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Major Birth Defects: Prevalence, Risk Facrors and Outcome

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Abstract

Major birth defects represent a future challenge to both neonatologists and obstetricians as for prevention, diagnosis and management. We analyzed data from all livebirth infants born with major birth defects at King Fahd Hofuf Hospital, AL Hasa, Saudia Arabia, during the period from 1411 to 1413 H. Our objectives were to determine: prevalence rate, patterns, geographic differences, associated maternal and infant risk factors, and the contribution of birth defects to mortality in our Newborn Unit. Out of 30,159 infants born alive during the study period, 687 (2.27%) had one or more major birth defects. Systems most commonly affected were the cardiac (20.8%), musculoskeletal (18.7%) and central nervous (18.3%) systems. We observed higher rates/1000 livebirths of life-threatening CNS and cardiac defects and diaphragmatic hernia in our infants than rates reported from other countries. Rate of birth defects/1000 livebirths increased from 0.79% in the birth-weight group = > 4000 g to 15.2% in the birth weight category < 1500 g. Mothers of infants with birth defects were compared with a control group of 1500 mothers for age, parity, history of previous abortion, and maternal disease. Diabetic mothers and those of infants with chromosomal anomalies had higher means of age and parity than the control mothers: 33.5 years (5.2), 31.4 years (7.5), and 8.8 (3.8), 7.39 (3.8), for age and parity of diabetic and chromosomal anomalies respectively vs. 26.8 years (6.4) and 5.2 (3.7) in the controls, ($p < 0.01$). 66 infants with birth defects were infants of diabetic mothers, and diabetes was the only identified disease associated with major birth defects (9.6% and 3.8% of mothers in the study and control groups respectively were diabetics, ($p < 0.05$). Out of the 687 infants with birth defects, 254 (36.97%) died; and birth defects were the commonest disease-specific cause of death in our Newborn Unit throughout the 3 years of the study.

Introduction

THE impact of major or serious birth defects on the fetus and newborn infant is great as they are now the leading cause of perinatal death both in developed [1] and developing [2] countries including Saudia Arabia [3]. One basic approach toward understanding the nature of the problem in an infant with congenital defect is to identify the possible risk factors. Therefore, studies that provide epidemiological data relevant to birth defects are needed. These data may have important implications for prevention, clinical care and etiologic research.

In this study, we present data on the prevalence and pattern of major birth defects at King Fahd Hofuf Hospital (K. F. H. H.), Al Hasa region, Kingdom of Saudia Arabia, between 1411 H and 1413 H.

Data were also analyzed to determine any infant or maternal factors associated with the defects, to study geographic differences, to evaluate the contribution of birth defects to mortality in our Neonatal Intensive Care Unit (NICU), and to describe other related findings.

Subjects and Methods

King Fahd Hofuf Hospital is one of the big referal hospitals in Saudia Arabia, with more than 9000 deliveries annually, approximately 10% of them are admitted to the NICU (table 1). In these three year retrospctive study, we analyzed data from all live-born infants with major birth defects admitted to this hospital during the period from 1411 H to 1413 H.

Major birth defects were defined as those affecting the infant's survival or cause serious structural, cosmetic and/or functional handicap that require substantial surgical or medical care. The sources of the study were the infant and maternal medical files, and the records of the NICU and the obstetric department. The available data collected included: identification, demographic, clinical and diagnostic information on the infants as well as information on the mother's prior illness and pregnancy history. The following cases were excluded from analysis: stillbirths, premature infants (< 37 weeks) with defects secondary to prematurity (patent ductus arteriosus, foramen ovale, undescended testicles and hydrocephalus following intravenricular hemorrahge), and infants with acquired hydrocephalus e.g. associated with ventriculitis.

Risk factors: Infants' conditions that were correlated with birth defects included: sex, birth weight and gestational age. To determine the relationship between defects and birth weight, infants were divided into five weight groups (<1500 g, 1500 g to 1999 g, 2000 g to 24900 g, 2500 g to 3999 g, and = > 4000 g), and we determined the weight-specific birth defect rates by dividing the number of infants with defects, in each weight group,

by the total number of live births with the same weight group born during the study period. In addition, we calculated the rate ratios by dividing the rate of defects for infants in each weight category by that of infants weighing 2500 g to 3999 g.

We also compared the rate of specific birth defects/1000 Livebirths in our place with that reported by two similar studies from Libya [4] and USA [5] to dtermine any geographic variation in the incidence and distribution of specific birth defects.

Maternal factors that were analyzed included age, parity, previous abortion or stillbirth and maternal disease. The medical files of 1500 mothers who gave birth to infants without birth defects during the study period were randomly selected and their data were compared with those of the study mothers.

Statistical analysis:

Statistical analysis was done with EPI-INFO version 5.01b [6]. Data were evaluated for significance with the Student's t test, Chi square, and Kruskal-Wallis test for non-homogenous variances as well as the Cornfield 95% confidence limits (CI) around the birth defect rates. $p < 0.05$ was considered statistically significant.

Results

Total deliveries and neontal admission at K. F. H. H., during the 3-year study period, are shown in table 1. Out of 30.159 liveborn infants, 687 (2.27%) had one or more major birth defects. Of these infants, 354 (51.5%) were females, 18 (2.6%) were non-Saudi, 10 (1.5%) were twins, 212 (30.9%) were preterm (< 37 weeks), and 36 (5.2%) were outborn. The yearly prevalence of birth defects was almost the same during the 3 years. The anatomical distribution of birth defects is shown in Fig. 1. the commonest system affected was the cardiac (20.8%) followed by the musculoskeletal (18.7%) and central nervous system (CNS) 18.3%). A total of 774 defects were detected in the 687 infants. The incidence of these specific birth defects is presented in table 2 which also shows comparison of our incidences with those reported from Libya [4] and USA [5]. In our survey, we observed a higher incidence of cardiovascular, CNS defects and diaphragmatic hernia, but lower incidence of cutaneous and musculoskeletal defects, hypospadius and congenital hip dislocation. Ventricular septal defect was the commonest noncyanotic cardiac defect while transposition of great arteries was diagnosed in 7 infants with cyanotic cardiac lesions. However, 17 infants in the latter group were refered and their specific diagnosis was not available. Hypertrophic cardiomyopathy was detected in 16 infants of diabetic mothers (IDM) who had other associated anomalies.

Hydrocephalus was the commonest CNS defect (50/140) followed by

Table (1): Deliveries at K.F.H.H., 1411 - 1413 H.

Year	Total Live Births	Males (%)	Preterm (%)	Males (%)	Stillbirths (%)	Outborn (%)
1411	9782	4976 (50.9)	840 (8.6)	4976 (50.9)	123 (1.3)	26 (0.3)
1412	10510	5427 (51.6)	927 (8.8)	5427 (51.6)	134 (1.3)	29 (0.3)
1413	9867	5137 (52.1)	987 (10.0)	5137 (52.1)	142 (1.4)	45 (0.3)
Total	30159	15540 (52)	2754 (9.2)	15540 (52)	399 (1.3)	100 (0.5)

Out of the total LBS, 3543 (11.9 %) and 9974 (33.5 %) infants were admitted to the NICU and observation area respectively.

microcephalus, encephalocele, and anencephaly. Karyotyping was the basis of diagnosis in all the cases with Edward and Patau syndromes and in 28 cases with Down's syndrome. Cases with suspected chromosomal anomalies were included in the miscelaneous group. All the 4 cases with icthyosis were of the severe type (Collodion baby). Hypospadius was of the anterior type in 10 cases, and was associated with inguinal hernia in 2 cases and cryptorchidism in other 2 cases.

Two out of the 6 cases with ambiguious genitalia were isolated and proved later to have congenital hyperplasia, the other 4 cases were associated with multiple defects. Diaphragmatic hernia was left sided in 12 cases, and bilateral in one case, it was associated with malrotation in one case and with de Lange syndrome in another case. Esophageal atresia was associated with communicating tracheoesophageal fistula in all the 8 cases, anal atresia in two cases, and with multiple defects in one case. The 4 infants with Hirschsprung disease presented with abdominal distension and vomiting, and the diagnosis was confirmed by rectal biopsy. Clubfoot was isolated in 19 cases, and was associated with spina bifida and multiple defects in 8 and 3 cases respectively. Hip dislocation was bilateral in 12 cases and was associated with arthrogryposis in 2 infants. Arthrogryposis was associated with Edward syndrome in one case but the underlying cause was not recorded in the rest of the cases. Choanal atresia was bilateral in all the 7 cases, associated with Down syndrome in one case and was present in one IDM.

There was no significant difference in the overall distribution of defects regarding sex of the infants. Specific defects that occurred with higher frequency in

Table (2): Prevalence of Major Birth Defects at K.F.H.H., 14411 - 1413 H; Comparison with Rates from Libya [4] and USA [5].

Place		K.F.H.H.		Libya		U.S.A	
Population		30, 159		32.332		317, 499	
Overall Prevalence		2.27 %		2.38%		3.6 %	
Defect	No. of cases	% of defect	Rate/ 1000 LBS,%	% of defect	Rate/ 1000 LBS,%	% of defect	Rate/ 1000 LBS,%
Caradiovascular :	161	20.8	8.7	12.05	3.15	-----	-----
Acyanotic	107	13.8	3.6	8.61	2.23	-----	-----
VSD	40	5.16	1.3	4.76	1.24	6.09	2.18
Cardiomyopathy	16	2.06	0.5	----	----	-----	-----
Cushion defect	9	1.16	0.3	----	----	0.94	0.34
ASD	10	1.29	0.3	----	----	-----	-----
Situs inversus	3	0.30	0.1	----	----	-----	-----
Cyanotic:	54	6.97	1.8	3.58	0.93	-----	-----
TGA	7	0.90	0.2	1.19	0.31	1.29	0.46
TOF	4	0.51	0.1	----	-----	0.96	0.35
Dextrocardia	4	0.51	0.1	----	----	-----	-----
C.N.S. :	142	18.3	4.8	5.26	1.36	-----	-----
Hydrocephalus	38	4.9	1.3	1.43	0.37	2.07	0.74
Mengingo / hydrocephalus	12	1.51	0.4	-----	-----	-----	-----
Microcephalus	38	4.90	1.3	0.72	0.18	1.64	0.58
Encephalocele	19	2.45	0.6	0.24	0.06	0.49	0.17
Anencephaly	18	2.32	0.6	1.67	0.43	0.55	0.19
Meningomyelocele	12	1.55	0.4	1.19	0.31	-----	-----
Chromosomal:	64	8.26	2.1	10.52	2.72	----	-----
Down	54	6.97	1.8	6.67	1.73	2.63	0.94
Edward	8	1.03	0.3	1.43	0.37	-----	-----
Patau	2	0.25	0.1	1.43	0.37	-----	-----
Cutaneous:	15	1.93	0.5	10.05	2.59	-----	-----
Icthyosis	4	0.51	0.1	0.96	0.25	-----	-----
Epidermolysis bulosa	3	0.38	0.1	-----	-----	-----	-----

Table (2): Cont.

Ear :	10	1.29	0.3	1.19	0.31	-----	-----
Absent ear	7	0.90	0.2	0.59	0.15	-----	-----
Malformed ear	3	0.38	0.1	0.59	0.15	-----	-----
Eye :	25	3.22	0.9	2.63	0.68	-----	-----
Glaucoma	7	0.90	0.2	0.00	0.00	-----	-----
Microphthalmos	5	0.64	0.1	0.24	0.06	-----	-----
Cataract	5	0.64	0.1	0.96	0.12	0.65	0.23
Corneal opacity	4	0.51	0.1	1.43	0.37	-----	-----
Urogenital tract:	58	7.49	1.9	9.57	2.47	-----	-----
Hypospadius	22	2.84	0.7	5.98	1.54	8.06	2.89
Cystic kidney	10	1.29	0.3	-----	-----	0.84	0.30
Prune belly	7	0.90	0.2	-----	-----	-----	-----
Ambiguous genitalia	6	0.77	0.2	-----	-----	-----	-----
Hydronephrosis	5	0.64	0.2	-----	-----	-----	-----
Renal agenesis	2	0.25	0.1	-----	-----	0.76	0.27
PUV	2	0.25	0.1	0.24	0.06	-----	-----
Gastrointestinal :	118	15.2	3.9	10.28	2.66	-----	-----
Cleft lip / palate	24	3.10	0.8	1.91	0.50	2.72	0.97
Cleft palate	9	1.61	0.3	-----	-----	1.35	0.48
Cleft lip	5	0.64	0.2	-----	-----	-----	-----
Diaph. hernia	13	1.67	0.4	0.72	0.18	0.56	0.20
Esoph. atresia	8	1.03	0.2	0.72	0.18	0.61	0.22
Intest. obstruction	23	2.97	0.8	-----	-----	-----	-----
Malrotation	4	0.51	0.1	-----	-----	-----	-----
Ileal atresia	4	0.51	0.1	-----	-----	-----	-----
Duodenal atresia	2	0.25	0.1	-----	-----	-----	-----
Jujenal atresia	2	0.25	0.1	-----	-----	-----	-----
Unknown	11	1.42	0.3	-----	-----	-----	-----
Omphalocele	8	1.03	0.3	0.48	0.12	0.64	0.23
Anal abnormalities	8	1.03	0.3	1.43	0.37	0.97	0.35
Hirschsprung	4	0.51	0.1	0.24	0.06	0.45	0.16
Gastroschisis	4	0.51	0.1	-----	-----	-----	----

Table (2): Cont.

Musculoskeletal :	145	18.7	4.8	34.45	8.91	-----	-----
Club feet	30	3.87	1.0	14.83	3.83	7.52	2.70
Polydactyly	33	4.26	1.1	5.98	1.54	6.42	2.30
Syndactyly	12	1.55	0.3	0.48	0.12	-----	-----
Polysyndactyly	3	0.39	0.1	-----	-----	-----	-----
Absent digits	15	1.93	0.5	-----	-----	-----	-----
Phocomelia	5	0.64	0.2	-----	-----	-----	-----
Hip dislocation	13	1.67	0.4	9.33	2.41	1.75	0.62
Achondroplasia	11	1.42	0.3	0.96	0.25	-----	-----
Arthrogryposis	8	1.03	0.2	-----	-----	-----	-----
Genurecurvatum	4	0.51	0.1	-----	-----	-----	-----
Osteogenesis imperfecta	3	0.39	0.1	0.48	0.12	-----	-----
Respiratory :	18	2.32	0.6	1.67	0.43	----	----
Choanal atresia	7	0.90	0.2	0.96	0.25	0.29	0.11
Pulmonary hypolasia	3	0.38	0.1	0.48	0.12	-----	-----
Diaph. laryngomalacia	3	0.38	0.1	-----	-----	-----	-----
Laryngomalacia	2	0.25	0.1	0.24	0.06	-----	-----
Miscelaneous :	18	2.32	0.6	2.15	0.62	-----	-----

males included: cystic kidneys (10/10), pulmonary hypoplasia (3/3) Treacher Collins syndrome (2/2) and clubfoot (21/30). Female preponderance was noted in osteogenesis imperfecta (3/3), epidermolysis bullosa (3/3), Patau syndrome (2/2), glaucoma (6/7) absent ears (6,7), and ichthyosis (3/4).

Table 3 shows the rates of major birth defects in different birth weight categories and Fig. 2 summarizes these rates. The rate of defects / 1000 LBs increased from 0.79% in the weight group = >4000 g to 15.2% in the weight group < 1500 g. The incidence of the following defects was higher in the low birth weight (< 2500 g) group than in the weight category > 2500 g: Patau (2/2), anophthalmia (2/2), phocomelia (5/5), Edward's (6/8), icthyosis (3/4), absent ears (5/7), omphalocele (5/8), esophageal atresia (5/8), arthrogryposis (6/8), achondroplasia (6/11), cyanotic heart defects (30/54), Down's (28/54), microphthalmia (3/5), and intestinal obstruction (15/24). However, defects that were observed to occur more frequently in the weight category 2500 g- 3999 g included: cushion defect (9/9), VSD (33/40), polydactyly (27/33), hydrocephalus with/without meningocele (39/50), cleft lip/

palate (21/24), and hip dislocation (10/13). Hypertrophic cardiomyopathy was the only defect that occurred with higher incidence in the weight group = > 4000 (12/16). The exact gestational age was recorded only for premature (< 37 weeks) infants (212 infants, 30.9%). Further data on gestational age have not been collected consistently among livebirths and infants admitted to the observation area therefore, we could not determine rates of birth defects according to gestational age. However, the number of infants with birth defects in the gestational age groups < 31 wk, 31-33 wk, 34-36 wk were 49, 129 infants respectively. There were only 4 infants recorded as postmature.

The means of mothers' age in the study and control groups were 27.2 years (SD 6.9) and 26.8 years (SD 6.4) respectively (p = > 0.05). Likewise, there was no significant difference in mothers' age between the 2 groups when mothers were divided into age categories. On the other hand, the mean age of diabetic mothers in the study group was significantly higher than that in the diabetics of control group (33.5 years (SD 5.2) vs 30.7 (SD 5.9), (p = > 0.010). The mean age of the mothers of infants with chromosomal anomalies was also higher than that of the controls (31.4 years (SD 7.5) vs 26.8 years (SD 6.4), (p = > 0.01). We found no statistically significant difference as for parity and history of previous abortion between mothers in the study group and their controls (mean (SD): 5.3 (3.7) vs (5.2 (3.7), (p = > 0.56; 0.59 (1.1) vs 0.49 (1.0), (p = > 0.27, for parity and previous abortion in the study and control groups respectively). The same insignificant differences were found when mothers in both groups were divided into groups according to number of parity and previous abortion. However, when diabetic mothers in both groups were compared, there was a

Table (3): Rates of Major Birth Defects by Birth Weight, K.F.H.H, 1411 - 1413 H.

Weight, g	No. of infants with birth defects	No. of Live Births	Rate of birth defects / 1000 Live Births, %	Rate Ratio (95% Confidence interval)
< 1500	51	335	15.2	8.00 (5.80, 11.02)
1500 - 1999	76	684	11.1	5.84(4.49, 7.59)
2000 - 2499	88	1437	6.12	3.22 (2.53, 4.10)
2500 - 3999	433	22763	1.90	1.0 (reference)
= > 4000	39	4940	0.79	0.84 (0.74, 0.94)

substantial difference as for parity but not for previous abortion (mean (SD): 8.8 (3.8) vs 7.3 (3.7), (p = 0.035; 1.1 (1.5) vs 0.85 (1.5) s 0.85 (1.5), p= 0.51, for parity and previous abortion in the diabetics of the study and control groups respectively). Means of parity and number of previous abortion in mothers of infants with chromosomal abnormality were significantly higher than in the control group (7.39 (3.8) and 0.78 (1.1) for parity and previous abortion respectively, ($\bar{p}$ = > 0.01 for both).

As shown in Fig. 3, the percentage of the control group was higher than that in the study group (17.7% vs 13.5%, (p = > 0.001). This was mainly due to higher number of sickler and hypertensive mothers in the control group. However, the percentage of diabetics in the study group was significantly higher than that in the controls (9.6% vs 3.8%, (p = > 0.05). It was not recorded consistently whether diabetes was pre-existing or gestational or was insulin dependednt or not in both groups. The most frequently found defects among IDMs (66 infants) were: hypertrophic cardiomyopathy associated with other defects (12), polydactyly (7), VSD (6), other acyanotic heart defects (4), cyanotic heart diseases (4), encephalocele (3), microcephalus (3), hydrocephalus with meningocele (4), hydrocephalus (2), and meningocele (2).

As shown in table 4, 254 (36.97%) infants in our series died. However, 17 and 8 infants with severe cyanotic heart and renal anomalies respectively were transfered to other centers and their outcome was not recorded. The highest mortality rate was in the group of micellaneous defects (83.3%), followed by the cyanotic heart defects (56.8%), CNS defects (51.4%) and respiratory system anomalies (50%). (table 4). Defects with 100% mortality included; anencephaly, intestinal obstruction of undetermined etiology, malrotation, duodenal atresia,

Table (4): Mortality Rate of Birth Defects According to System Affected.

	AHD	CHD	Chrom	CNS	Skin	Ear	Eye	GIT	Misc	Mskel	UG	Resp	Total
Total number	86	51	64	136	15	10	20	99	18	122	54	12	687
Number died	17	29	24	70	4	1	3	38	15	27	20	6	254
Percent	19.8	56.8	37.5	51	26.7	10	15	38.4	83.3	22.1	37	50	36.9

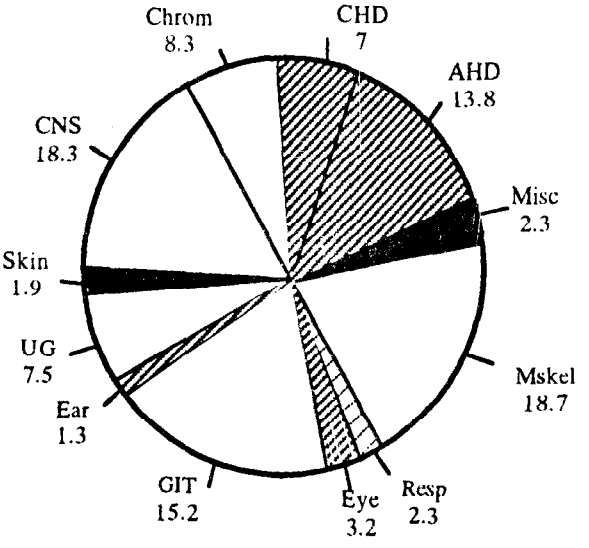

Fig. (1): Overall incidence of major birth defects, K. F. H. H>, 1411-1413.

AHD = acyanotic heart disease; CHD = cyanotic heart disease; Chrom = chromosomal
CNS = central nervous system; GIT = gastrointestinal; UG = urogenital;
Mics = miscellaneous; mskel = musuloskeletal; resp = respirtory.

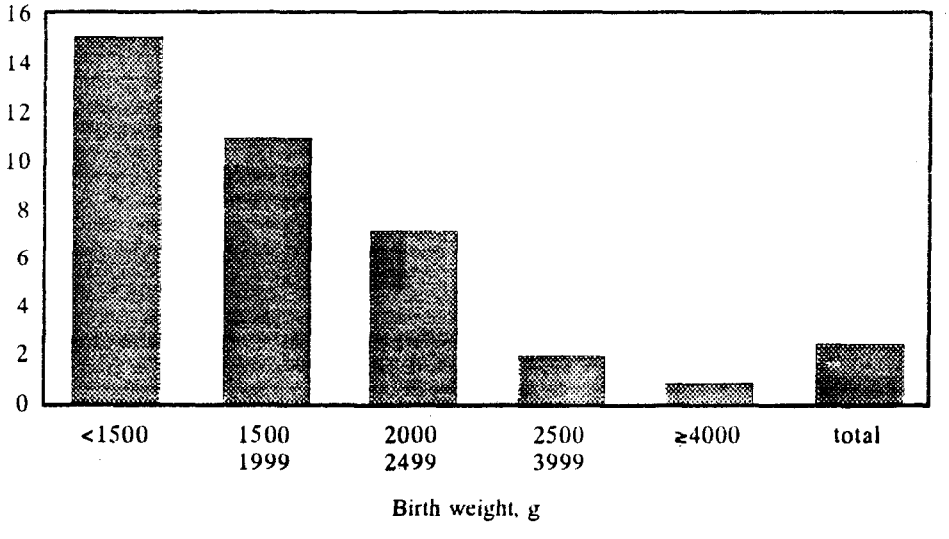

Fig. (2): Rates of major birth defects by birth weight, K. F. H. H, 1411-1431. Lines at tops of bars represent the 95% confidence interval around the rate.

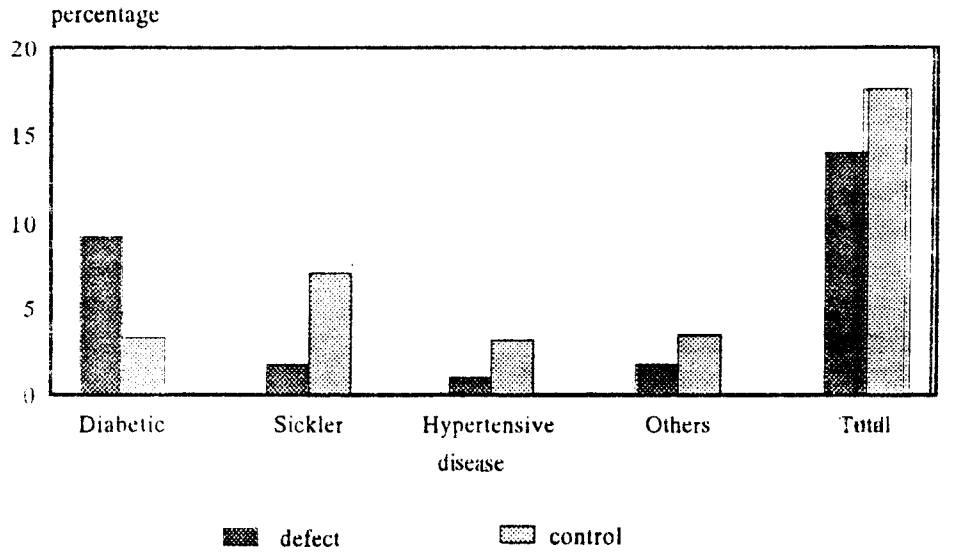

Fig. (3): Comparison of maternal diseases between study and controls.

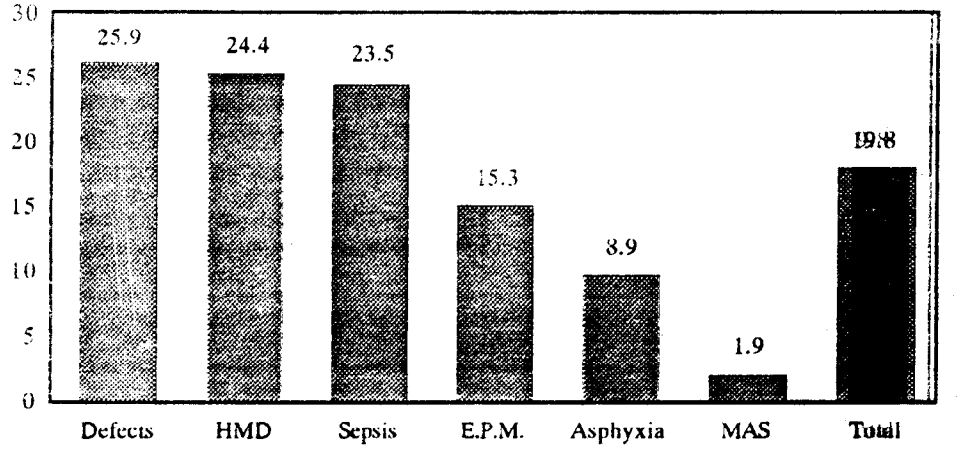

Fig. (4); Cause specific mortality rate, NICU, K. F. H. H, 1411-1413.
Defects = major birthdefects, HMD = hyaline membrane disease, EPM = extreme prematurity (<1000 g), MAS = meconium aspirationn syndrome.

gastroschisis, TGA, pulmonary hypoplasia, Edward and Patau syndoromes, renal agenesis, Arnold Chirari malformation, prune belly, and osteogenesis imperfecta. Birth weight appeared to be a determining factor in increasing mortality. The percentages of infants who died for the weight group < 1500 g, 1500-1999 g, 2000-2499 g, 2500-3999 g, and = > 4000 g were 80.4%, 50.0% 48.9%, 25.4%, and 30.8% respectively. Likewise, and percentages of infants who deceased in the gestational age categories <30 wk, 31-34 wk,a nd 34-36 wk were 79.6%, 47.1% and 44.2% respectively. 17 (27.3%) of the IDMs died, out of these, 6 with CNS defects, and 6 with heart defects.

Major birth defects represented the commonest cause of death in the NICU of K. F. H. H. during the study period (25.9%), followed by hyaline membrane disease (24.4%), and sepsis (23.5%) (Fig. 4). This contribution of birth defects to mortality remained unchanged throughout the 3 years of the study.

Finally, the mean duration of NICU stay for all infants with birth defects was 12.44 days (SD 18.61), the longest duration was for IDMs with cardiomyopathy (36.2 days, SD 20.68), and infants with intestinal obstruction (36.11 days, SD 20.4), followed by hydrocephalic infants (31.25 days, SD 24.65).

Discussion

As the problems of prematurity and intrauterine growth retardation are becoming less serious by advances made in perinatology, major birth defects will become the future challenge to the pediatricians and obstetricians as for diagnosis, management and prevention. The first step in defeating this challenge is to define the magnitude and nature of the problem in the locality. In the present study, only major and easily identified birth defects were included, the information was ascertained from different sources, and a big number of the infants born during the study period were admitted to the NICU and observation area, and examined thoroughly. We believe, therefore, that there is a complete identification of the cases with major defects presenting at birth.

The incidence rate (2.27%) of major birth defects found in this study is relatively high considering that stillbirths, known to have higher frequency of serious defects, were not included and that only defects manifesting at birth were studied. The rate of recognized major birth defects doubles at one year of age with the inclusion of defects that may not be evident in the neonatal period such as those involving the heart, kidneys or hrain [7]. We ohserved a higher incidence of serious or life-threatening malformations, in our place such as cardiovascular, CNS, diaphragmatic hernia and intestinal obstruction than that reported for Libya and USA (table 2). In addition, Wiswell and collegues [8] in their 17-year

retrospective survey on an American popluaiton of both livebirth and stillbirth infants found incidence rates of 0.36, 0.15, 0.48 and 0.69/1000 infants for anencephaly, encephalocele, hydrocephalus, and spina bifida respectively. These investigators and some others [18-19] have also observed a declining incidence of these neural tube defects. In the present survey, that excluded stillbirths, we found approximately double these rates for all the four defects (table 2) and there was no change in their incidences in the 3 years of the study. An important management implication, based on the high prevalence and death rates of serious heart defects found in this study, is the urgent need for cardiac surgery facilities in Al Hasa region.

On the other hand, the lower incidence of some other defects such as congenital hip dislocation and coarctation of the aorta in our study may be due to geographic differences, underdiagnosis, or due to detection bias as an inherent limitation of a retrospective study. However, we undertook a one-month pilot study as a part of The Saudi Arabian Registry for Congenital Anomalies (SARCA) study, and out of the 757 infants born in that month and screened carefully for birth defects no single case of hip dislocation or coarctation was identified. Therefore, the possibility of detection bias in our study, although it can not be excluded completely for asymptomatic defects such as hip dislocation, is unlikely for severe and obvious defects such as cardiovascular and CNS anomalies.

We found no significant sex ratio in the majority of our infants with birth defects and, with the exception of clubfoot, all other defects that showed sex difference were small in number. Sex differences among infants with certain birth defects have been found by some investigators such as female preponderance in neural tube defects [8], chromosomal abnormalities and hip dislocation [4]. This is in contrast to our finding and the findings of other investigators [9].

The high frequency of birth defects among LBW infants (<2500 g) was reported before by several investigators [10-11]. Our data are consistent with this finding. We have also shown that the rate of birth defects increases greatly with decreased birth weight, where approximately 15% of infants weighing less than 1500 g at birth had major birth defects compared with 1.9% of infants weighing 2500-3999 g at birth. This finding has previously been shown by Mili and coworkers [5] in a similar retrospective study from USA.

In addition, population-based studies conducted in the United Kingdom [12-13] have found that 10% to 20% of stillbirth and livebirth infants weighing less than 200/ g at birth had birth defects. In the present study, 7.7% (212/2754), and 12.5% (127/1019) of premature and

livebirth infants weighing < 2000 g respectively had major birth defects (tables 1 and 3). Two mechanisms have been postulated to explain the association between LBW and birth defects: (1) birth defects can predispose infants to LBW if they lead to intrauterine growth retardation (IUGR), preterm delivery or both and (2) LBW and birth defects may coexist because of common underlying factors [5, 14].

Our finding of the association between LBW and birth defects support the recommendations of Mili and associates [5] to target medical records of LBW infants in order to improve the overall ascertainment of birth defects in the population and that prevention strategies should include the complex etiology of LBW and prevent risk factors that infleunce the occurrence of birth defects.

Older maternal age (>35 years), grand multiparity (> 4 pregnancies) and previous pregnancy loss have been described to be associated with adverse pregnancy and neonatal outcome including higher frequency of some birth defects [4, 15-17]. Further, changing maternal age and decreased parity are among the factors that led to the recent decline in the incidence of neural tube defects in different areas of the world [18,19]. However, with the exception of diabetic mothers and mothers of infants with chromosomal abnormalities,we found no significant differences in mothers' age, parity, and history of previous abortion between the study and control mothers. This may be explained be the heterogeneous etiology of birth defects, small sample size of both groups, and/or the relatively high mean overall parity rate in the general population of Hofuf (means of parity were 5.3 and 5.2 for the study and control mothers respectively). It is known that the risk of trisomy 21 due to meiotic nondisjunction increases sharply with maternal age [20]. On the other hand, our finding of increased age of diabetic mothers in the study group might be related to prolonged duration of diabetes and consequent increased frequency of birth defects among their infants. However, neonatal morbidity indices among IDMs are still related to the severity of maternal diabetes rather than to other factors such as maternal age or obesity [21].

Inspite of the dramatic fall of the stillbirth rate and overall perinatal mortality in IDMs over the past 4 decades, the incidence of congenital defects is virtually unchanged [22]. Nowadays, these malformations account for approximately 50% of the total mortality rate for IDMs [23, 24]. In the present study, diabetes mellitus was the only maternal disease identified to be associated with birth defects inspite of the high percentage of maternal diseases in both the study and control groups (fig. 3). The most common birth defects reported among IDMs are sacral

agenesis, neural tube defects, and congenital heart defect [24]. The latter defects were the commonest in our IDMs, and hypertrophic cardiomyopathy was the commonest specific defect recorded (18.2%), althouh it was associated with other defects such as polydactyly, clubfoot, and meningomyelocele. This condition is considered unique to macrosomic IDMs, and it occurs in approximately one third of cases. It is thought to be a manifestation of septal hypertrophy as a consequence of fetal hyperinsulinism [24]. Although only one case with this condition died because of heart failure, yet it was the commonest cause of prolonged hospitalization among all other defects. Well designed prospective studies are needed in AL Hasa region to ascertain the incidence of birth defects in IDMs and to examine the relationship between birth defects and risk factors in diabetic mothers such as metabolic control and the presence of microvascular diseases.

Major birth defects occupied the first place among all causes of neonatal mortality in the NICU of K. F. H. H. during the 3 years of the study. The factors that may have contributed to this high mortality in our infants with birth defects included: low birth weight and prematurity, the high rate of sepsis in our NICU during the study period, the seriousness of the defects themselves, and / or combination of all. Mortality data from USA [25] indicate that the contribution of birth defects to infant mortality is relatively high among LBW (< 2500 g) infants. The proportional mortality due to birth defects was 30% to 50% among those weighing 1500 g to 2499 g, compared with 20% to 30% among those weighing 2500 g or more. We have similar data for LBW and preterm infants. On the other hand, 57 (22.4%) out of the 254 infants who died had sepsis, but it was not recorded whether or not sepsis was responsible for their death. We have shown that serious or life-threatening birth defects were frequent in our infants than in infants from Libya and USA (table 2); and our mortality rate was approximately five times that reported from Libya (7.5%). Further, in areas where sepsis rate is lower, and the problems of prematurity and IUGR were defeated, birth defects are now the commonest cause of infant mortality [1-3]. We, therefore, believe that although sepsis and LBW were adding factors yet the seriousness of birth defects was the primary factor behind our excess mortality due to birth defects. Further, with the use of surfactant and control of sepsis that started this year in K. F. H. H., it is expected that mortality due to hyaline membrane disease and sepsis will be lower while that caused by major birth defects will remain unchanged. Every effort, therefore, should be made to prevent the high incidence of serious birth defects among infants of Al Hasa region, and to reduce the excess mortality caused by these defects. This should

include: improving clinical care, intense etiologic research, and health education of the community.

In summary, there is a high rate of serious birth defects in Hofuf area, and this has contributed significantly to excess mortality among newborn infants at K. F. H. H. Special attention should be made to identify and prevent underlying risk factors such as teratogens, and to manage curable defects such as heart anomalies, in order to reduce the excessively high mortality rate in this community. The rate of birth defects increases in the low-birth-weight infants, and birth defects prevention strategies should include better identification of the complex etiology of low birth weight. Maternal diabetes is a potential risk factor that increased the frequency of birth defects in the area, and there is a need to undertake further studies to evaluate the influence of maternal metabolic control and microvascular disease on the occurrence of birth defects in infants of diabetic mothers.

Finally, based on the findings of this retrospective analysis, we plan to participate in the prospective study of Saudi Arabian Registry For Congenital Anomalies (SARCA) that aim at studying epidemiology of congenital anomalies in the kingdom and establish a national registry for these anomalies.

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