# Profile of major congenital malformations in neonates in Al-Jahra Region of Kuwait

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## مُرْتَسَم التشوُّهات الخَلقية الرئيسية لدى المواليد في منطقة الجهراء بالكويت

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**الخلاصة:** تناولت هذه الدراسة التشوُّهات الخَلقية الرئيسية لدى الوِلْدان في مستشفى الجهراء بالكويت في ما بين شهرَيْ كانون الثاني/يناير 2000 وكانون الأول/ديسمبر 2001. وقد وجد أنه من بين 7739 من المواليد الأحياء والأموات الذين ولدوا في هذه الفترة، كان هناك 97 وليداً (12.5 لكل ألف ولادة) يعانون من تشوهات خَلقية رئيسية، و49 (50.6 لكل ألف ولادة) يعانون من تشوهات متعدِّدة في أجهزة البدن، و48 (4.94 لكل ألف ولادة) يعانون من تشوهات جهازية منفردة. وكان لدى 21 من أصل الأطفال التسعة والأربعين (أي 42.8٪ منهم) متلازمة أمكن التعرُّف عليها، معظمها جسدية متنحيّة، ولدى 17 شذوذات صبغية. أما التشوهات الجهازية المنفردة فقد تركَّزت في الجهاز العصبي (12 حالة) وفي الجهاز القلبي الوعائي (9 حالات)، وفي الجهاز الهيكلي (7 حالات) وفي الجهاز الهضمي (6 حالات). وكان 68٪ من الوالدين من أولي القربى. وقد كانت العوامل الوراثية ذات شأن في 79٪ من الحالات. ويرى الباحثون أن أقسام الوراثيات ينبغي اعتمادها كإجراء فعَّال للوقاية من هذه الاضطرابات.

ABSTRACT We investigated major congenital abnormalities in babies born in Al Jahra Hospital, Kuwait from January 2000 to December 2001. Of 7739 live and still births born over this period, 97 babies had major congenital malformations (12.5/1000 births): 49 (50.6%) babies had multiple system malformations, while 48 (49.4%) had single system anomalies. Of the 49 babies with multiple malformations, 21 (42.8%) had recognized syndromes, most of which were autosomal recessive and 17 had chromosomal aberrations. Isolated systems anomalies included central nervous system (12 cases), cardiovascular system (9 cases), skeletal system (7 cases) and gastrointestinal system (6 cases). Of the parents, 68% were consanguineous. Genetic factors were implicated in 79% of cases. Genetic services need to be provided as an effective means for the prevention of these disorders.

**Profil des principales malformations congénitales chez les nouveau-nés dans la Région d'Al Jahra (Koweït)**

RÉSUMÉ Nous avons étudié les principales anomalies congénitales chez les bébés nés à l'hôpital d'Al Jahra au Koweït de janvier 2000 à décembre 2001. Sur les 7739 naissances vivantes et mortinaissances survenues durant cette période, 97 bébés présentaient des malformations congénitales majeures (12,5 pour 1000 naissances) : 49 (50,6 %) des bébés avaient des malformations multiples, tandis que 48 (49,4 %) avaient des anomalies touchant un seul système. Sur les 49 bébés ayant des malformations multiples, 21 (42,8 %) avaient des syndromes reconnus, dont la plupart étaient récessifs autosomiques, et 17 avaient des aberrations chromosomiques. Lorsqu'elles étaient isolées,les anomalies concernaient le système nerveux central (12 cas), l'appareil cardio-vasculaire (9 cas), le système ostéo-articulaire (7 cas) et l'appareil gastro-intestinal (6 cas). Soixante-huit pour cent (68 %) des parents étaient consanguins. Des facteurs génétiques étaient impliqués dans 79 % des cas. Des services génétiques doivent être fournis en tant que moyen efficace de prévention de ces troubles.

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## Introduction

Birth defects are a major clinical problem: 3% of all children born in any hospital, country or year will have a significant congenital abnormality and they represent 30% of all admissions in hospitals [*1–4*]. The etiology of birth defects often remains unknown. Parental interview and family history are often used to validate the cause of congenital abnormalities. Babies with birth defects have a high risk of death in the perinatal period and infancy [*5*]. The later survival or reproduction of the affected individuals are less well known [*6,7*]. Birth defects can recur in families and the risks of recurrence have been investigated in clinical-based studies [*8*].

The aim of the national health goals in Kuwait (and many other countries) is to reduce the morbidity attributable to birth defects and developmental disabilities. Population-based surveillance has made notable contributions towards preventing such disabilities, monitoring changes in their incidence and identifying the reproductive hazards in the environment [*9–11*].

There is a higher incidence of major congenital malformations among Arabs of the Gulf region [*12,13*]. In the Al-Jahra region of Kuwait, 80% of the population is of Bedouin origin and they have a high rate of consanguinity. We aimed to investigate major congenital abnormalities in this region of Kuwait and determine the different patterns of congenital malformations, their incidence and the implicated genetic factors so as to establish appropriate strategies for prevention of these disorders in Kuwait.

## Methods

We examined data from the newborn register at Al-Jahra Hospital of all 7739 live births and stillbirths from January 2000 to December 2001. Al-Jahra hospital serves more than 300 000 individuals in this region. The neonates with major congenital malformations were clinically evaluated, diagnosed and statistically registered. These data were reconfirmed by the data available in the genetics outpatient clinic and genetics centre. Major congenital malformations were defined as abnormalities that impede the normal body functions and reduce life expectancy. A thorough perinatal history, 3 generations family pedigree and clinical examination were carried out to assess the major congenital abnormalities. Several investigations were carried out such as chromosomal analysis, FISH and other appropriate analyses, e.g. ultrasound, neuroimaging and histopathology. We categorized each baby with major malformation(s) as having either isolated abnormalities affecting a single body system or multiple congenital abnormalities affecting several body systems. The latter category was further subdivided into the following groups.

- Syndromes that are classified as monogenic
- Chromosomal aberrations
- Sequences that are the associated abnormalities which can be interpreted as a sequence of primary malformation
- Associations that are disorders characterized by non-random occurrence of several anomalies but do not represent a specific syndrome, e.g. VACTERL
- Unrecognizable patterns of multiple birth defects including multiple anomalies that do not fit into any of the above categories.

## Results

In all, 97 neonates were found to have major congenital malformations during the

study period, giving an incidence of major malformations of 12.5/1000 births. Eleven per cent of the 82 stillbirths had major anomalies. Of all babies (live and stillborn), 49 (50.5 %) had multiple congenital anomalies and 48 (49.5%) had one system congenital malformation (Table 1).

The distribution of cases with multiple system involvement according to type of condition is shown in Table 2. Major malformation syndromes were found in 21 cases.

Chromosomal aberrations were found in 17 cases, sequences in 3 cases, associations in 1 case and 7 cases of unidentified/ unclassified multiple system anomalies.

Forty-eight cases of single system malformations were found (Table 3). Of these, 12 had central nervous systems anomalies, 9 had cardiovascular defects, 7 had skeletal malformations, 6 had gas-

Table 1 **Major congenital abnormalities in 7739 births in Al-Jahra region of Kuwait (2000–2002)**

| Type | No. | Incidence/ 1000 births |
|---|---|---|
| ***Multiple major malformations*** | | |
| Monogenic syndromes | 21 | 2.7 |
| Chromosomal aberrations | 17 | 2.2 |
| Sequences | 3 | 0.4 |
| Associations | 1 | 0.1 |
| Unclassified | 7 | 0.9 |
| Subtotal | 49 | 6.3 |
| ***Single system malformation*** | | |
| Cardiovascular | 9 | 1.2 |
| Skeletal | 7 | 0.9 |
| Central nervous system | 12 | 1.6 |
| Gastrointestinal tract | 6 | 0.8 |
| Urogenital anomaly | 5 | 0.6 |
| Skin | 3 | 0.4 |
| Eye | 3 | 0.4 |
| Others | 3 | 0.4 |
| Subtotal | 48 | 6.2 |
| Total | 97 | 12.5 |

Table 2 **Distribution of the 49 cases of major malformations involving multiple systems**

| Type | No. of cases | Family history |
|---|---|---|
| 1. Major malformation syndromes | | |
| ***Monogenic autosomal dominant*** | (5) | |
| Treacher–Collins | 1 | – |
| Ehlers–Danlos | 1 | + |
| Woolly hair | 1 | + |
| Crouzon | 1 | – |
| Apert | 1 | + |
| ***Monogenic autosomal recessive*** | (12) | – |
| Zellweger | 1 | + |
| Joubert | 1 | + |
| Spinal muscular atrophy | 2 | + |
| Familial cholestasis | 1 | – |
| Congenital adrenal hyperplasia | 1 | – |
| McKusick–Kaufman | 1 | + |
| Al-Awadi | 1 | + |
| Bardet–Biedl | 1 | + |
| Facial clefting | 2 | – |
| Larsen | 1 | – |
| ***Environmental*** | (1) | |
| Congenital rubella | 1 | |
| ***Sporadic*** | (3) | |
| Noonan | 2 | |
| Sotos | 1 | |
| 2. Chromosomal aberrations | (17) | |
| Trisomy 21 | 12 | |
| Trisomy 18 | 3 | |
| Trisomy 13 | 1 | |
| Wolf–Hirschhorn syndrome | 1 | |
| 3. Sequences | | |
| Pierre Robin | 2 | |
| Holoprosencephaly | 1 | |
| 4. Associations | | |
| VACTERL | 1 | |
| 5. Unclassified MSA | 7 | |

***MSA = multiple system anomalies.***

trointestinal anomalies, 5 had urogenital defects, 3 cases each for skin and eye malformations and 3 cases had single anomalies involving other systems of the body.

Genetic factors were implicated in 77 cases (79%) (Table 4). Monogenic factors were found in 37 cases (autosomal recessive gene in 32 cases and autosomal dominant in 5 cases). Chromosomal aberrations were found in 17 cases. Multifactorial etiologies were also found in 23 cases.

### Role of consanguinity

There were 47 babies with consanguineous parents. The computed consanguinity rate was 59% which is slightly higher than the general population rate (52.9%) [*19*]. Of the 47 babies, 25 (53%) had first-cousin consanguineous parents compared with 33% in the general population. The consanguinity rate among neonates with multiple major malformation syndromes was 86% (18/21 babies) (Table 5). The other cases with multiple system malformations had a consanguinity rate of 57% (16/28 babies). The consanguinity rate among abnormalities of isolated systems was 46% (22/48). The rates of the aforementioned categories, multiple systems (syndromes and non-syndromes) and isolated abnormalities involving single systems showed a highly significant difference ($\chi^2 = 29.5$, degrees of freedom = 2, $P < 0.0001$.). The relative risk for consanguineous parents was 1.5 (95% CI: 1.27–2.24) indicating that these parents were more likely to have infants with multiple congenital anomalies than controls, i.e parents who had babies with single system malformations.

Table 3 **Distribtion of the 24 cases with major malformations involving single systems according to system affected**

| System | No. of cases |
|---|---|
| ***Skeletal malformations*** | (7) |
| Thanatophoric dysplasia | 2 |
| Achondroplasia | 1 |
| Metaphyseal dysplasia | 1 |
| Spondyloepiphyseal dysplasia | 1 |
| Dysostosis | 2 |
| ***Cardiovascular system anomalies*** | (9) |
| ***Cental nervous system malformations*** | (12) |
| Anencephaly | 3 |
| Meningomyelocele | 2 |
| Primary microcephaly | 2 |
| Isolated hydrocephalus | 1 |
| Meckel–Gruber syndrome | 3 |
| Holoprosencephaly | 1 |
| ***Gastrointestinal tract system malformations*** | (6) |
| Tracheoesophageal fistula | 1 |
| Facial clefting | 2 |
| Diaphragmatic hernia | 2 |
| Imperforate anus | 1 |
| ***Urogenital system*** | (5) |
| Polycystic kidney (infantile) | 2 |
| Urethrovaginal fistula | 1 |
| Ambigeous genitalia | 2 |
| ***Genodermatosis*** | (3) |
| Icthyosis | 2 |
| Epidermolysis bullosa | 1 |
| ***Eye malformations*** | (3) |
| Congenital buphthalmos | 1 |
| Congenital microphthalmia | 1 |
| Congenital cataract | 1 |
| ***Others*** | (3) |
| Congenital stenosis of external auditory meatus | 1 |
| Teratoma of oral cavity | 1 |
| Cystic hygroma of neck | 1 |

## Discussion

In the present study the incidence of major congenital malformations was 12.5/1000 births which is comparable to the results of Al-Jawad et al. [*12*] but slightly higher than those of Al-Ghazali et al. [*13*]. Both studies

Table 4 **Genetic contributions to congenital abnormalities**

| Type | No. of cases |
|---|---|
| ***Single gene defect*** | (77) |
| ***Autosomal recessive disorders*** | (32) |
| Thanatophoric dysplasia | 2 |
| Facial clefting | 2 |
| Zellweger syndrome | 1 |
| Joubert syndrome | 1 |
| Congenital buphthalmos | 1 |
| Congenital microphthalmia | 1 |
| Congenital cataract | 1 |
| Tracheoesophageal fistula | 1 |
| Diaphragmatic hernia | 2 |
| Familial cholestasis | 1 |
| Spinal muscular atrophy | 2 |
| Ectrodactyly (dysostosis) | 1 |
| Congenital adrenal hyperplasia | 1 |
| Meckel–Gruber syndrome | 3 |
| McKusick–Kaufman syndrome | 1 |
| Al-Awadi syndrome (LPAH) | 1 |
| Bardet–Biedl syndrome | 1 |
| Larsen syndrome | 1 |
| Primary microcephaly | 2 |
| Polycystic kidney (infantile) | 2 |
| Icthyosis | 2 |
| Epidermolysis bullosa | 1 |
| ***Autosomal dominant*** | (5) |
| Treatcher–Collins | 1 |
| Ehlers–Danlos | 1 |
| Woolly hair syndrome | 1 |
| Crouzon syndrome | 1 |
| Apert syndrome | 1 |
| ***Chromosomal abnormality*** | (17) |
| ***Multifactorial etiology*** | (23) |
| Cardiovascular system anomalies | 9 |
| Neural tube defects | 7 |
| Gastrointestinal tract | 1 |
| Urogenital disorders | 1 |
| Holoprosencephaly | 1 |
| Others | 3 |

Table 5 **Consanguinity rates among the different categories of major malformations syndrome**

| Major anomalies | Rate (%) |
|---|---|
| Multiple major malformation syndromes | 86[a] |
| Other multiple malformations | 57 |
| Isolated systems abnormalities | 46 |

[a] $\chi^2 = 29.5$, degrees of freedom = 2, P < 0.0001.

were carried out in the United Arab Emirates. Our results are lower than those reported by other researchers [*14–17*]. The lower figure in the our study could be due to cases being missed after delivery (owing to reluctancy to register and notify the authorities) as well as parental refusal for postmortem.

The rate of monogenic autosomal recessive congenital anomalies in this study was 12/21 cases (38%), which is higher than the incidence reported by Van Regemater et al. [*18*]. Autosomal recessive disorders gave a higher incidence 33% (32/97) than dominant disorders 5% (5/97). The high incidence of autosomal recessive disorders could be due to the high rates of consanguineous marriage among Bedouins; 80% of the population in Al-Ahra region is of Bedouin ancestry. Al-Awadi et al. reported 56% and 68% consanguinity rates among controls and index cases respectively and compared these with other reports by Badr et al. and Hafez et al. [*19–21*]. The average coefficient was found to be high also (0.0219) that is almost double that of the Egyptian population 0.01 [*21*]. In Kuwait, the consanguinity proportion of first cousin marriage was 60% [*19*]. A similar study in UAE reported 51% and 88% consanguinity (first cousin) among controls and and those with of congenital syndromes respectively [*22,23*]. Sogaard suggested that the risk of a child

having a recessively inherited disorder is higher if the parents are blood related and the more closely related the parents are, the higher the risk [*24*].

Most of the major malformations in our study could be prevented by using methods of pregnancy screening for neural tube defects, screening of older mother for Down syndrome, assessing family history and prenatal diagnosis. In Kuwait there are no well-accepted preventive measures despite the high risk of recurrence of single gene conditions, which indicates the strong need for comprehensive preventive measures for congenital abnormalities in this country. There have been some efforts to address this issue, such as maternal care during pregnancy and educational programmes on congenital malformations and the consequences of consanguineous marriages [*25*] (genetic counseling is done in the genetics center and the related genetics outpatient clinics). Talaat et al. reported the congenital malformations register showed a dramatic decline in the prevalence of anencephaly (1.33/1000) among those with Bedouin ancestors as a result of a mass educational dietetic programme for Bedouin women in Al-Jahra Region [*25*]. In the present study we found a further decline in anencephaly prevalence (0.3/1000).

## Conclusion

The present study showed a high incidence of congenital malformations among our population and also a high rate of consanguinity which can lead to the recurrence risk of these conditions. This study inidcates the need to establish preventive programmes for such disorders in this community.

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