ORIGINAL ARTICLE

Audit of Birth Defects in 34,109 Deliveries in a Tertiary Referral Center

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Summary

The objective of the study is to determine the proportion and different types of birth defects among the children born in Hospital Kuala Lumpur. A cross-sectional study was conducted for a period of 18 months where all consecutively born infants, dead or alive were included. There were total of 34,109 births recorded during this period. The proportion of birth defects in Hospital Kuala Lumpur was 3.1% (n=1056). The commonest involved were the hematology system, (157.7 per 10,000 births), the central nervous system, genitourinary system and chromosomal anomalies. The proportion was significantly higher in males and in the Chinese ($p<0.001$). The commonest abnormalities are Glucose 6 Phosphate Deficiency (157.7/10000), Down's syndrome (12.6/10000), thalassaemia (8.8/10000), cleft lip and/or palate (7.6/10000) and anencephaly (7.3/10000). Neural tube defect is common and ranked second after G6PD deficiency. There is a need for a birth defect registry to assess the extent of the problem in Malaysia.

Key Words: Congenital anomaly, Birth defects, Audit

Introduction

Birth defects are a major cause of mortality and handicap all over the world. The World Health Organisation (W.H.O) reported an estimated 495,000 deaths due to congenital anomaly in 1997[1]. In Malaysia there is an increase in certified infant deaths due to congenital anomalies even though the infant mortality rate has declined from 7.5% (1957) to 1.16% (1992) due to improved nutrition and better obstetric and neonatal services[2]. Congenital abnormalities were the second leading cause of neonatal death and contributed to almost half (42%) of all neonatal deaths throughout Malaysia[3]. In the Maternity Hospital, Kuala Lumpur (MHKL), it contributed up to the 28% to 35% of neonatal mortality from 1996–2001[4-7].

Unfortunately, only three previous published and two unpublished studies on this problem in the Malaysian population have been performed[8-12]. These published studies have been performed more than 10 years ago. Information on the prevalence and the pattern of congenital anomaly will be valuable to the health care providers, educators and genetic counselors. This is in view of the future planning and implementation of the policies and guidelines in the management and prevention of birth defects that is in parallel with the development of new technologies. In the new genetic age, there is rapid development and technological advances in diagnosis (e.g. preimplantation genetic diagnosis and analysis of fetal cells in maternal blood) and the treatment of congenital anomaly even though some procedures may still be in the research stages

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(e.g. gene therapy)[13]. Moreover, prevention of specific diseases is also possible through prenatal counseling[14] and periconceptual consumption of folic acid and vitamin supplements[15-17].

There is a need to acquire more information on the spectrum of birth defects especially in the MHKL. It is the national referral center with a feto-maternal unit and prenatal diagnostic services established since 1992[18]. It receives referral cases from various health clinics, private centres and hospitals from other states[18-20]. Information is needed to ascertain the need for screening, prenatal diagnosis and prenatal counseling of common diseases and for setting up of birth registries and genetic laboratories. Therefore, the prevalence, pattern, proportion and types of birth defects of children born in a national referral center with an estimation of 24,000 deliveries per year will be ascertained.

Materials and Methods

Congenital abnormality is defined as any structural, functional or biochemical abnormality present at birth, regardless of whether it is detected at birth[21]. The International Statistical Classification of Diseases (ICD) published by the World Health Organisation and which has been revised (tenth revision) has been widely used for classifying birth defects and genetic disorders[22]. It is based on involvement of organ system and this ICD classification will be utilised in this study. A cross sectional study will be conducted at the Maternity Hospital Kuala Lumpur (MHKL). This study included all consecutively born infants, alive or dead, with birth defects (congenital anomalies, birth defects and chromosomal disorders) both minor and major, delivered between the periods of 18 months from January 1999 to June 2000. The source of data is from the labour room records and the hospital records from the Record office. The policy of the hospital is to clinically examine all births within the first 24 to 48 hours of life. Newborns found to have congenital anomalies were referred to the pediatricians for verification and further investigations to confirm the clinical findings. If the disorder is severe, the newborns will be admitted to Neonatal Special Care nursery to have further intensive care. For those malformed babies who died in the hospital, autopsy is not a must in the hospital due to cultural and religious sensitivities, and consent has to be obtained from parents.

Statistical Package for Service and Solution (SPSS) software version 10.01 and EpiInfo version 6.01 were used to analyse the data. Chi-square (χ^2) test was used to test the significance of the results. The p value was set at $p<0.05$.

Results

During these 18 months, there were a total of 34,109 babies delivered out of which 1,056 (3.1%) infants were diagnosed to have birth defects. Among the 1,056 cases with birth defects, sex status was recorded in 969 cases, out of which 696 (72%) were males and 260 (27%) were females. The remaining 13 (1.3%) were of 'undetermined' sex.

Among the ethnic groups, out of the 1,056 cases, the Chinese had the highest proportion of birth defects (4.4%), followed by the Malays (3.5%) and the Indians (1.4%). The proportion of Indonesians with birth defects was 1.8%. The difference in the proportion of birth defects was statistically significant by race groups (χ^2=99.03, df=5, $p<0.001$). The proportion of birth defects was significantly higher in the Chinese as compared to the Malays (χ^2=7.53, df=1, $p<0.01$) and Indians (χ^2=69.83, df=1, $p<0.001$). Furthermore, the proportion of birth defects was also significantly higher in the Malays as compared to the Indians (χ^2=54.48, df=1, $p<0.001$).

Regarding the different types of birth defects, these were first examined by organ systems (Table I-IV and Fig. 1). The commonest was the haematology system, which accounted for more than half (51.04%) of the birth defects. This was followed by the central nervous system, chromosomal anomalies and genitourinary system (each contributing from 5 to 10% of cases) and these three systems accounted for 19.56% of birth defects (Fig: 1). Infants with multiple congenital anomalies (affecting more than 1 system) accounted for 8.2% of the overall birth defects. Musculoskeletal, cardiovascular, orofacial and neck and the gastrointestinal tract anomalies each contributes up to 5% of cases (Fig. 1).

Regarding specific abnormalities, the commonest is G6PD deficiency, followed by Down's syndrome, thalassaemia, cleft lip and palate, congenital hydrocoele, anencephaly, clubfoot, congenital hydrocephalous, hydronephrosis and imperforate anus (Table I-IV). However, neural tube defects (n=65) that include anencephaly, hydrocephalus, spina bifida, myelomeningocoele, encelophalocoele etc. constituted 90.3% (1 in 525) of all birth defects of the central

nervous system, giving the proportion of 19.1 per 10,000 births (Table I). Therefore, neural tube defects as a group occur quite commonly and rank second after the G6PD deficiency.

In addition, multiple congenital anomalies (that includes anomaly affecting more than one system and also specific syndromes) occur in 26.7 per 10,000 births. Out of this, in 73 (80.2%) cases, more than one system of the infants was affected. Out of the 73 cases only 46 cases could be identified as the remaining 27 case records were not available. There were 15 cases (16.5%) with 'specific syndrome' (e.g. Pierre Robin syndrome and Holt Oram syndrome) and three (3.3%) cases with dysmorphic facies. The miscellaneous group (n=18) includes two cases (11%, 0.6 per 10,000 births) of conjoined twins and one case (5.5%, 0.3 per 10,000 births) of congenital adrenal hypoplasia.

Table I: Disorders in the first three commonest systems affected.

		Frequency	Percentage	Proportion (per 10,000 births)
A)	**Hematology - Total**	**538**	**100**	**157.7**
	(G6PD) Deficiency			
	a. Absent Activity	456	84.76	133.7
	b. Minimal Activity	46	8.55	13.5
	Thalassaemia	30	5.58	8.8
	Haemophilia A	1	0.19	0.3
	Haemophilia B	1	0.19	0.3
	Von Willebrand's Disease	1	0.19	0.3
	Others	3	0.56	0.9
B)	**Central Nervous System - Total**	**72**	**100**	**21.1**
	Anencephaly	25	34.7	7.3
	Congenital Hydrocephalus	20	27.8	5.9
	Spina bifida	7	9.7	2.1
	Microcephaly	5	6.9	1.5
	Meningocoele	3	4.2	0.9
	Myelomeningocele	2	2.8	0.6
	Others	10	13.9	2.9
C)	**Genitourinary System - Total**	**67**	**100**	**19.6**
	Congenital hydrocele	25	37.3	7.3
	Hydronephrosis	12	17.9	3.5
	Undescended testes	8	11.9	2.3
	Abnormal male external genitilia	6	8.95	1.8
	Ambiguous genitalia	3	4.48	0.9
	Potter's syndrome	3	4.48	0.9
	Phimosis	2	2.99	0.6
	Hypospadias	2	2.99	0.6
	Epispadias	1	1.49	0.3
	Infantile polycystic kidney	1	1.49	0.3
	Penile vesicle	1	1.49	0.3
	Others	3	4.48	0.9

Table II: Disorders in the chromosomal, musculo-skeletal and cardiovascular systems

Type of defects	Frequency	Defects - per 10,000 birth
Chromosomal-Total	**65**	**19.1**
Down's syndrome	43	12.6
Edward's syndrome	10	2.9
Patau's syndrome	9	2.6
Turner's syndrome	2	0.6
Noonan's syndrome	1	0.3
Musculo-Skeletal-Total	**49**	**14.4**
Clubfoot	21	6.2
Upper and lower limbs	7	2.1
Polydactyly	6	1.8
Congenital dislocation	3	0.9
Achondroplasia	2	0.6
Osteogenesis imperfecta	2	0.6
Genurecurvatum	1	0.3
Thanatophoric dysplasia	1	0.3
Congenital torticollis	1	0.3
Cardiovascular- Total	**46**	**13.5**
Congenital acyanotic	29	8.5
Congenital cynotic	17	2.2

Table III: Disorders in the Oro-facial and neck, gastrointestinal and respiratory systems

Type of defects	Frequency	Defects - per 10,000 birth
Oro-Facial & Neck-Total	**33**	**9.7**
Cleft lip & palate	26	7.6
Natal teeth	2	0.6
Cyclopia	1	0.3
Partially blindness	1	0.3
Others	3	0.9
Gastrointestinal - Total	**28**	**8.2**
Imperforated anus	10	2.93
Exomphalos	7	2.1
Biliary atresia	1	0.3
Duodenal atresia	1	0.3
Duodenal stenosis	1	0.3
Umbilical cyst	1	0.3
Others	7	2.1
Respiratory – Total	**25**	**7.3**
Pulmonary hypoplasia	8	2.3
Congenital diaphragmatic hernia	6	1.76
Choanal atresia	2	0.6
Deformities of thoracic cage	9	2.6

Table IV: Disorders in the mass and growth, integument and inborn errors of metabolism systems

Type of defects	Frequency	Defects - per 10,000 birth
Mass & Growth - Total	**11**	**3.2**
Haemangioma	3	0.9
Neurofibromatosis	2	0.6
Hygroma	1	0.3
Sacral teratoma	1	0.3
Sphenoid wing meningioma	1	0.3
Spinal cord tumor	1	0.3
Others	2	0.6
Integument - Total	**8**	**2.3**
Dimple & ear tag	4	1.2
Ectodermal dysplasia	1	0.3
Petechial rash	1	0.3
Hypopigmentation	1	0.3
Scalded skin syndrome	1	0.3
Others	2	0.6
Inborn errors of metabolism-Total	**4**	**1.2**
Biotinidase deficiency	1	0.3
Gaucher's disease	1	0.3
Methylmalonyl-CoA	1	0.3
Unspecific metabolic disorder	1	0.3

Table V: Comparisons of Proportion of birth defects in different studies

Year	Author	Place	Prevalence of birth defects	Types of study
1966	Stevenson et al 1966.	24 centers (throughout the world)	Ranges from 0.31% to 2.25% at birth[8]	WHO study
1988	Goh et al. 1988	Alor Setar	1.53% for major anomalies between livebirths[10]	Hospital study
1995	Thong, 1995	UH Kuala Lumpur	1.58% for major anomalies between livebirths and 17.5% for minor anomalies[11].	Hospital study
1954	Mc Intosh et al. 1954	USA (New York)	3.2% at birth, 7.5% at 1 year[23]	Hospital study
1983-1995	Riley et al. 1998	Australia (Victoria)	2.8%-3.66% for major anomalies[24]	Population based registry
1991	Ho et al. 1991	Singapore	2.47% among livebirths (major and minor)[25]	Hospital study
1980	Siriponya et al. 1980	Thailand	2.05% among livebirths[26]	Hospital study
1980	Irwan et al. 1980	Indonesia	1.64% at birth[27]	Hospital study
1980-1994	Eurocat 1997	Europe	2.3% at birth (236/10000 births)[28]	Population based
1980-1997	Dastgiri et al. 2002	England and Wales	2.5% at birth (382/10000 births)[29]	Population based
1998	Thalabani et al. 1998	United Arab Emirates	1.66% for major anomalies at birth[30]	Hospital study
1993	Chatuverdi et al. 1993	Maharashtra	2.72% for congenital anomaly at birth; 2.06% for major anomalies[31]	Hospital study
2000	(Present study), 2000	Malaysia (Kuala Lumpur)	3.1% for birth defects at birth	Hospital study

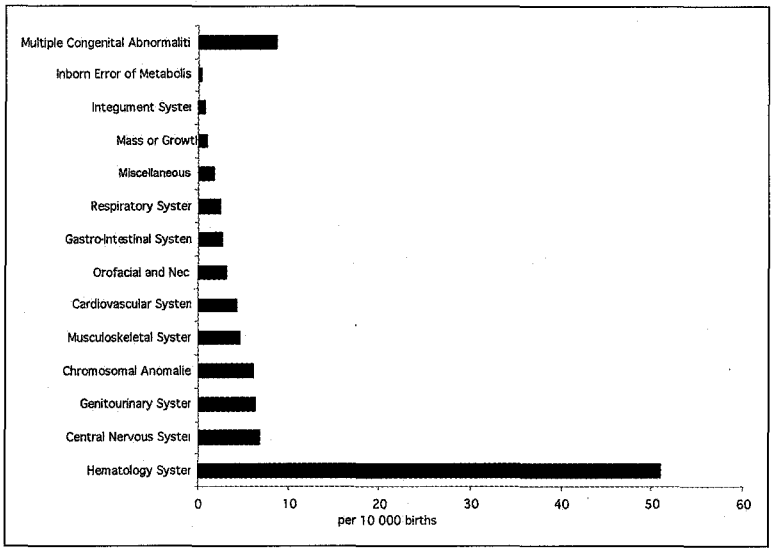

Fig. 1: Overall distribution of birth defects of children born in Hospital Kuala Lumpur

Discussion

According to the various studies that have been performed, the proportion of congenital anomaly ranges from 0.33 to 3.7%[8, 10, 11, 23-31] (Table V). Overall, the proportion of 3.1% in MHKL is higher compared to the other hospitals and population based studies (Table V).

Furthermore, in Malaysia, the incidence in MHKL is high compared to Alor Setar (1.58%)[10]. The reasons could be MHKL is a tertiary referral center with facilities and experienced specialists hence will receive more referrals for fetal abnormality. This study is quite recent and facilities for prenatal diagnosis with the availability of feto maternal experts, enables the detection rate to be higher. Moreover, Goh et al., (1988) excluded the minor congenital anomaly[10]. However, Thong et al., (1995) reported a high proportion at 20%, one of the highest recorded but the reason for this could be due to an established feto-maternal unit in University Hospital Kuala Lumpur that receives referrals from all over Malaysia[11]. In addition, the incidence in MHKL is higher than the other studies in South East Asia, compared to the one reported by Singapore (2.47)[25], Thailand (2.05%)[26] and Indonesia (1.64%)[27]. The prevalence is also higher in comparison to other studies performed in Glasgow[29] and Europe[28]. Factors that can affect the proportion are environmental factors, ethnic composition, type of study population (hospital or community based, live births or total births, singletons or multiple births, newborn with low or normal birth weight), nature of study (prospective or retrospective), criteria of definition of birth defects or congenital malformation (major, minor or both), age at diagnosis, duration of follow-up, enthusiasm and clinical skill of the investigator; whether further diagnostic investigation are carried out (e.g. ultrasound, chromosomal analysis, echocardiography) and the postmortem rate.

In this study population, males were more significantly ($p<0.001$) affected, consistent with the findings by other studies[10, 11]. The proportion of males was higher in most communities and this also includes the Malaysian community[3, 11]. Moreover, males were more prone to X-linked disorders such as G6PD Deficiency in this series, which was the highest among the different types of birth defects. The proportion of birth defects was higher in the Chinese as compared to Malays and Indians ($p<0.01$). These results were consistent with the study by Thong et al., (1995)[11]. This was due to the high prevalence of G6PD in Chinese.

The hematology system was most frequently affected in this series (Fig: 1) and this is not reflected in the other studies. The reason is the genetic predisposition of Malaysians to G6PD defects and thalassaemia. Moreover there is a national screening program for all babies at birth for G6PD deficiency as this is one of the leading causes of Kernicterus in newborn period[32].

NTD is second commonest at 19.1 per 10,000. The proportion is higher than Europe (9.6/10,000)[28] but lower in the U.K (24.1/10,000)[29]. The reason for the high prevalence is largely unexplained as the aetiology is multifactorial.

The proportion of Down syndrome is the third commonest at 12.6/10,000 births, which is comparable to the UK where the prevalence is 14/10,000[29]. In Europe, the prevalence ranges from 5.6 to 21.3/10,000[33]. Here, there is likely to be an increasing rate associated with increasing maternal age as women put off child bearing for their careers. Thalassaemia is the fourth commonest at 8.8/10000 deliveries. The high incidence is due to the genetic predisposition of both the Malays and Chinese to this condition. Moreover it is one of the commonest genetic diseases in South East Asia. Cleft lip and palate (7.6/10,000) is the fifth commonest but the prevalence is less than the UK (14/10,000)[29]. The reason for the high prevalence is also unexplained as the cause is multifactorial and there is geographical variation. The EUROCAT working group reported associated geographical variation with a high prevalence in certain areas in Netherlands and Denmark[33].

Specific strategies have to be considered to prevent or reduce these defects. Thong et al., (1995) reported that 33.6% of major birth defects are potentially preventable[11]. Czeizel (1993) however, suggested that although 52% of birth defects are preventable, no single strategy could be undertaken, as all the birth defects are not a single pathological category[34].

The high incidence of Down syndrome and neural tube defects for example make pre pregnancy counseling invaluable. The role of prenatal diagnosis in the management of these diseases however has to be evaluated in the context of the country where termination of pregnancy is illegal. There is a need to take into account cultural and religious sensitivities. However, maternal age and the risk of Down syndrome make patient education on awareness of its age association all the more important.

Other strategies include the role of folic acid, which has been shown to reduce the risk of NTD[35, 36]. Moreover the addition of multivitamins has been shown to reduce cleft lip[17], urinary tract and cardiovascular defect[15] and may be beneficial in vascular disease[16]. Further population-based study on the prevalence of NTD should be carried out to determine the overall prevalence and the need for food fortification with folic acid if necessary.

The high proportion of G6PD and thalassaemia makes genetic counseling imperative. The screening of thalassaemia takes place only in patients with family history unlike the national screening for G6PD. The incidence is expected to be higher as the presentation is much later after the fetal haemoglobin has been replaced by adult haemoglobin. There is a need to ascertain whether a national screening programme is cost effective and should be implemented and further prospective population based studies are needed in this direction.

Limitations of this study include incomplete hospital data and missing records. Autopsy is not compulsory in stillbirths and neonatal deaths and the parent's consent is necessary. The actual proportion of birth defects at birth is always underestimated as most internally situated organ such as cardiac and urinary anomalies go undiagnosed at birth. McIntosh et al., (1954) has shown that only 43% of congenital malformations were diagnosed at birth; the rest were detected during the one-year follow up[23]. Van Regemorter et al., (1984) had recorded an increase in the proportion of congenital defects from 43% at birth to 82% at the age of 6 months[37].

A population-based study should be conducted prospectively over a longer period, in order to determine the proportion more accurately. Further research is needed to identify the underlying aetiology of the birth defects. This could help in the planning of specific strategies to reduce the incidence. Birth defects registries should be established to provide a way to track trends in the occurrence of malformations in Malaysia. In addition, registries can be used for health planning, for needs assessments, and follow-up studies of their associated long-term effects.

Conclusion

The proportion of birth defects in HKL is high. The system frequently involved is the haematology system followed by the central nervous system and the genitourinary system. The highest proportion of defect is the G6PD followed by NTD, Down syndrome, thalassaemia and cleft lip and palate. There is a need to establish a birth defect registry in Malaysia to help plan a comprehensive strategy, which includes public education, pre-pregnancy counseling, genetic counseling and prenatal diagnostic centers in an effort to reduce the incidence of birth defects in this country.

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References

1. World Health Organization. World Health Report, 1998. Geneva: WHO, 1998; 43-47.
2. ASEAN Perinatal Health Issues. Proceedings of the ASEAN Paediatric Federation Workshop on perinatal morbidity and mortality, Kuala Lumpur. 1983; 5-15.
3. Malaysia Vital Statistics, Peninsular Malaysia, Department of Statistics, Malaysia, Kuala Lumpur September 1999.
4. Annual Report Hospital Kuala Lumpur 1996.
5. Annual Report Hospital Kuala Lumpur 1997.
6. Annual Report Hospital Kuala Lumpur 2000.
7. Annual Report Hospital Kuala Lumpur 2001.
8. Stevenson AC, Johnson HA, Stewart MIP, Golding DR. Congenital Malformations. A report of a study of series of consecutive births in 24 centres. Bull World Health Organisation 1966; 34: suppl.
9. Sengupta S, Sinnathuray TA. Role of congenital abnormalities in perinatal and infant mortality. Malaysia-Singapore Congress of Medicine, Kuala Lumpur, Proceedings 1974; 9: 284-91.
10. Goh PP, Yeo TC. Major congenital anomalies in live births in Alor Setar General Hospital during a three-year period. Med. J. Malaysia 1988; 43(2): 138-49.
11. Thong MK. The Epidemiology of Birth Defects in Malaysian Livebirths in Hospital University. Dissertation submitted to the University of Malaya, in partial fulfillment for the degree of Master of Medicine (Paediatrics). (1995).
12. Nurkhatijah N, Jacqueline H, Thong MK. Feasability of a birth defect registry. Abstract from the Proceedings of the 13th Congress of the Federation of Asia and Oceania Perinatal Societies FAOPS 2004; pp 12.
13. Chuah MK, Collen D, Vandendriessche T. Preclinical and clinical gene therapy for haemophilia. Haemophilia. 2004 Oct; 10 Suppl 4: 119-25.
14. Czeizel AE. Ten years of experience in periconceptional care. European Journal of Obsterics & Gynaecology and Reproductive Biology 1999; 84: 43-49.
15. Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. Am. J. of Med. Gen 1996; 62(2): 179-83.
16. Roger ES, William PA, G. Shashidhar P et. al., Decline in Prevalence of Neural Tube Defects in a High-Risk Region of the United States. Pediatrics. 2000; 106(4): 677-83.
17. Shaw GM, Wasserman CR, O'Malley CD et. al. Risk of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. Lancet 1995; 346 (8972): 393-96.
18. Annual Report Hospital Kuala Lumpur 1992.
19. Annual Report Hospital Kuala Lumpur 1993.
20. Annual Report Hospital Kuala Lumpur 2003.
21. World Health Organization. Human genetics and non-communicable diseases, 1999. Facts sheet No 209.
22. International Classifications of Diseases 10th Revision. Geneva WHO 1992; 2.
23. McIntosh R, Merritt KK, Richards MK, Samuels MH, Bellows MT. The incidence of congenital malformations: A study of 5964 pregnancies. Pediatric 1954; 14: 505-22.
24. Riley MM, Halliday JL, Lumley JM. Congenital malformations in Victoria, Australia 1983-95: An overview of infant characteristics. J Paediatr Child Health. 1998; 34(3): 233-40.

25. Ho NK. Congenital malformation in Tao Payoh Hospital-An 18-year experience (1972-1989). Annals Academy of Medicine 1991; 20(2): 183-89.

26. Siriponya P, Tevavej A. Congenital malformation in early neonatal period. Ten years incidence at Ramathibody Hospital. J. Med A. Thailand 1980; 63(10): 544-47.

27. Irwan, Surjono A, Iman S, Ismangoen. The incidence of congenital malformation in the Gadjah Mada University Hospital, Yogyakarta During 1974-1979. Peadiatrica Indonesiana 1983; 23: 25-31.

28. EUROCAT Working Group. Eurocat Report 7. Scientific Institute of Public Health-Louise Pasteur, Brussels, 1997.

29. Dastgiri S, Stone DH, Le-Ha C, Gilmour WH. Prevalence and secular trend of congenital anomalies in Glasgow, United Kingdom. Arch Dis Child 2002; 86: 257.

30. Thalabani JAL, Shubbar AI, Mustafa KE. Major congenital malformations in United Arab Emirates (UAE): need for genetic counseling. Ann. Hum. Genet 1998; 62: 411–18.

31. Chaturvedi P, Banerjee KS. An epidemiological study of congenital malformations in Newborn. Indian J Pediatr 1993; 60: 645-53.

32. Tang TH, Balakrishnan S, Zamri A. Hyperbilirubinaemia and erythrocytic G6PD deficiency in Malaysian children. Med J. Malaysia 1989; 44: 30-34.

33. Stoll C, Ayme S, Beckers R. Distribution of single organ malformations in European populations. EUROCAT Working Group. Ann. Hum. Genet 1995; 38(1): 32-43.

34. Czeizel AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. Br Med J 1993; 306: 1645-648.

35. Czeizel AE, Dudas I. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. N Engl J Med 1992; 32: 1832-835.

36. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991; 338(8760): 131-37.

37. Van Regemorter N, Dodian J, Druart C. Congenital malformation in 10,000 consecutive births in a University Hospital; need for genetic counseling and prenatal diagnosis. J Pediatr. 1984; 104 (3): 386-90.