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Prevalence of major congenital anomalies at King Fahad Medical City in Saudi Arabia: a tertiary care centre-based study

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BACKGROUND AND OBJECTIVES: The prevalence of major congenital anomalies in Saudi Arabia is a largely understudied area. Knowing the prevalence of birth defects and their trends is important in identifying potential factors that are either causative or preventative. Early antenatal diagnosis of major congenital anomalies is important for possible termination of pregnancy, fetal or neonatal. We determined the prevalence of major congenital anomalies in our hospital population since implementation of an improved screening system.

PATIENTS AND METHODS: This single-centre prospective cross-sectional study was conducted in a tertiary care hospital in Riyadh. A total of 63 452 obstetrical ultrasound examinations were performed for 30 632 female Saudi obstetric patients from the period of January 2007 to December 2012.

RESULTS: A total of 1598 fetuses were diagnosed with major congenital anomalies, including 1064 (66.6 %) fetuses with isolated major anomalies and 534 (33.4%) fetuses with non-isolated major anomalies. The antenatal prevalence of congenital anomalies was 52.1 per 1000 pregnancies. The median maternal age at diagnosis was 29 years. The median gestational age at diagnosis was 30 weeks of gestation. Two hundred and eighty five cases (17.85%) had a previous family history of similar anomalies. The most commonly diagnosed anomalies involved the genitourinary system (652 cases). The birth prevalence of major congenital anomalies was 46.5 per 1000 live births.

CONCLUSION: The prevalence of major congenital anomalies in our hospital population appears to be higher than international prevalences, with a high recurrence rate. Environmental, nutritional and social factors may be contributing to this phenomenon.

Congenital anomalies or birth defects are defined as structural abnormalities diagnosed antenatally, at the time of birth or in the first few years of life.[1] These often result in increased perinatal mortality, if not long-term disability in the diagnosed infant and are a burden to families, society and the healthcare system.[2] In January 2014, the World Health Organization (WHO) reported that birth defects are estimated to affect one in every 33 infants globally and account for approximately 3.2 million birth defect-related disabilities every year.[2]

Knowing the prevalence of birth defects and their trend is important in identifying potential novel factors that are either causative or preventative.[1] Ultrasound examination is beneficial in the early detection of congenital malformations; in low risk populations the sensitivity is low, varying from 17% to 35 %, and the specificity is 99%, whereas in high-risk populations the sensitivity is greater than 90%.[2] Early antenatal diagnosis of major congenital anomalies is important for the appropriate counselling of parents, possible termination of pregnancy, fetal or neonatal intervention, delivery in the appropriate centre, and future prevention.

In 2008, we reported for the first time the antena-

tal prevalence of major congenital anomalies in Saudi Arabia.[3] The antenatal prevalence of major congenital anomalies within two years (2005-2006) was 27.96 per 1000 pregnancies. However, this result may significantly have under-reported the actual incidence because during that time period a large proportion of patients at King Fahad Medical City were not booked and did not have an antenatal ultrasound scan. Since this initial study we have implemented an improved screening system including a proper, antenatal booking system and follow-up of pregnant women. The goal of this study is to report on the perinatal prevalence of various types of major congenital anomalies at King Fahad Medical City covering a period of six years, from January 2007 to December 2012.

Figure 1. Distribution of total patients versus patients who delivered according to: A) Maternal age (years); B) Maternal parity and C) Gestational age at diagnosis (weeks).

PATIENTS AND METHODS

Study site and design
This single-centre prospective study was conducted in the Obstetrics and Gynaecology Ultrasound Unit of the Maternal and Fetal Medicine Department, Women's Specialized Hospital at King Fahad Medical City, Riyadh, Saudi Arabiaa. The study site is a tertiary hospital that is the official referral centre for congenital anomalies in Saudi Arabia as appointed by the Ministry of Health. First trimester scans are routinely performed between 11 to 14 weeks of gestation, followed by early morphology scans between 16 to 17 weeks of gestation for some cases as indicated, and also morphology ultrasound examinations between 18 to 22 weeks of gestation or later upon booking, and fetal echo at 22-24 weeks. All ultrasound examinations are reviewed and reported by maternal-fetal medicine consultants. Ethical approval was obtained from the Institutional Review Board (IRB number 11-102) prior to study commencement.

Subjects
A total of 63 452 obstetrical ultrasound examinations were performed for 30 632 obstetric Saudi patients from the period of January 2007 to December 2012. Subjects were excluded if the ultrasound revealed a non-viable fetus or viable fetuses with soft markers only (e.g., borderline ventriculomegaly less than 13 mm, pylectasis, short femur, choroid plexus cyst, echogenic cardiac foci, and echogenic bowel). Data were gathered from the following sources: ultrasound unit, records from the labour and delivery ward, antenatal clinics and neonatal infant care unit records. Data included demographics, ultrasound findings and other pertinent maternal and fetal information such as maternal age, maternal parity, gestational age, history of consanguinity and previous fetal anomalies. All data were entered using Microsoft Excel 2010.

Ultrasound examination and diagnosis of congenital anomalies
All subjects underwent standard obstetrical ultrasound examinations based on the recommendations of the American Institute of Ultrasound in Medicine (AIUM) and the American College of Obstetricians and Gynaecologists (ACOG).[4] The ultrasound system used was the Philips IU-22, Netherlands. Once fetal structural anomalies were identified, the following steps were taken based on the recommendations proposed by Gagnon and colleague.[5] The pregnant woman was offered a timely consultation with a
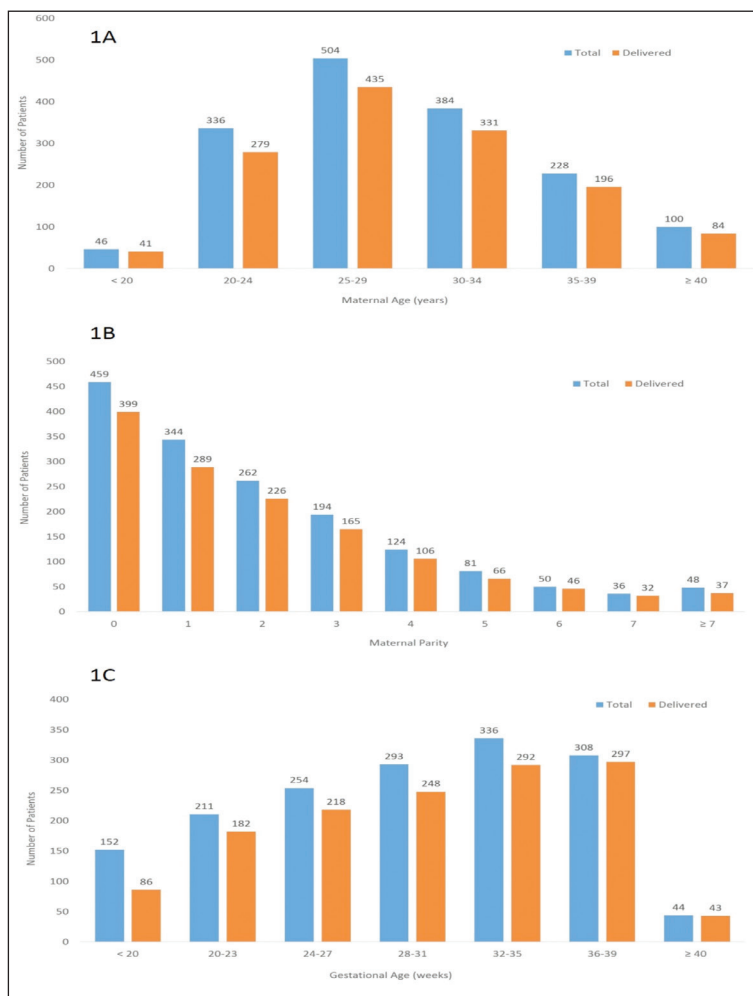
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maternal-fetal medicine specialist and with a trained genetic counsellor. The counselling was unbiased and respected the patient's choice, culture, gestational age and religion (according to Saudi regulations; termination of pregnancy was allowed only before 120 days of fetal life). Ultrasound examination was repeated (at a frequency depending on the anomaly) to assess the evolution of the anomaly, but also to detect other anomalies not previously identified, as this may influence the counselling as well as the obstetrical or perinatal management. Once a fetal structural anomaly was identified by 2-D ultrasound, other imaging techniques such as fetal echocardiography, 3-D obstetrical ultrasound, and occasionally fetal MRI were considered in specific cases, depending on the fetal anomaly identified.

To diagnose a potential genetic anomaly of a fetus with isolated or multiple structural anomalies, prenatal invasive testing for karyotyping was performed. Chorionic villus sampling (CVS), amniocentesis or cordocentesis was performed in females who gave consent for a fetal anomaly that required karyotyping. Women received the information on the abnormal ultrasound findings in a clear and timely fashion, and in a supportive environment that ensured privacy. Parents were referred to the appropriate pediatric or surgical subspecialist(s) to receive accurate information concerning the anomaly or anomalies of the fetus and the associated prognosis. Parents were informed that major or minor fetal structural anomalies, whether isolated or multiple, may be part of a genetic syndrome, sequence, or association, despite a normal fetal karyotype. If early or urgent postnatal management was required, delivery at a centre that could provide the appropriate neonatal care was considered. A comprehensive clinical assessment of the newborn was essential for diagnosis and counselling on the etiology, prognosis, and recurrence risk for future pregnancies. In cases of termination of pregnancy, stillbirth, or neonatal death, the option for an autopsy was offered, which was, however, declined in the majority of cases.

Data analysis
The antenatal prevalence was calculate per 1000 pregnancies, and birth prevalence was calculate per 1000 live births.

RESULTS
During the study period, 30 632 pregnant women were screened. We diagnosed and managed 1598 cases of major congenital anomalies, including 1064 (66.58%)

Table 1. Cases of congenital anomalies per system, with maternal and fetal characteristics.

System	Total cases	Mean parity	Mean maternal age	Mean GA at diagnosis	Isolated (%)	Non-Isolated (%)	Total deliveries	Delivery GA	Male Fetus (%)	Female Fetus (%)	NICU (%)	NND (%)	Consanguinity (%)	Family History (%)
Cranial	415	2	29	31	155 (37.3)	260 (62.7)	365	38	145 (39.7)	148 (40.5)	160 (43.8)	142 (38.9)	151 (36.4)	66 (15.9)
NTD	189	1	28	27	79 (41.8)	110 (58.2)	149	37	46 (30.1)	77 (51.7)	66 (44.3)	86 (57.7)	59 (31.2)	23 (12.3)
Face and neck	231	2	30	28	36 (15.6)	195 (84.4)	187	36	84 (44.9)	70 (37.4)	63 (33.7)	117 (62.6)	85 (36.8)	40 (17.3)
Thorax	180	2	28	27	31 (17.2)	149 (82.8)	146	32	66 (45.2)	56 (38.6)	38 (26.0)	107 (73.3)	74 (41.1)	35 (19.4)
Cardiac	245	2	30	30	96 (39.2)	149 (60.8)	199	37	72 (36.2)	87 (43.7)	84 (42.2)	80 (40.2)	58 (23.7)	34 (13.9)
Abdomen	275	1	28	28	84 (30.5)	191 (69.5)	236	34	96 (40.7)	91 (38.6)	69 (29.2)	134 (56.8)	100 (36.4)	41 (14.9)
GUS	652	1	29	32	500 (76.7)	152 (23.3)	576	38	307 (53.3)	144 (25)	121 (21)	162 (28.1)	201 (30.1)	78 (11.9)
Skeletal	417	2	28	29	105 (25.2)	312 (74.8)	353	36	156 (44.2)	127 (36)	109 (0.9)	187 (53)	159 (38.1)	76 (18.2)

NTD: Neural Tube Defect, GUS: Genitourinary System, GA: Gestational Age, NICU: Neonatal Intensive Care Unit, NND: Neonatal Death

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Table 2. Karyotyping results for study population.

System	Total cases	Karyotyped cases	Cases with abnormal karyotype, (%)	Trisomy 18, (%)	Trisomy 13, (%)	Trisomy 21, (%)	Turner Syndrome, (%)	Other, (%)
Cranial	415	117	29 (6.99)	10 (2.41)	9 (2.17)	5 (1.2)	1 (0.24)	4 (2.76)
NTD	189	21	1 (0.53)	1 (053)	0 (0)	0 (0)	0 (0)	0 (0)
Face and Neck	231	117	42 (18.18)	16 (6.93)	10 (4.33)	7 (3.03)	7 (3.03)	2 (087)
Thorax	180	66	13 (7.22)	16 (8.89)	1 (056)	3 (1.67)	6 (3.33)	0 (0)
Cardiac	245	76	31 (12.65)	10 (4.08)	8 (3.27)	6 (2.45)	3 (1.22)	4 (1.63)
Abdomen	275	98	23 (8.36)	14 (5.09)	4 (1.45)	8 (2.91)	3 (1.09)	1 (0.36)
GUS	652	55	14 (2.15)	6 (0.92)	3 (0.46)	1 (0.15)	1 (0.15)	3 (0.46)
Skeletal	417	119	29 (6.95)	14 (3.36)	2 (0.48)	5 (1.19)	6 (1.44)	2 (0.48)

NTD: Neural tube defect, GUS: Genitourinary system

fetuses with isolated congenital anomalies and 534 (33.42%) fetuses with non-isolated (multiple) congenital anomalies. The antenatal prevalence of major congenital anomalies was 52.17 per 1000 pregnancies. The median maternal age at diagnosis was 29 years, the median maternal parity was one, and the median gestational age at diagnosis was 30 weeks of gestational age (**Figure 1**).

Of 1598 cases of major congenital anomalies, 67 (4.19%) patients underwent termination of pregnancy, 1351 (84.54%) patients delivered in our institution, and 180 (11.27%) patients were either lost to follow-up or referred back to their primary healthcare centres. During the study period the number of live births was 29,084 and the birth prevalence of major congenital anomalies was 46.45 per 1,000 live births. The median gestational age at delivery was 38 weeks of gestation. Genitourinary system anomalies were the most common, with 652 cases diagnosed and 576 delivered. The second most common identified birth defects were skeletal anomalies with 417 cases diagnosed and 353 cases delivered. The occurrence of anomalies in other systems as well as maternal and fetal characteristics for these cases are shown in **Table 1**. The percentage of isolated anomalies was highest in the genitourinary system group (n=500, 76.7%) followed by neural tube defects (NTD) (n=79, 41.8%), whereas the percentage of non-isolated anomalies was highest in the face and neck (n=195, 84.4%), followed by the skeletal system group (n=312, 74.8%).

Karyotyping was performed in females who gave consent (**Table 2**). In 267 karyotypes, 65 cases had abnormal results with trisomy 18 being the most common

finding (n=23) followed by trisomy 21 (n=14), trisomy 13 (n=11), and monosomy X (n=9).

The most common congenital abnormalities were in the genitourinary system (652 cases) with an antenatal prevalence of 21.28 per 1000 pregnancies and a birth prevalence of 19.80 per 1000 live births. In the genitourinary system, the leading anomaly was hydronephrosis (either unilateral or bilateral) with 266 cases; the antenatal prevalence and birth prevalence were with 8.7 and 8.5, respectively. For the cranial anomalies, ventriculomegaly (either mild less than 15 mm or severe more than 15 mm), was the most frequently diagnosed anomaly (259 cases of 415 cases of cranial anomalies); the antenatal and birth prevalence of ventriculomegaly were 8.5 and 7.7, respectively (**Table 3**). Further details of antenatal and birth prevalence of other systems are shown in **Table 3**. The consanguinity rate was 37.86% (605 of 1598 cases) (**Table 4**). In some cases, structural anomalies were associated with a previous family history with a variable incidence per system group.

Tables 5 and 6 show factors associated with consanguinity, and ultrasonographic findings and neonatal outcomes.

DISCUSSION

The antenatal prevalence of major congenital anomalies was 52.17 per 1000 pregnancies and the birth prevalence of major congenital anomalies was 46.45 per 1000 live births. Genitourinary system anomalies were the most commonly identified anomalies because renal defects are usually easy to diagnose in comparison to other systems such as cardiac and cranial anomalies. The consanguinity rate of 37.9% was high. The diagnosis of ma-

Table 3. Outcome of cases with congenital anomalies.

System	Total cases	Diagnosis	Number	Abortion <23 week	Delivery >23 week	Lost to follow-up	Antenatal prevalence (per 1000 pregnancies)	Birth prevalence (per 1000 live births)
Cranial	415		415	8	365	42	13.55	12.55
		Ventriculiomegaly	156	2	137	17	5.1	4.7
		Hydrocephalus	103	2	88	13	3.4	3.0
		Holoprosence-phaly	28	0	26	2	0.9	0.9
		Dandy Walker	33	1	30	2	1.1	1.0
NTD	189		189	28	149	12	6.17	5.12
		Anencephaly	62	22	37	3	2.0	1.3
		Encephalocele	46	4	39	3	1.5	1.3
		Spina Bifida	87	3	77	7	2.8	2.6
Face and neck	231		231	15	187	29	7.54	6.43
		Cleft lip and/ or palate	45	1	37	7	1.5	1.3
		Cystic hygroma	49	11	32	6	1.6	1.1
Thorax	180		180	11	146	23	5.88	5.02
		Diaphragmatic hernia	33	0	26	7	1.1	0.9
		Hydrops	117	11	95	11	3.8	3.3
Cardiac	245		245	6	199	40	8.00	6.84
		VSD	84	1	71	12	2.7	2.4
		AVSD	28	1	23	4	0.9	0.8
		HPLH	18	0	14	4	0.6	0.5
		TGA	11	0	7	4	0.36	0.2
Abdomen	275		275	16	236	23	8.98	9.46
		Doudenal Atresia	9	0	7	2	0.3	0.2
		Omphalocele	21	3	16	2	0.7	0.7
		LBWC	12	3	8	1	0.4	0.28
		Gastoschiasis	2	0	2	0	0.065	0.069

NTD: Neural tube defect, VSD: Ventricular septal defect, AVSD: Atrio-ventricular septal defect, HPLH: hypoplastic left heart, TGA: transposition of great arteries. LBMC: limb-body wall complex, GUS: Genito-urinary system, PUV: posterior urethral valve, OI: osteogenesis imperfecta

jor congenital anomalies has improved dramatically in the past few years and is mainly attributable to advancements in ultrasound systems technology, which are also being operated by skilled sonographers and perinatologists. This may explain the increased number of cases currently being diagnosed compared to the past, which consequently reflects a higher prevalence and incidence of congenital anomalies. The management of birth defects has also improved in terms of an early diagnosis and termination of pregnancy if needed as well as postnatal care of newborns by a skilled neonatal intensive care unit team in tertiary care centres.[3]

The main finding of the present study is the relatively high prevalence of congenital anomalies in the

Table 3 cont. Outcome of cases with congenital anomalies.

System	Total cases	Diagnosis	Number	Abortion <23 week	Delivery >23 week	Lost to follow-up	Antenatal prevalence (per 1000 pregnancies)	Birth prevalence (per 1000 live births)
GUS	652		652	14	576	62	21.28	19.80
		Renal agenesis-B	6 8	3	54	11	2.2	1.86
		Renal agenesis unilateral	40		37		1.3	1.3
		Hydronephrosis - Right	104	2	97	5	3.4	3.3
		Hydronephrosis - Left	83	0	76	7	2.7	2.6
		Hydronephrosis - Bilateral	79	0	76	3	2.6	2.6
		Multicystic bilateral	48	1	41	6	1.6	1.4
		Multicystic unilateral	38	0	35	3	1.2	1.2
		Polycystic	58	4	44	10	1.9	1.5
		PUV	36	0	31	5	1.2	1.06
Skeletal	417		417	24	353	40	13.61	12.14
		Thanatophoric dysplasia	8	0	7	1	0.261	0.241
		Achondrogenesis	7	2	5	0	0.229	0.172
		OI type II	10	1	8	1	0.301	.0275
		Achondroplasia	17	0	14	3	0.555	0.481
		Arthrogryposis	16	0	12	4	.0526	.0413

NTD: Neural tube defect, VSD: Ventricular septal defect, AVSD: Atrio-ventricular septal defect, HPLH: hypoplastic left heart, TGA: transposition of great arteries. LBMC: limb-body wall complex, GUS: Genito-urinary system, PUV: posterior urethral valve, OI: osteogenesis imperfecta

KFMC population, more specifically 52.1 cases per 1000 pregnancies and 46.5 cases per 1000 live births. This occurrence is higher than previously reported in 2008, when the antenatal prevalence of major congenital anomalies within two years (2005 and 2006) was found to be 27.96 per 1000 pregnancies.[5] However, these results may be significantly compromised by the fact that during that period of time, a large proportion of our patients were not booked for an antenatal ultrasound scan.

The prevalence of birth defects in Saudi Arabia reported in this study is considerably higher compared to other countries. EUROCAT, the European Surveillance of Congenital Anomalies, reported a prevalence of 23.9 per 1000 births in Europe for 2003-2007.[6] The Centres for Disease Control and Prevention (CDC) in the United States reported that approximately 3% of all live births are complicated with congenital abnormalities.[7]

This high incidence of birth defects in the country may largely be attributed to consanguinity, a well-established major risk factor for congenital anomaly.[8] On a regional level, the increased risk for congenital anomalies secondary to consanguinity has already been observed from recent Middle-Eastern and North African studies with similarly high incidence of consanguineous marriages.[9-11] The present findings are no exception, with a rate of consanguinity of almost 40% for the congenital anomalies cohort.

There is growing evidence of a link between maternal prenatal environmental exposures and an increased risk of congenital abnormalities. More specifically, epidemiological studies have shown that exposure during pregnancy to environmental factors including tobacco smoke, outdoor air pollution (e.g. PM_{10}, NO_2, and SO_2), water contaminated with chlorination disinfection byproducts and pesticides, is significantly associated with an increased risk of congenital abnormalities.[12-15] As a result of the recent urbanization and in-

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Table 4. Consanguinity by patient characteristics.

		Non-consanguineous		Consanguineous		Total		P
		%	n	%	n	%	n	
Nationality	Non-Saudi	25	71.4	10	28.6	35	2.5	.040
	Saudi	746	53.9	637	46.1	1383	97.5	
Age (y)	Mean (SD) (min, max)	29.8 (6.0) (16, 49)		28.6 (6.0) (16, 53)		29.2 (6.0) (16, 53)		.001
	16 to 24	157	46.7	179	53.3	336	24.0	
	25 to 53	614	56.7	468	43.3	1082	76.0	
History family		93	36.6	161	63.4	254	17.9	<.001
Diabetes mellitus	Type 1	35	47.9	38	52.1	73	5.1	.272
	Type 2	44	48.9	46	51.1	90	6.3	
Gestation age at presentation (week)	≤22	156	54.4	131	45.6	287	20.2	.995
	≥23	615	54.4	516	45.6	1131	79.8	
Parity	Nulliparous	225	55.1	183	44.9	408	28.8	.710
	Multiparous	546	54.1	464	45.9	1010	71.2	
Previous anomalies		235	54.7	195	45.3	430	30.3	.889

dustrialization that has taken place in Saudi Arabia, the levels of air and water pollution have increased substantially. Therefore, such environmental factors may partly explain the high prevalence of congenital abnormalities in Saudi Arabia.

Vitamin deficiencies could also explain the increased prevalence of congenital abnormalities in Saudi Arabia. Prenatal folic acid deficiency is correlated with neural tube defects, a very common congenital abnormality. A recent cross-sectional study among 1000 Saudi females 18-45 years old showed that only 4.4% of these took folic acid before pregnancy.[16] Increasing awareness of the benefits of folic acid prenatal supplementation, especially among less educated women, may contribute towards decreasing the prevalence of neural tube defects in Saudi Arabia.

Additional risk factors identified in Western countries include an increased maternal age,[17,18] maternal age lower than 25 years and non-Hispanic white maternal ethnicity,[19] as well as maternal smoking history.[20] These risk factors, which were not assessed in the present study, are worthy of future investigation to determine whether they contribute to the high incidence of birth defects in Saudi Arabia.

Our study has several important limitations. A Saudi Registry for Congenital Anomalies is still not available.

Table 5. Factors associated with consanguinity.

Characteristic	OR	95% CI	P
Nationality (Saudi)	2.22	(4.76 - 1.02)	.045
Age (16 to 24)	1.56	(2.04 - 1.22)	<.001
Family History	2.33	(3.13 - 1.75)	<.001
Number of Anomalies (>1)	1.52	(1.89 - 1.22)	<.001

Despite the large sample size, the present study is limited because it did not include more centres across the country. Furthermore, our database has no information on the regional distribution of the subjects. If this was available, we would be able to observe regional variations in anomalies across the country. Furthermore, we have no information on anomalies seen in other centers. We can estimate the incidence of congenital anomalies in our KFMC population, which may or may not be generalizable to the Saudi population. Another limitation is that we have a referral population that may artificially inflate the prevalence of anomalies. In addition, late referral and diagnosis of fetal anomalies is a challenging issue that significantly affects perinatal outcomes. We encourage all patients and doctors to have

Table 6. Ultrasonographic findings and neonatal outcome by consanguinity.

		Non-Consanguineous		Consanguineous		Total		P
		%	n	%	n	%	n	
Number of anomalies	One	392	50.8	253	39.1	645	45.5	<.001
	> One	379	49.2	394	60.9	773	54.5	
	median (min, max)	1 (1,7)		2 (2,8)		1 (1,8)		
Major congenital anomalies	Isolated (Single)	544	70.6	402	62.1	946	66.7	.001
	Non-isolated (Multiple)	227	29.4	245	37.9	472	33.3	
Status	Terminated Pregnancy	37	4.8	30	4.6	67	4.7	.886
	Delivered	734	95.2	617	95.4	1351	95.3	
Gestation age at delivery (week)	23 to 28	41	5.6	31	5.0	72	5.3	.294
	29 to 36	182	24.8	176	28.5	358	26.5	
	37 to 42	511	69.6	410	66.5	921	68.2	
Delivery type	Term	511	69.6	410	66.5	921	68.2	.213
	Preterm	223	30.4	207	33.5	430	31.8	
Gender of baby	Female	349	45.3	299	46.2	648	45.7	.738
	Male	421	54.7	348	53.8	769	54.3	
NICU admission		277	37.7	251	40.7	528	39.1	.270
Neonatal outcome	Survived	240	32.7	260	42.1	500	37.0	<.001

early antenatal care and referrals, as well as control of pregnancy termination.

CONCLUSION

The prevalence of major congenital anomalies in KFMC was found to be higher than that reported for international data. The high rate of consanguinity may partly explain this high prevalence. Creating a Saudi Registry for Congenital Anomalies as well as a database for the regional distributions of fetal anomalies is warranted.

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