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Incidence and Determinants of Birth Defects and Enzyme Deficiencies among Live Births in Oman

A review of the 2005 National Register

*Rajiv Khandekar,[1] Yasmin Jaffer[2]

حدوث وتحديد العيوب الخِلْقِيّة وقصور الإنزيم لدى المواليد الأحياء في سلطنة عُمان

مراجعة السجل الوطني لعام 2005م

راجيف خانديكار، ياسمين جعفر

الملخص: الهدف: شرعت وزارة الصحة في عام 2003 ممثلة ببرنامج رعاية الطفولة ببدء تسجيل حالات التشوهات الخِلْقِيّة. هذه الورقة تستعرض مقدار عَوامل الاخْتطار لدى الأطفال ذوي التشوهات الخِلْقِيّة بين المواليد الأحياء بسلطنة عُمان والمسجلة بالسجَل عام 2005م. **الطريقة:** قام الأطباء المَختصّون بطب الأطفال وطب حديثي الولادَة بفحص الأطفال ذوي العيوب الخِلْقِيّة الذين تم تسجيلهم والتبليغ عنهم إما أثناء فحصهم عند الولادة أو في خلال السنة الأولى من العمر أثناء ترددهم للعيادات.تم إجراء الفحوصات السريرية والمختبرية والتصوير الشعاعي والتَخْطيط التَصْوَاتيّ. قبل الفحوصات تم كتابة التفاصيل الشخصية، نوع التشوهات الخِلْقِيّة بالإضافة إلى استخدام التصنيف الدولي للأمراض – 10 (ICD–10) مع عَوامل اخْتطار مختارة. تم حساب معدلات الإصابة بالنسبة المَئوية.**النتيجة:** كان معدل الإصابة السنوية في سلطنة عُمان 2.53% (فترة ثقة 95: 2.68–2.38). كان لدى الذكور اخْتطار أعلى بالتشوهات الخلقية من الإناث. (اخْتطارٌ نسْبيّ = 2.0). التباين المناطقي كان معتدا إحصائيا أيضا (مربع كاي = 363). كانَ معدل الإصابة بفقر الدم نتيجة اضطرابات الإنزيمات 1.4%. أما تشوهات الجهاز البولي–التناسلي واليدين والقدمين ومتلازمة داون فكانت تُمثّل العيوب التشريحية الرئيسية. كان الزواج لدي الأقارب (اخْتطارٌ نسْبيّ = 0.85) وانخفاض الوزن عند الولادة ((اخْتطارٌ نسْبيّ = 0.28) مرتبطين سلبيا مع التشوهات الخِلْقِيّة. كان الاخْتطارٌ النسْبيّ (1.89) لَدىَ الأمهات اللواتي يلدن <37 أسبوعا حيث تبينَ أن التَشوهات الخلقِيّة عالية عند أطفالهن. لم نجد اَرتَباطا.بين عمرَ كل مَن الأب والأم. **الخلاصة:** يعتبر السجل الوطني للتشوهات الخِلْقِيّة أداة هامة للتقييم. إنَ عَوامل الاخْتطار الناتجة عن العوامل الوراثية والمكتسبة يمكن أن تؤثر على معدل العيوب الخِلْقِيّة ونوعيتها في سلطنَة عُمان.

مفتاح الكلمات: التشوهات الخِلقية، العيوب الخِلقية، سلطنة عُمان.

abstract: ***Objectives:*** In 2003, the Omani Ministry of Health Child Health Care Program initiated a national Birth Defects (BD) Register. This paper reviews the magnitude and risk factors of birth defects in children born and registered in 2005 using data from the BD Register. ***Methods:*** Pediatricians and neonatologists examined children with BDs found either during screening at birth or when attending clinics in their first year of their life. Clinical examination, laboratory, sonographic and radiological investigations were carried out. A pre-tested form was used to note personal details, type of birth defect including International Classification of Diseases-10 (ICD-10) codes of BD and selected risk factors. The incidence rates per 100 live births were calculated. ***Results:*** The annual incidence of BD in Oman was 2.53% (95% CI 2.38–2.68). Males had a significantly higher risk of BD than females (relative risk (RR) = 2.0). The regional variation of BD was also significant (χ 2 = 363). The incidence of anaemia due to enzyme disorders was 1.4%. BD of urogenital organs, hands and feet and Down's syndrome were the main types of anatomical defects. Consanguinity among parents (RR = 0.85) and low birth weight (RR = 0.28) was negatively associated to birth defects. Mothers giving birth at gestational age of <37 weeks (RR = 1.89) had a higher risk of having children with BD. Maternal and paternal age were not associated to BD. ***Conclusion:*** The national Register for BD is an important evaluation tool. Both genetic and acquired risk factors seem to affect BD rates and types in Oman.

Keywords: Birth defects; Congenital anomalies; Oman.

[1]Eye & Ear Health Care, Department of Non-communicable Diseases Control, Directorate General of Health Affairs, Ministry of Health, Oman; [2]Department of Maternal & Child Health Care, Ministry of Health, Oman

To whom correspondence should be addressed. Email: rajshpp@omantel.net.om

Advances in Knowledge

1. *This review provides a profile of infants with birth defects (BD) as reported in the Oman BD Register*
2. *The incidence of different BD in relation to live births for 2005.*
3. *Down's syndrome and anomalies of extremities were common in Oman.*
4. *To meet international standards, the Register should include BDs of aborted fetuses.*
5. *The current methodology of including enzyme deficiencies as BDs, although important for Oman, is not as per the international database on BD.*
6. *Incidence of BD in Oman in this study could be underestimated.*

Application to Patient Care

1. *Countries experiencing a significant decline in the infant mortality rate due to less communicable and nutrition-related diseases still have to face the burden of genetic and birth defect related problems in infants.*
2. *Knowledge of the magnitude of the BD problem, the profile of birth defects and risk factors will enable the child health care programme of a country improve its implementation and planning.*
3. *The prevalence of BDs in Oman in 2005 was 2.53% (95% CI 2.38–2.68). Males, children with low birth weight, and residents of specific regions were significantly associated with BDs in children.*
4. *A well maintained national BD register is an important tool for global and national efforts to address this problem.*

The United Nation's Millennium Developmental Goal-4 to reduce child mortality by two-thirds from 1990 levels by 2015 will not be met unless the mortality from birth defects and preterm birth is recognised and addressed.[1] Worldwide, the prevalence rates of all genetic birth defects combined range from a high of 82/1,000 live births in low-income regions to a low of 39.7/1,000 live births in high-income regions.[2] Countries like Oman, which has undergone rapid socioeconomic development, are currently undergoing epidemiological transition. Communicable disease rates are declining, but chronic and non-communicable diseases are on the rise.[3] The magnitude of genetic disorders is high in Omani children and it is likely to increase unless known risk factors like consanguinity, better survival of preterm babies due to improved child health care, and limited acceptance of therapeutic abortions are addressed.[4]

The Maternal and Child Health Care Program as well as the programme for controlling genetic disorders in Oman has recognised this health problem and included it in 6th Five Year Health Plan.[5] A national BD Register was started in 2003 with BD defined as physical abnormalities or enzyme deficiency, mainly glucose-6-phosphate dehydrogenase deficiency (G6PD). Paediatricians provide the information for the Register and its programme managers improved its quality of Register in the initial years. The authors analysed the national BD Register for 2005 to estimate the incidence of BDs for live births and their epidemiological determinants. On this basis, public health related recommendations were proposed.

Methods

This was a review of the national BD Register. The Ethical and Research Committee of the Ministry of Health gave permission for the study. Paediatricians and neonatologists at ten regional hospitals were our study investigators. All babies born in the year 2005 in Oman were our total study population. Children with BDs, found either during screening at birth or when attending clinics in their first year of their life, were our specific study population. Those identified with anatomical deformities were registered after detailed clinical examination. Blood tests were performed for children suspected to suffer from genetic blood disorders. Children with BDs also underwent radiological and sonographic evaluation to identify any other anomalies in addition to the principal defect. Personal information like date of birth, sex, area of residence, tribe, mother's age at birth, father's age, order of birth, birth weight, gestational age on birth, status of child in the first year of life (alive or dead), medical history and degree of consanguinity among parents were noted on a standardised pre-tested form. The principal BD as per the International Classification of Diseases-10 (ICD-10) code was also noted. All the children with Down's syndrome had their condition confirmed by laboratory tests. The children were managed by paediatric services either in regional hospitals or with the help of a paediatric surgeon

Table 1: Characteristics of the children born in 2005 and children with birth defects in Oman

	Children born in 2005		Children with birth defects	
	#	%	#	%
Gender				
Male	21,264	50.6	582	54.6
Female	20,801	49.4	288	27.0
Undetermined	-	-	5	0.5
Missing	-	-	190	17.8
Region				
Muscat	9,861	23.4	184	17.3
Dhofar	4,115	9.8	66	6.2
Dhakhiliya	5,727	13.6	338	31.7
North Sharqiya	3,466	8.2	40	3.8
South Sharqiya	4,088	9.7	105	9.9
North Batinah	6,856	16.3	190	17.8
South Batinah	3,778	9.0	78	7.3
Dhahira	3,578	8.5	41	3.8
Musandam	436	1.0	21	2.0
Al Wusta	160	0.4	2	0.2
Total	**42,065**	**100**	**1,065**	**100**

at tertiary hospitals. If treatment was possible, but facilities were not available within the country, the child's treatment, in a reputed centre abroad, was paid for by the Omani government.

The BD Register was initiated in the year 2002. The first year was the pilot phase to strengthen the registration system. From 2003, a national data collection system was implemented by the national Health Information Management System (HIMS). The Department of Mother and Child Health (MCH) of the Ministry of Health (MoH) liaised with regions to monitor and follow the registration of children with BD. Neonatologists and other specialists like paediatric ophthalmologists, ear, nose and throat surgeons, cardiologists, etc, in regional and wilayat (district) MoH hospitals reported information on BD. The attending physician of the institution where such a child was first reported was labelled as the reporting person. As information in the Register was based on identity of the parent health institution, duplications were avoided. The national supervisor for MCH followed through with the attending physicians to ensure the completion of all relevant information in the BD Register.

The data on live births, children with low birth weights (< 2.5 kg) and the proportion of twin births, to determine plurality, was provided by the Department of Health Information and Statistics.[6] The proportion of preterm babies in general population was 9.4% in a study in Saudi Arabia.[7] We took it as reference for calculating preterm babies in the cohort of live births in 2005 in Oman.

The regional health information officers computed the data from the pre-tested forms by using Epi Info™ 6 software (Center for Disease Control, USA).The statistician of the Oman Ministry of Health's (MoH) Maternal & Child Health Care (MCH) Department compiled the national Register. After ensuring completion of information, univariate analysis was carried out using the parametric method and the Statistical Package for Social Studies (SPSS, Version 12). Frequencies and incidence of BDs nationally and of regional subgroups were calculated per 100 live births. The risk of BD was compared to the children born without BD in 2005 in Oman by calculating relative risk, 95% confidence intervals (CI) and *P* values (set at (< 0.05).

The identities of children with BD and their parents were de-linked from information on risk factors of BD and only the principal investigator had access to this information. The results of this study were shared with regional paediatricians and the staff of the programme for the control of genetic diseases. Policies for strengthening the BD Register and the care of children with BD were then proposed to the members of the national Mother and Child Health Care Committee.

Results

The BD Register of Oman had 1,393 children registered in 2005. Of them, 1,065 (76.5%) children were born in 2005. Fifty-seven (4.02%) children with BD died in the first year of life. The characteristics of children with BD were compared to all the Omani children born in 2005 [Table 1]. Five children with BD had undetermined gender on clinical examination.

The incidence of BDs was calculated for different epidemiological variables. Live births were used as the denominator to calculate the incidence of BD. Data on the birth cohort, number of children with BD, incidence per 100 live births, the relative risk, their 95% CI and the *P* values are given in Table 2. The incidence of BD in Oman during 2005

Table 2: Incidence of Birth Defect (BD) per 100 live births in Oman in 2005.

Variant	Live births	No. with BD	% of BD	95% CI
Gender*				
Male	21,264	799	2.74	2.52–2.96
Female	20,801	390	1.38	1.23–1.54
Region**				
Muscat	9,861	184	1.87	1.60–2.13
Dhofar	4,115	66	1.60	1.22–1.99
Dhakhiliya	5,727	339	5.90	5.29–6.51
N. Sharqiya	3,466	40	1.15	0.80–1.51
S. Sharqiya	4,088	105	2.57	2.08–3.05
N. Batinah	6,856	190	2.77	2.38–3.16
S. Batinah	3,778	78	2.06	1.61–2.52
Dhahira	3,578	41	1.15	0.80–1.49
Musundam	436	21	4.82	2.81–6.83
Wousta	160	2	1.25	-0.47 -2.97

*Legend: RR = relative risk; *Validity: RR = 1.98, 95% CI = 1.72 – 2.27, P value = <0.001; **Validity:* χ 2 = 363*, 95% CI :* Df =8*, P value = <0.001*

was 2.53 per 100 live births and was significantly higher in boys compared to girls. (RR = 1.98 (95% CI 1.72–2.27), *P* = <0.001). The regional variation of reporting BD in children was significant. The Dhakhiliya region had significantly higher BD rates (5.90 per 100 live births; 95% CI 5.29–6.51), whereas the North Sharqiya and Dhahira regions had lower incidences of BD (1.15/100 live births). The types of BDs as per the ICD-10 codes with incidence per 100 live births are given in Table 3. Of the 1,065 children with BD, 589 (55.3%) had anaemia due to G6PD enzyme disorders. Deformities of hands and feet were noted in 106 children with an incidence of 0.25 per 100 live births.

The rate of BDs was compared among the different subgroups of children born in 2005; the frequencies, relative risks, 95% CI and *P* values are given in Table 4. We did not find a significant association between maternal age at birth and the presence of BD. The information on other variables was missing for nearly half of the participants.

Discussion

This is the first attempt at national level in Oman to review the profile of children with BD. The infant mortality rate (IMR) in Oman of 10.28/1,000 live births is now mainly due to non-communicable diseases. The high rate of hospital deliveries in Oman, together with a nearly 100% immunisation rate of children against infectious diseases (including rubella) as well as free access to high standard, regional neonatal and child health care services have resulted in a marked decline in deaths due to avoidable conditions.[8] Unfortunately, risk factors for genetic disorders such as the high rate of diabetes in women,[9] consanguineous marriage practices, [10] limited therapeutic abortions and mothers of older age are still present in Oman. In such a situation, knowledge of the incidence of BDs and their risk factors is crucial in order to formulate future prevention and intervention policies.

In 2005, the overall incidence of BD in Oman was 2.53% (95% CI 2.38–2.68), but a study in one of the regions of Oman showed a BD prevalence of 2.46%.[11] The rate in Oman was more than that reported in Iran (1.01%),[12] Kuwait (1.25%)[13] Bangladesh (2.3%)[14] and the UAE (0.79%).[15] It is worth noting that, in spite of variations in all these studies, the populations were all of Muslim religion. Apart from Bangladesh, the other study areas were in Middle Eastern countries, where the health services are accessible and of a high standard. Therapeutic abortion is also not widely accepted in these countries. Despite the similarities among these countries the differences in the rates cannot be explained. Perhaps the high incidence of diabetes in the >20 population in Oman and diabetes in mothers being a known risk factor of BD, could be a logical explanation for the higher incidence of BD in our study.[16,17,18] Further studies of specific BDs in Oman are recommended to explain the reason for the higher incidence of BD in Oman compared to neighbouring countries. However, Oman has the following factors which militate against the higher incidence of BDs found in this study: 1) only 0.5% prevalence of smoking among females;[19] 2) a religious taboo on the consumption of alcohol and controls on its availability; 3) low incidence of malnourishment and folic acid provision to females during antenatal period points at a lower risk of central nervous system congenital malformation;[20] 4) universal immunisation against rubella,[21] and 5) controlled prescription of medicines with teratogenic properties.

The incidence of BD was significantly higher in males compared to females in our study. This was also reported in Iran and in a study by Cui *et*

Table 3: Birth Defect (BD) by type in Oman in 2005

(42,065 live births in 2005)	Children with BD	Incidence of BD	95% Confidence Interval
Type of BD			
Anaemia due to enzyme disorders	589	1.40	1.29–1.51
Deformities of hand & feet	106	0.25	0.20–0.30
Urogenital anomalies	80	0.19	0.15–0.23
Anomalies of skull & spine	41	0.10	0.07–0.13
Anomalies of heart & great vessels	41	0.10	0.07–0.13
Down's syndrome	32	0.08	0.05–0.10
Musculoskeletal anomalies	23	0.05	0.03–0.08
Cleft palate/lip	21	0.05	0.03–0.07
Anomalies of alimentary canal	21	0.05	0.03–0.07
Malformations of eye & ear	19	0.05	0.02–0.07
Respiratory anomalies	6	0.01	0.00–0.03
Other	86	0.20	0.16–0.25
Oman	**1,065**	**2.53**	**2.38–2.68**

al.[12, 22] A study of opposite sex twins suggested that males had a 29% higher risk of BD compared to their sisters.[23] A study with a large sample showed that a higher percentage of males was noted with obstructive cardiac defects while females were more likely to have all types of neural tube defects.[24] Folic acid supplementation and high take-up rates of antenatal care in Oman may have resulted in a lower incidence of neural tube defects and less females with BD of these types.

The regional variation in BD was marked in Oman. Different tribes in different regions could explain this variation. Regional variation was noted in the prevalence of congenital heart defects in a study done in Saudi Arabia.[20]

A maternal age of more than 25 years was associated with BDs in the United Arab Emirates.[15] In our study also, younger mothers had children with BD. In contrast, mothers of >35 years of age had a significantly higher risk of having children with autism and heart defects BD.[25, 26] In another study in Oman, older aged mothers had a significant risk of giving birth to children with Down's syndrome.[27] We cannot explain the reason for this negative association in the present study. We did not include stillborn and naturally aborted preterm infants when calculating the incidence and risk factor in our study. Multi-system genetic disorders could be higher in the group that died prematurely. Perhaps this could be the reason of the observed non-association in our study.

The influence of paternal age (>35 years) was associated with a higher incidence of Down's syndrome.[28] Factors related to the father's occupation also have been attributed to incidence of BD.[29] In our study, we did not find such an association. Information on the father's age was missing for 29 children and these fathers are more likely to be in the >45 years age group. If we review the risk of BD on this assumption, then paternal age was a significant risk factor for BD in Oman.

Low birth weight and preterm babies are known risk factors for BD.[13, 15, 30] Surprisingly, low birth weight was negatively associated to BD in our study. The non-inclusion of stillbirths with BD might be the reason for such an association. The risk of BD has been noted in twin and multiple pregnancies especially those arising from artificial reproductive techniques.[31] Since there was no information on weight and plurality for a large number of children in our cohort, the association of BD with birth weight and plurality should be viewed with caution. Given the fact that there were only seven pairs of twin children, we did not calculate the risk of BD to plurality. It should be noted that BD could be the reason for preterm deliveries and low birth weight of infants.

Consanguinity has been documented as a risk factor for many congenital anomalies.[32, 33] However, in our study, it was not found to be a risk factor for BD. Since we excluded still births and aborted fetuses, we may have found less multi-syndromic congenital anomalies with a strong genetic link. In addition, small and close-knit communities, such as the Kabila tribe in Oman, could have a long history of consanguinity; however, given better education

Table 4: Risk factors for Birth Defects (BD)

Risk factor	Live births	Children with BD	RR	95% Confidence Interval	*P* value
Mother's age					
< 35 years	36,122	874	0.89	0.77– .07	0.25
≥ 35 years	5,929	128	-	-	-
Missing		13	-	-	-
Father's age					
< 45 years	37,981	1,217	1.11	0.95–1.29	0.19
≥ 45 years	4,084	147	-	-	-
Missing		29	-	-	-
History of consanguinity in parents					
Yes	23,683	555	0.85	0.75–0.96	0.007
No	18,382	510			
Birth weight					
< 2.5 kg	3,470	114	0.28	0.23–0.35	< 0.0001
≥ 2.5 kg	38,595	350	-	-	-
Missing		601	-	-	-
Gestational age at birth					
< 37 weeks	3,954	77	1.98	1.55–2.53	< 0.001
≥ 37 weeks	38,111	371			
Missing		617			
Plurality					
Single birth	41,689	457	1.70	0.81–3.56	0.20
Multiple births	376	7	-	-	-
Missing	-	601	-	-	-

in the younger generation, consanguinity, a known risk factor for BD, may now be less than in the past.

Migration to urban areas and the growth of the nuclear family has also been postulated to dilute the role of consanguinity and that could be the reason for the observed association of consanguinity with BD in our study. [34]

Anaemia due to G6PD enzyme disorders was the main reported BD in Oman. This agreed with earlier observations in Oman.[35, 36] There were a significant number of BDs of the urogenital system, Down's Syndrome children and deformities of the hands and feet in our study. Further studies with a larger sample of these BDs are recommended. The surveillance for BD in different countries as reported by International Center for Birth Defect Surveillance and Research (ICBDSR) suggested that rate of Down's syndrome in our study matched that of Cuba and Italy. However, it was lower than USA, Canada and France.[37] Inclusion of BD among aborted fetuses in other countries could be the reason for the higher rate compared to our study. In these countries, the registration included BD among aborted fetus and paid special attention to factors during pregnancy associated to BD. In Oman, the BD Register included genetic blood disorders and excluded aborted fetuses therefore comparison of rates should be done with great caution.

As this study was a retrospective Register review, loss of data or incomplete data was an inherent limitation. In spite of communicating with regional programme managers to complete the Register as well as using indirect indicators from other sources like the child health registers at primary health institutions and records of infant deaths at regional hospitals, we still had missing information that could have introduced bias into our study especially while reviewing the association of risk factors to BD.

Our study suggested that the incidence of BD in surviving infants was high. The Maternal and Child Health Program should emphasise the

need for improved quality of registration in order to ensure complete records. Both genetic and acquired factors seem to interact and result in a high incidence of BD in Oman. The health services at regional level should be well equipped to identify and manage children with BD. Some of the children with BD, even after successful management, will need long term follow-up and rehabilitation. Hence prevention, care and rehabilitation should be an integral component of the BD control programme. Further studies of important BDs and their risk factors would enable the programme to formulate a preventive and rehabilitative approach for each of them.

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