, Carmichael SL, Jamieson DJ, Canfield MA, Honein MAfor the National Thyroid Defects Prevention Study. Maternal thyroid disease as a risk factor for craniosynostosis. Obstet Gynecol 2007;110(2):369–77.
[75] Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz A-M, et al. Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med 2007;161(8):745–50.
[76] Drug use during pregnancy: women's health issues: Merck Manual Home Edition. http://www.Merck.com/mmhe/sec22/ch259/ch259a.html.
[77] Honein MA, Rasmussen SA, Reefhuis J, Romitti P, Lammer EJ, Sunl, et al. Maternal smoking, environmental tobacco smoke, and the risk of oral clefts. Epidemiology 2007;18(2):226–33.
[78] Clementi M, Causin R, Marzocchi C, Mantovani A, Tenconi R. A study of the impact of agricultural pesticide use on the prevalence of birth defects in northeast Italy. Reprod Toxicol 2007;24(1):1–8.
[79] Bentov Y, Kordysh E, Hershk Ovitz R, Belmaker I, Polyakov M, Bilenko N, Sarov B. Major congenital malformations and residential proximity to a regional industrial park including a national toxic waste site: an ecological study. Environ Health 2006;5:8.
[80] Ruzici J, Hair spray linked to birth defects. 2008. http://www.presstv.ir/detail.aspx?id=76314&sectionid=3510210.
[81] Ruzicic, environmental working group. Chemicals linked to birth defects-Bisphenol A-found at unsafe levels in canned food. http://www.ewg.org/reports/bisphenol/execsumm.php; 2007.
[82] Fortune DW, Kitchen WH. Malformations in infants of very low birth weight. Med J Aust 1977;1(8):239–42.
[83] Grover N. Congenital malformations in Shimla. Indian J Pediatr 2000;67(4):249–51.
[84] Kofman-Alfaro S, Penchaszadeh VB. Community genetic services in Latin American & Regional Network of Medical Genetics. Recommendations of the World Health Organization Consultation on Medical Genetics in Latin American, Ports Alegre 19 June 2003, World Health Organization, Geneva, 2004. WHO/HGN/WG/04.01.