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Birth defects and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

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Abstract

Background: Birth defects (BD) are a recognized global health priority because of their increasing impact on childhood survival and health worldwide. However, information on the three key areas of risk factor prevalence, BD occurrence, and BD-related outcomes are limited in low and middle-income countries, where most BD occurs.

Objective: To assess the three key issues for birth defect prevention and care, namely risk factor prevalence, birth defects occurrence, and survival, in a well-defined longitudinal cohort in Riyadh, Saudi Arabia.

Design: Longitudinal, prospective cohort study with a nested case-control study.

Setting: Prince Sultan Military Medical City, Riyadh Saudi Arabia.

Participants: Pregnant Saudi women enrolled over three years, and their 28646 eligible births. The nested case-control study evaluated the underlying cohort's birth defects risk factor profile. All cases (1 179) and the unaffected controls (1 262) were followed through age 2 years.

Main outcome measures: Frequency of birth defects related risk factor, the prevalence and pattern of major birth defects, and survival through age 2 years.

Results: In this cohort of women, the burden of potentially modifiable risk factors included high rates of diabetes (7.3%), maternal age >40 years (7.0%), consanguinity (54.5%), and lack of periconceptional folic acid use (90.8%). The birth prevalence of birth defects was 41.2/1,000 births, driven mainly by congenital heart disease (14.8 per 1000), renal malformations (11.3), neural tube defects (1.9), and chromosomal anomalies (2.7). Mortality for live births with BD at 2 years of age was 15.8%.

Conclusions: This study documented specific opportunities for primary prevention and for better care. Folic acid fortification (the rate of neural tube defect was more than 3 times higher than what might be achieved with full fortification), preconception diabetes screening and consanguinity-related counseling could have significant health benefits, in this cohort and arguably in the larger Saudi population.

Article summary:

Strengths and limitations of this stud

- Babies with birth defects are diagnosed prospectively; prenatally, postnatally, and followed up to 2 years of age.
- Involvement of multidisciplinary teams in establishing the final diagnosis.
- Inclusion of elective termination of pregnancies with lethal birth defects and stillbirth.
- Single center study. The pregnancy cohort was mainly from families of Saudi army personnel dependents. could present a limiting factor.

The original protocol of the study: See supplementary file.

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Competing interests statement:

All authors have completed the ICMJE uniform disclosure from at www.icmje.org-coi_disclosure.pdf and declare: no support from any organization for the submitted research article; no financial relationship with any organization that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Key Words: Birth defects, Prevalence, Risk factors, Prevention, and outcome

Birth defects and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

Introduction

Birth defects (BD) are increasingly recognized as a global health priority because of their lifelong impact on health and survival[1,2]. As causes of early mortality such as infections are being brought under control, BD are becoming increasingly important drivers of child survival and health also in low- and middle-income countries [1,3]. BD affect approximately an estimated 1 in 33 newborns, contribute each year to 300,000 deaths in the first month of life, and are associated with 3·2 million birth-related disabilities [3]. Accordingly, the World

Health Assembly has emphasized the urgent need for action to help prevent, diagnose, and provide timely intervention [1].

However, local action, whether focused on primary prevention or on improving care, is most effective when based on by reliable information on key indicators on causes and outcomes of BD in the underlying population. These data are typically scarce outside a few high-resource countries. In this study, we implemented an integrated approach to generate these data in well-defined cohort of women, tracked from mid-gestation through the second year of life of their children, to assess concurrently the burden of potentially modifiable risk factors, the occurrence of BD, and survival of affected children, as a basis for better prevention and care [4].

Methods

Setting. The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution with 1250 beds and approximately 10,000 annual deliveries. PSMMC primarily serves Saudi army personnel and their families and is a referral center for the other 16 military hospitals in the Kingdom of Saudi Arabia. The fetal medicine unit includes advanced imaging facilities, including 3D and 4D scanning. The paediatric department includes all major subspecialties, including medical genetics, paediatric surgery, and paediatric cardiology.

Study Design (Figure 1). Observational, prospective cohort design with a nested case-control study. The eligible cohort included pregnancies of women who had their antenatal care and their routine antenatal anomaly ultrasound scan examination (USS) between 18 weeks and 22 weeks of gestation at PSMMC from 1 July 2010 through 30 June 2013.

In addition, Saudi women who are eligible for their antenatal care at PSMMC but did not have antenatal screening ultrasound examination and later delivered at PSMMC are included in the study.

Inclusions and Exclusions. Pregnancy outcomes included in the study were live births, stillbirths (fetal deaths at 20 weeks' gestation or later), and pregnancies electively terminated because of fetal anomalies (ETOPFA). The study excluded spontaneous abortions, pregnancies referred from other hospitals because of a diagnosis of a fetal anomaly, and babies with BD delivered elsewhere and referred to PSMMC for evaluation and management.

Evaluations. Initial antenatal screening tests included a complete blood count, liver and kidney function tests, blood group and antibodies screening, rubella and toxoplasma status, hepatitis B screen, random blood sugar and HbA1c level, VDRL, sickle cell screen and urine analysis. A glucose tolerance test was done at 24-28 weeks of gestation.

When a structural birth defect was diagnosed or suspected antenatally, mothers were counseled by one of the investigators (MSR, AMK), demographic and exposure information was gathered, and both parents were scheduled within 2-4 weeks in a dedicated clinic developed for the study. At that time, a detailed diagnostic and care plan was developed, which may have included further blood tests and fetal imaging, or amniocentesis, chorionic villous and/or fetal blood sampling for genetic studies. Consent was requested for cord blood collection for future molecular testing.

On the first day of life, all newborns in the cohort (with and without birth defects) were examined by a pediatrician as part of the first clinical screening examination. Babies with BD, whether identified antenatally or postnatally, underwent diagnostic investigations as clinically indicated (e.g., echocardiogram, cardiac catheterization, or other imaging studies; metabolic and molecular testing) and were referred to the appropriate subspecialists. A clinical geneticist evaluated all babies with suspected syndromes or multiple birth defects. A letter was distributed to all clinical departments describing the study and requesting that they inform the study team about all infants and children with BD born at PSMMC.

Evaluations for specific BD. If congenital heart disease (CHD) was detected or suspected antenatally on USS examination, the mother

was referred to the paediatric cardiologist for a fetal echocardiogram. All these infants were also re-evaluated after birth by a pediatric cardiologist. Isolated atrial septal defects (ASD II) were reevaluated at 6 to 12 months of age, and if at that time the echocardiogram showed no evidence of ASD II at the time, the infant was not considered a case. Congenital hydronephrosis (HN) was graded using the Society of Fetal Urology grading system [5]. Babies with grade one HN was given a repeat US examination within the first year of life; if it had resolved, the baby was not considered a case. Chromosomal analysis was done according to standard procedures, and a minimum of 20 metaphases was analyzed (Applied imaging CytoVision Karyotyping System). Reports followed the International System of Human Cytogenetic Nomenclature (ISCN 2013). Molecular studies were performed at Biocenthia health group in Germany (http://www.bioscientia.de/en/), Mayo medical laboratories in the United States, and Developmental Genetic laboratory at King Faisal specialist hospital and research center in Saudi Arabia.

Nested Case-Control Study. The nested case-control study included as cases all women in the cohort with a pregnancy diagnosed with a birth defect, and as controls a random sample of women in the cohort with a normal USS. The random sample was generated daily by taking the morning list of scheduled USS and using a random number generator (http://www.random.org) to select potential controls, so that the control sample would be eventually at least as

large as the estimated total number of cases. If a woman initially selected as a control had a pregnancy diagnosed with a birth defect at the initial or later date, she was then included in the case group. Investigators administered an in-person structured interview to case and control mothers. The interview included information on age (for both parents); weight before pregnancy; height; parity; family income (father's income or combined parental income if the mother worked); maternal education level (illiterate, primary school graduate, secondary school graduate, or university graduate); parental occupation (mother; housewife, teacher, student and others, father; soldier, officer or civilian employee); folic acid (FA) supplement use (regular use before and during 1st trimester of pregnancy; irregular or only post-conception use; no use or uncertain use per mother report); parental smoking (one or both parents smoking during current pregnancy); maternal radiation exposure during first trimester; maternal diabetes (overt or gestational) as defined by the International association of diabetes and pregnancy study groups [6], and HbA1c level; family history of BD (in previous pregnancies and in maternal or paternal lineages); drug and medication use during the first trimester; chronic maternal systemic illnesses (hypothyroidism, epilepsy, depression, essential hypertension, and bronchial asthma). Consanguinity was defined as women being first or second cousins to their husbands.

Follow up. Case-infants (with BD) and control-infants were examined in the dedicated study clinic at 1, 6, 12, 18 and 24 months of age. Two neonatologists and a clinical geneticist supervised the clinic. Babies with BD also continued to be followed by the relevant subspecialty clinics. The remaining cohort (babies without birth defects not selected as controls) was re-examined at 4-8 weeks by the pediatrician for a second screening examination. A head ultrasound and a postductal pulse oximetry reading were completed in all babies attending the clinics. If the O_2 saturation was below 95%, the baby was referred to the pediatric cardiologist for evaluation. If any BD were detected at the second screening examination, the babies were referred to the genetics clinic for further evaluation and diagnosis. If the second screening examination proved to be normal, then no further follow up was arranged. However, if BD were discovered later in babies up to 2 years of age, they were included in the study.

Case review, coding, classification. BD were coded following the International Statistical Classification of Diseases and Related Health Problems, 10th revision, (ICD10, WHO-2010) according to EUROCAT recommended procedures [7]. We did not include isolated minor anomalies or prematurity-related conditions such as patent ductus arteriosus or hydrocephalus complicating intraventricular hemorrhage diagnosed in preterm babies (<37 completed weeks of gestation). Data were entered in a version of EUROCAT Data Management

Program (EDMP) modified to include control records and the additional variables generated by the case-control study and the follow up.

Patient and public involvement: Our long-time experience with the families and their offspring has helped us to shape the research question and the study design. All the families recruited were informed about the study objectives. None of the parents were involved in the study. The study results were disseminated to the community and professional health care provider through social media interviews, newspapers, presentation at various conference, and scientific publications.

Institutional Ethics Review. The study approved by the Ethical Committee of the PSMMC (Project No. 366, series of 2009).

Statistical analysis. Proportions were compared with Chi-square or Fisher's exact tests. Odd ratios for BD were computed first via univariate logistic regression, then with a multiple logistic model. The latter was developed by first including uncorrelated significant factors ($p < 0{\cdot}05$) from the univariate analysis, then reducing the number of variables by stepwise backward elimination for a more parsimonious model. The final model included as covariates consanguinity, maternal age group, education level, diabetes and history of sib with congenital anomaly. Model fit was assessed with Hosmer and

Lemeshow goodness of fit (p=0·08). The Nagelkerke R2 was 0·055 (explaining 6% of the effect on BD). Statistical analysis was done with SPSS for Windows, version 15 (SPSS Inc., Chicago, Illinois).

Results

Of the 31 032 birth outcomes of the 30351 women followed since pregnancy, 30753 (99·1%) occurred at PSMMC (Figure 2). Of these, 2107 were spontaneous abortions (6·9%) and were not included in the study, leaving 28646 eligible births (27726 singleton births and 920 multiple births). The overall stillbirth rate was slightly less than 1 percent (Figure 2).

Birth defect occurrence, detection, and mortality (Table 1). Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a BD, for an overall prevalence of 412/10000 total births, or 1 in 24 births. Of these 1179 cases, 38 (3.2%) were stillbirths and 18 (1.5%) were electively terminated because of lethal malformations (13 with anencephaly, 3 with severe hydrops fetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis). The antenatal detection rate among women who has had antenatal ultrasound screening examination was 70.6%(561/795), and in 90% of these (505/561) the diagnosis was made by ultrasound scan at 22 weeks of gestation or later. Of the 618 babies diagnosed postnatally, 296 (47.9%) were diagnosed at birth; 239 (38.7%) between 1-7 days, 29 (4.7%) between 1-4 weeks, 52 (8.4%) between 1-12 months, and 2

(0.3%) after one year of age. Mortality among livebirths with BD (Table 1) was 14.1% in the first year, nearly half of which occurred in the first week of life, with a total mortality of 15.8% by the end of the second year of life. Mortality at two years was 0.9% in the unaffected cohort.

Contribution of specific BD (Table 2*).* Approximately half of the overall birth prevalence was due to congenital heart disease and central nervous system anomalies. Neural tube defects occurred at a rate of 1.9 per 1000 (1 in 526 births). Severe CHD occurred at a rate of 3.2 per 1000 (1 in 313 births) and accounted for 21.4% of all CHD cases. Chromosomal conditions whose risk is associated with increased maternal age (trisomies 21, 18, and 13) occurred at combined prevalence of 2.5 per 1000 (1 in 392 births), with trisomy 21 accounting for most of the cases (2.2 per 1000 or 1 in 456 births).

Risk factors. Figure 3 summarizes the frequency of selected maternal or parental risk factors for BD among controls in the nested case-control study. Among potentially modifiable factors, lack of periconceptional folic acid supplement use, consanguinity, high body mass index, advanced maternal age, smoking (first or second-hand) and maternal diabetes were particularly frequent. Nearly 6% of non-primiparous women had one prior child with a major BD. The nested case-control study (Table 3) detected overall increased odds ratios for all BD combined for consanguinity, advanced maternal age, high

parity, maternal diabetes, and positive family history of BD in a sib. Increased odds ratios with confidence intervals including unity were also found for maternal depression and hypertension (Table 3).

Discussion

This longitudinal study of BD in a pregnancy cohort in Saudi Arabia followed from mid-gestation through age 2 years had three integrated aims: describe the population's risk factor profile, document the associated birth prevalence of BD, and assess survival as critical health outcome [4]. This information is crucial when planning and then evaluating policies and interventions, be they aimed at primary prevention (e.g., folic acid fortification) or at improving care of those affected.

In terms of the burden of BD, the study documented a remarkably high birth prevalence of 41.2 per 1000, or 1 in 24 total births. This rate is higher than that in many high-income countries, as reported by EUROCAT (26.1/1000 births)[8], BINOCAR (20.6/1000 births)[9] and the Bradford (BIB) study (30.5/1000)[10]. It is also higher than previously reported from Saudi Arabia (11.5 to 25.7 per 1000 live births)[11-13].

Sallout and colleagues reported an antenatal BD prevalence of 52.1/1000 pregnancy screened and 46.5/1000 LB[14]. These high prevalences are biased because of the inclusion of mothers referred from other institutions, which lead to an imprecise denominator. In addition, none of their cases discovered postnatally, which reflect an underestimation. In the current study findings could be related in part to methodological factors leading to better detection – for example, the follow-up starting in pregnancy and extending through the second year of life; the inclusion of stillbirths and elective termination of pregnancies for fetal anomalies (ETOPFA); and the inclusion of some genetic conditions that tend to be diagnosed after the newborn period.

However, the high prevalence is likely related also to the high frequency of adverse risk factors in the underlying population, as documented in the controls of the nested case-control study. Focusing on factors that are potentially modifiable, three factors seem to stand out. The first is insufficient folic acid use in this cohort (<10% in the periconceptional period). Concurrently, the rate of neural tube defects was 1.9 per 1000/births (Table 2), approximately three times higher to the rate of 0.6 per 1000/births that seems achievable by providing sufficient folic acid to women of childbearing age [15,16] . Although legislation for mandatory flour fortification had been in place in Saudi Arabia for years prior to this study (Kingdom of Saudi Arabia, 2000; Food fortification initiative, 2013)[17,18], our data suggests that there are gaps in coverage or effectiveness, which could

be better documented with nutrition or blood folate surveys as a first step for improvement. Because of the inclusion of stillbirths and pregnancy terminations, this study also provides a fuller estimate of the potential benefits of primary prevention, compared to if only livebirths had been identified (representing just over half of all cases, 30/54).

The second factor is maternal diabetes (Table 3). Diabetes is an established risk factor for many BD and whose control before conception is associated with a near normalization of BD risk [6,19,20]. Several avenues for preventing diabetes and its health effects are available, including population screening (many diabetic women are undiagnosed), health care and counseling, and education on healthy lifestyle and dietary choices starting from childhood. The current reported prevalence in Saudi Arabia of overt diabetes in women above age 40 years range from 7.7% – 21.7% [21-23]. In the study cohort, overt diabetes was seen in 2% of women, and even higher in women 30 years old or older. Al-Nozha and colleagues (Al-Nozha et al., 2004) reported a prevalence of overt diabetes of 11.6% at 30-39 years and >22% at women of ≥40 years [24] compared to 2.7% and 7.1% in our study respectively. Though lower than these estimates, the prevalence of overt diabetes in the study cohort is alarmingly high.

Third, we observed a high rate of parental consanguinity (54.5%), especially first-cousin marriages (48.0%). These marriages are common in many parts of the Middle East, Africa, and the Indian subcontinent [25-27], with one estimate suggesting that "one billion people live in communities with a preference for consanguineous marriage" (Hamamy, 2012)[26]. This preference has deep social roots. Nevertheless, education combined with preconception and premarital counseling can be important prevention strategies, focusing on increasing awareness to allow couples to make more informed choices. Close consanguinity is a known risk factor for BD[26] as well as Mendelian conditions such as inborn errors of metabolism (occurring in 1 in 770 births in this study), confirmed prior reports from Saudi Arabia and the world literature [28,29].

Finally, the impact of BD in this population is reflected not only in the birth prevalence but also in the associated early mortality (Table 1), which was 15.8% by the second-year life (nearly all in the first year). Supporting the high impact of BD in early mortality is the study by Majeed-Saidan and colleagues, which showed that 36% of deaths in a large neonatal intensive care unit in Riyadh was due to lethal BD[30]. These findings highlight the need to improve care in addition to primary prevention, in order to improve survival associated with BD.

The study has some limitations. Because of the cohort design, the study sample did not allow a more detailed analysis of specific BD groups. Some key risk factors such folic acid insufficiency was based on maternal reports of supplement use rather than biomarkers. The pregnancy cohort was mainly from families of Saudi army personnel dependents. Although the Saudi Army recruits from all sectors of the Saudi society, a more generalized survey of the Saudi population would be ideal to assess gaps and opportunities for prevention and care.

Conclusion. This longitudinal surveillance program that encompassed the causal chain from risk factors to health outcomes documented specific opportunities for primary prevention and for better care. Folic acid fortification, preconception diabetes screening, and consanguinity-related counseling could have significant health benefits, in this cohort and arguably in the larger Saudi population, particularly if associated with a national BD monitoring program to support and track the impact of interventions.

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Author's statement:

AMK study conception and design, revised the manuscript. **MAMS**, study conception and design, drafting and revising the manuscript., **MSR**, study design, data collection. **AMH**, data collection, revised the manuscript. **LDB**, study design, criticaly revised the manuscript for intellectual content. **HSB**, statistical analysis and revised the manuscript. **ANA**, study design, data collection, revised the manuscript. All authors approved the submission of the manuscript.

Patient consent form: n/a

Data sharing statement:

Dataset can be obtained on request through a third party "King Abdulaziz city for science and technology.

References

1. World Health Organization. Sixty -Third World Health Assembly. Birth defects Report by the Secretariat, A63/10. Geneva, Switzerland: World Health Organization, 2010.

2. World Health Organization. Global Health Observatory (GHO) data. Under-five mortality 2016. http://www.who.int/gho/child_health/mortality/mortality_under_five_text/en/ (accessed 12 December 2017).

3. Christianson AL, Howson CP, Modell B. Global report on birth defects: the hidden toll of dying and disabled children. White Plains (NY): March of Dimes Defects Foundation 2006.

4. Botto LD, Mastroiacovo P. Triple surveillance: a proposal for an integrated strategy to support and accelerate birth defect prevention. Ann. N. Y. Acad. Sci 2018; (1414):126-36.

5. Avni FE, Maugey-Laulom B, Cassart M, *et al*. Fetal genitourinary tract. In: Callen PW, ed. Ultrasonography in Obstetrics and Gynecology. 5th Ed. New York: W.B. Saunders 2007; 640-75.

6. Metzger BE, Gabbe SG, Persson B, *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33(3): 676–82. doi: 10.2337/dc09-1848.

7. EUROCAT. Eurocat Guide 1.3. Instructions for registration and surveillance of congenital anomalies. Belfast, Northern Ireland University of Ulster 2005. http://www.eurocat-network.eu/content/Section%202.4-%2027_Oct2016.pdf

8. EUROCAT. Prevalence Tables, 2011-2015. http://www.eurocat-network.eu/newprevdata/showPDF.aspx?winx=1896&winy=940&file=allsubgroups.aspx 2015. (accessed 12 December 2017).

9. Springett A, Budd J, Draper ES, *et al*. Congenital Anomaly Statistics 2012 England and Wales, London 2014. www.binocar.org/content/Annual%20report%202012_FINAL_nologo.pdf.

10. Sheridan E, Wright J, Small N, *et al*. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet 2013; 382(9901): 1350–9. doi: 10.1016/S0140-6736(13)61132-0.

11. Al Bu Ali WH, Balaha MH, Al Moghannum MS, *et al*. Risk factors and birth prevalence of birth defects and inborn errors of metabolism in Al Ahsa, Saudi Arabia. Pan Afr Med J 2011; 8: 14.

12. Fida NM, Al-Aama J, Nichols W, *et al*. A prospective study of congenital malformations among live born neonates at a University Hospital in Western Saudi Arabia. Saudi Med J 2007; 28(9): 1367–73.

13. Refat MY, Al-Moghanem M, McDonald, *et al*. Major birth defects at King Fahd Hofuf Hospital: Prevalence, risk factors and outcome. Ann Saudi Med 1995; 15(4): 339–43.

14. Sallout B, Obedat N, Shakeel F, *et al*. Prevalence of major congenital anomalies at King Fahad Medical City in Saudi Arabia: a tertiary care centre-based study. Ann Saudi Med 2015; 35(5): 343–51.

15. Kancherla V, Oakley GP Jr, *et al*. Urgent global opportunities to prevent birth defects. Semin Fetal Neonatal Med 2014; 19(3): 153–60.

16. Youngblood ME, Williamson R, Bell KN, *et al*. Update on global prevention of folic acid-preventable spina bifida and anencephaly. Birth Defects Res A Clin Mol Teratol 2013; 97(10): 658–63. doi: 10.1002/bdra.23166. Epub 2013.

17. Kingdom of Saudi Arabia, Ministry of health, Nutritional department directive. Number 652/1/26, 2000; 13/09/2000.

18. Food Fortification Initiative. (2013). http://www.ffinetwork.org/country_profiles/country.php?record=194 (accessed 12 December 2017).

19. Kitzmiller JL, Wallerstein R, Correa A, *et al.* Preconception care for women with diabetes and prevention of major congenital malformations. Birth Defects Res A Clin Mol Teratol 2010; 88(10): 791–03. doi: 10.1002/bdra.20734.

20. Simeone RM, Devine OJ, Marcinkevage JA, *et al* Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. Am J Prev Med 2014; 48(2): 195–204. doi: 10.1016/j.amepre.2014.09.002.

21. Al-Nuaim AR, Al-Rubean K, Al-Mazrou Y, *et al*. Prevalence of diabetes mellitus, obesity and hypercholesterolemia in Saudi Arabia: national chronic disease survey. Riyadh (KSA): Ministry of Health and King Saud University. ISBN: 1995; 9960-603-01-6.

22. El-Hazmi M, Warsy A, Al-Swailem AR, *et al*. Diabetes mellitus as a health problem in Saudi Arabia. East Mediterr Health J 1998 (4): 58–67.

23. Warsy AS, el-Hazmi MA. Diabetes mellitus, hypertension and obesity--common multifactorial disorders in Saudis. East Mediterr Health J 1999; 5(6): 1236–42.

24. Al-Nozha MM, Al-Maatouq M, Al-Mazrou YY.] *et al*. Diabetes mellitus in Saudi Arabia. Saudi Med J 2004; 25(11): 1603–10.

25. El-Mouzan MI, Al-Salloum AA, Al-Herbish AS, et al. Regional variations in the prevalence of consanguinity in Saudi Arabia. Saudi Med J 2007; 28(12): 1881–4.

26. Hamamy H. Consanguineous marriages: Preconception consultation in primary health care settings. J Community Genet 2012; 3(3): 185–92.

27. Majeed-Saidan MA, Ammari AN, AlHashem AM, *et al.* Effect of consanguinity on birth defects in Saudi women: results from a nested case-control study. Birth Defects Res A Clin Mol Teratol 2015; 103(2): 100–4. doi: 10.1002/bdra.23331.

28. Mak CM, Lee HC, Chan AY, *et al*. Inborn errors of metabolism and expanded newborn screening: review and

update. Crit Rev Clin Lab Sci 2013; 50(6): 142–62. doi: 10.3109/10408363.2013.847896.

29. Moammar H, Cheriyan G, Mathew R, *et al*. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med 2010; 30(4): 271–7. doi: 10.4103/0256-4947.65254.

30. Majeed-Saidan MA, Kashlan FT, Al-Zahrani AA, *et al*. Pattern of neonatal and postneonatal deaths over a decade (1995--2004) at a Military Hospital in Saudi Arabia. Saudi Med J 2008; 29(6):879-83.

Tables

Legend: Table 1 Distribution and rates of birth defects among the cohort's pregnancy outcomes, and associated mortality.

Total	With birth defects	Mortality among babies with birth defects		
		Overall (0-2 years)	1st week	Total 1st year

Birth outcome	No	%	No.	%	Rate /100	No.	%	No.	%	No.	%	No.	%
Live births	28376	99	1123	95.3	4.0	505	45.0	177	15.8	64	5.7	158	14.1
Stillbirths	252	0.9	38	3.2	15.1	38	100						
ETOPFA†	18	0.1	18	1.5	100	18	100						
Total	28646	100	1179	100	4.1	561	47.6						

Footnote:

†ETOPFA, Terminations of Pregnancy for Fetal Anomalies.

Stillbirth (fetal death at 20 weeks of gestation or greater).

Legend: Table 2 Prevalence and distribution of BDs, overall and by pregnancy outcome.

Birth defects	Number†	%	Prevalence per 1000 births (total births = 28646)	Live birth		Stillbirth		ETOPFA	
				No.	(%)	No.	(%)	No.	(%)
Any	1179	100	41.2	1123	95.3	38	3.2	18	1.5
Nervous system	160	13.6	5.6	129	80.6	18	11.3	13	8.1
Neural Tube Defects	54	4.6	1.9	30	55.5	11	20.4	13	24.1
Anencephalus	26	2.2	0.9	7	26.9	8	30.8	11	42.3
Encephalocele	11	0.9	0.4	9	81.8	1	9.1	1	9.1
Spina Bifida	17	1.4	0.6	14	82.4	2	11.8	1	5.9
Hydrocephaly	25	2.1	0.9	23	92.0	2	8.0		
Microcephaly	28	2.4	1.0	24	85.7	4	14.3		
Eye	33	2.8	1.2	33	100				
Anophthalmus/microphthalmus	11	0.9	0.4	11	100				
Congenital cataract	5	0.4	0.2	5	100				
Congenital glaucoma	9	0.8	0.3	9	100				
Ear, face and neck	7	0.6	0.2	7	100				
Anotia/microtia	7	0.6	0.2	7	100				
Cardiac	425	36.0	14.8	420	90.9	4	0.9		
Severe congenital heart defects ‡	91	7.7	3.2	89	97.8	2	2.2		
Common arterial truncus	3	0.3	0.1	3	100				

Transposition of great vessels	13	1.1	0.5	13	100				
Single ventricle	6	0.5	0.2	6	100				
Atrioventricular septal defect	17	1.4	0.6	15	88.2	2	11.8		
Tetralogy of Fallot	15	1.3	0.5	15	100				
Tricuspid atresia and stenosis	4	0.3	0.1	4	100				
Pulmonary valve stenosis	22	1.9	0.8	21	95.5	1	4.5		
Pulmonary valve atresia	9	0.8	0.3	9	100				
Aortic valve atresia/stenosis	5	0.4	0.2	5	100				
Hypoplastic left heart	15	1.3	0.5	15	100				
Hypoplastic right heart	5	0.4	0.2	5	100				
Coarctation of aorta	14	1.2	0.5	14	100				
Total anomalous pulmonary venous return	2	0.2	0.1	2	100				
Ventricular septal defect	171	14.5	6.0	171	100				
Atrial septal defect	214	18.2	7.5	214	100				
Oro-facial clefts									
Cleft lip with or without palate	42	3.6	1.5	35	83.3	5	11.9	2	4·8
Cleft palate only	11	0.9	0.4	11	100				
Respiratory	33	2.8	1.2	33	100				
Choanal atresia	5	0.4	0.2	5	100				
Digestive system	74	6.3	2.6	71	95.9	3	4.1		
Esophageal atresia with/without fistula	12	1.0	0.4	12	100				
Ano-rectal atresia and stenosis	26	2.2	0.9	25	96.2	1	3.8		

Diaphragmatic hernia	18	1.5	0.6	16	88.9	2	11.1		
Abdominal wall defects	7	0.6	0.2	6	85.7	1	14.3		
Gastroschesis	2	0.2	0.1	1	50.0	1	50.0		
Omphalocele	5	0.4	0.2	5	100				
Urinary	323	27.4	11.3	318	98.5	4	1.2	1	0.3
Bilateral renal agenesis	18	1.5	0.6	15	83.3	2	11.1	1	5.6
Renal dysplasia	60	5.1	2.1	58	96.7	2	3.3		
Congenital hydronephrosis	194	16.5	6.8	194	100				
Genital	127	10.8	4.4	126	99.2	1	0.8		
Hypospadias	108	9.2	3.8	108	100				
Indeterminate sex	3	0.3	0.1	2	66.7	1	33.3		
Limb	99	8.4	3.5	92	92.9	4	4.0	3	3.0
Limb deficiencies, all	17	1.4	0.6	17	100				
Upper limb deficiency	12	1.0	0.4	12	100				
Lower limb deficiency	7	0.6	0.2	7	100				
Club foot - talipes equinovarus	19	1.6	0.7	15	78.9	2	10.5	2	10.5
Hip dislocation and/or dysplasia	24	2.0	0.8	23	95.8			1	4.2
Polydactyly	23	2.0	0.8	23	100				
Syndactyly	9	0.8	0.3	9	100				
Musculo-skeletal	40	3.4	1.4	33	82.5	7	17.5		
Craniosynostosis	6	0.5	0.2	6	100				
Achondroplasia	3	0.3	0.1	2	66.7	1	33.3		
Thanatophoric dysplasia	2	0.2	0.1	2	100				

Jeune syndrome	2	0.2	0.1	1	50.0	1	50.5		
Other malformations	42	3.6	1.5	40	95.2	1	2.4	1	2.4
Situs inversus	10	0.8	0.3	10	100				
By underlying cause									
Chromosomal	82	7.0	2.9	79	96.3	3	3.7		
Down Syndrome/trisomy 21	63	5.3	2.2	62	98.4	1	1.6		
Edward syndrome/trisomy 18	8	0.7	0.3	7	87.5	1	12.5		
Patau syndrome/trisomy 13	2	0.2	0.1	2	100				
Turner syndrome	3	0.3	0.1	2	66.7	1	33.3		
Wolff-Hirschhorn syndrome	1	0.1	0.03	1	100				
Genetic syndromes (including microdeletions)	38	3.2	1.3	36	94.7	1	2.6	1	2.6
Teratogenic (Carbamazepine embryopathy)	1	0.1	0.1	1	100				
Conditions outside Q chapter of ICD-10									
Inborn error of metabolism	37	3.1	1.3	37	100				
Endocrine disorders	7	0.6	0.2	7	100				
Other	11	0.9	0.4	11	100				

Footnote:

† The total number of birth defects is greater than the total umber of affected births because some had more than one major BD.

‡ Severe congenital heart disease (EUROCAT definition): common arterial trunk (Q200), double outlet right ventricle (Q201), transposition of great arteries (Q203), single ventricle (Q204), atrioventricular septal defect (AVSD) (Q212), tetralogy of Fallot (Q213), pulmonary valve atresia (Q220), Ebstein anomaly (Q225), hypoplastic right heart (Q226), aortic valve atresia and stenosis (Q230), mitral valve anomalies (Q232, Q233), hypoplastic left heart (Q234), coarctation of the aorta (Q251), aortic atresia / interrupted aortic arch (Q252), total anomalous pulmonary venous return (Q262).

Legend: Table 3 Distribution of parental socio-demographic characteristics and association with birth defect risk.

Variable	Cases (total n=1179)		Controls (total n=1262)		Odds Ratio†	95% CI	
	No.	%	No.	%		Lower	Upper
Consanguinity							
Non-consanguineous	537	45.5	693	54.9	Ref	-	-
Consanguineous	642	54.5	569	45.1	1.5	1.30	1.8
Maternal age (years)							
<20	24	2.0	48	3.8	0.58	0.35	0.96
20-30	599	50.8	694	55.0	Ref	-	-
31-40	473	40.1	474	37.6	1.16	0.98	1.37
>40	83	7.0	46	3.6	2.09	1.43	3.05
Paternal age (years)							
20-30	341	28.9	403	31.9	0.92	0.76	1.10
31-40	548	46.5	593	47.0	Ref	-	-
41-50	240	20.4	225	17.8	1.15	0.93	1.43
> 50	50	4.2	41	3.2	1.32	0.86	2.03

Maternal body mass index‡							
<18·5	24	2.1	35	2.8	0.75	0.44	1.29
18·5-24·99	324	27.8	388	30.8	0.91	0.74	1.12
25·0-29·99	352	30.2	385	30.5	Ref	-	-
≥30	464	39.9	453	35.9	1.12	0.92	1.36
Previous deliveries (parity)							
Nulliparous	216	18.3	273	21.6	0.92	0.74	1.16
Para 1-2	374	31.7	436	34.5	Ref	-	-
Para 3-4	283	24.0	273	21.6	1.21	0.97	1.50
Para ≥5	306	26.0	280	22.2	1.27	1.03	1.58
Family monthly income Saudi riyals (US $)							
<3,000 SR (<800$)	19	1.9	12	1.0	1.87	0.89	3.92
10,000-14,000 SR (2667-3999$)	235	23.2	277	22.3	Ref	-	-
3,000-6,999 SR (800-1866$)	232	22.9	291	23.4	0.94	0.74	1.20
7,000-9,999 SR (1867-2666$)	367	36.3	496	39.9	0.87	0.70	1.09
≥15, 000 (≥4000$)	158	15.6	167	13.4	1.12	0.84	1.47
Maternal education							
Illiterate	391	33.2	333	26.4	1.50	1.26	1.80
Schooling up to high school	671	56.9	859	68.1	Ref	-	-
University	117	9.9	70	5.5	2.05	1.49	2.81
Folic acid intake							
Periconceptional	109	9.2	128	10.1	Ref	-	-
Improper use§	1070	90.8	1134	89.9	1.04	0.79	1.36

Parental Smoking							
Neither parent smoked	837	71.0	888	70.4	Ref	-	-
One or both parents smoked	342	29.0	374	29.6	0.97	0.82	1.16
Radiation exposure in pregnancy							
None	1161	98.5	1254	99.4	Ref	-	-
Radiation exposure in pregnancy	18	1.5	8	0.6	2.43	1.05	5.61
Diabetes mellitus (DM)							
No DM	956	81.1	1062	84.2	Ref	-	-
DM on insulin (all, overt & gestational	86	7.3	41	3.2	2.34	1.60	3.43
Gestational DM on diet only	137	11.6	157	12.6	0.91	0.62	1.16
Sibs of cases and controls (primiparous mothers excluded)							
No affected sibling	757	78.6	932	94.2	Ref-	-	-
Sibling with birth defects	85	8.8	58	5.7	1.61	1.14	2.27
Medication use in pregnancy							
None	792	67.2	951	75.3	-	-	-
Thyroxin	102	8.7	106	8.4	1.03	0.78	1.37
Insulin	86	7.3	40	3.2	2.34	1.59	3.45
Methyldopa	14	1.2	14	1.1	1.07	0.51	2.26

Maternal systemic illnesses							
None	808	68.5	971	76.9	Ref-	-	-
Mothers with Hypothyroidism	123	10.4	128	10.1	1.03	0.80	1.34
Mothers with Bronchial asthma	106	9.0	97	7.7	1.19	0.89	1.58
Mothers with depression	12	1.0	6	0.5	2.15	0.81	5.75
Mothers with essential hypertension	23	2.0	15	1.2	1.65	0.86	3.19

Footnote:

[†]Odds ratio adjusted for multiple potential confounders in multiple logistic regression model.

[‡]BMI not available for 15 mothers

Some families declined reporting their income.

[§]Improper-use includes FA taken post conception and 49 mothers (43 case mothers and 6 control mothers) who were not sure about their intake.

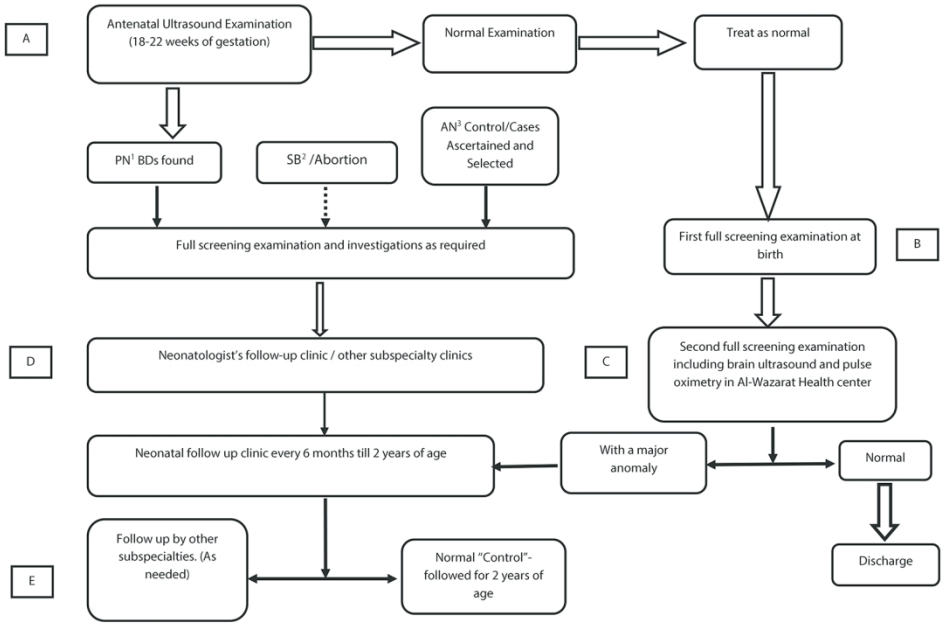
Figures legend:

Legend: Figure _1 Catchment site and the study flow chart.

Legend: Figure _2 Study population and distribution of pregnancies and their outcomes.

Legend: Figure _ 3 Frequency among control subjects of selected risk factors for birth defects.

Figure 1- Catchment site and the study flow chart.

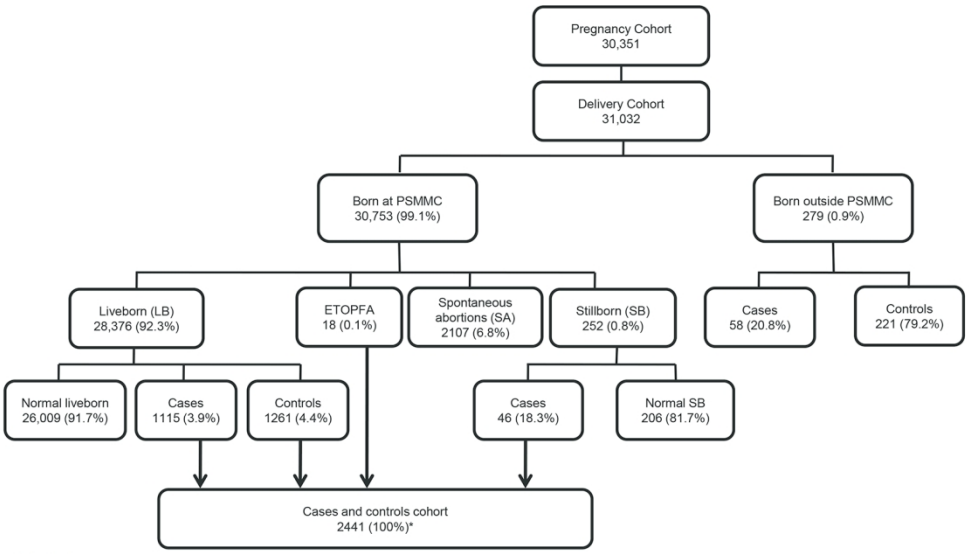


Legend: Case catchment areas (A to E). A: antenatal clinic, B: at birth, C: the "one-month clinic, D: geneticist "one-month clinic", and E: other areas. 1,2,3 are postnatal, stillbirth and antenatal respectively. BD. Birth defect

Legend: Figure _1 Catchment site and the study flow chart.

150x120mm (300 x 300 DPI)

Figure 2. Study population and distribution of pregnancies and their outcomes.



Legend:

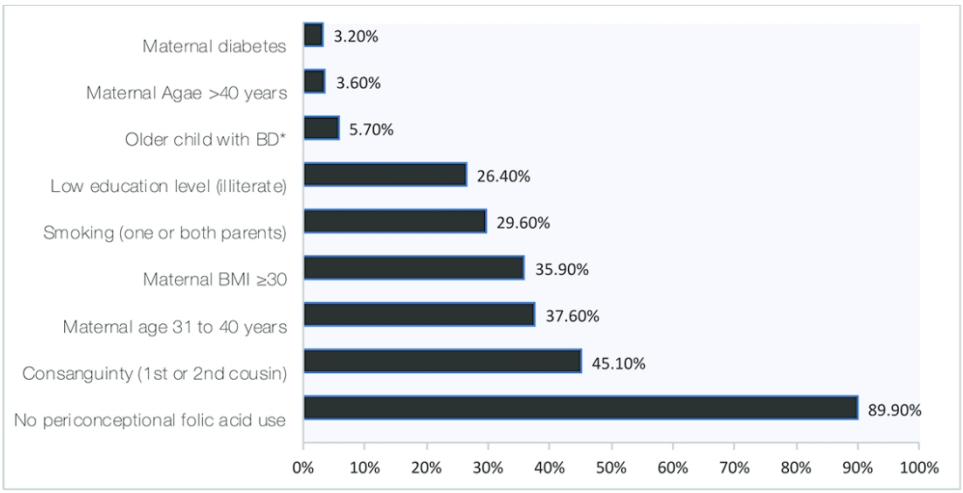
PSMMC, Prince Sultan Military Medical City; Sp Ab, Spontaneous abortions; ETOPFA, Elective termination of pregnancy for fetal anomaly.

*One control fetus was a Stillbirth.

Legend: Figure _2 Study population and distribution of pregnancies and their outcomes.

150x112mm (300 x 300 DPI)

Figure 3. Frequency among control subjects of selected risk factors for birth defects.



Legend:
BMI, pre-pregnancy maternal body mass index
BD, birth defect
*Frequency of prior child with BD computed among non-primiparous women

Legend: Figure _ 3 Frequency among control subjects of selected risk factors for birth defects.

99x79mm (300 x 300 DPI)

Supplement file

Appendix

Confidential

PSMMC

Booklet of

"Pattern of Fetal Malformations in a Saudi Population"

☐ Study ☐ Control

Local ID No.: _____ / Year 201

Mother's Name: _____

Mother's MRN: _____

Baby's Name: _____

Baby's MRN: _____

Date of Birth: ____ / ____ / ____

Contact No: Mobile (husband) _____

Mobile (wife) _____

Home _____

Confidential

Keep in a safe place

Pattern of Malformations Study – PSMMC

(Baby and mother)

Local ID No _____

D.O.B. (dd/mm/yy): ____ /_____ / _____ Year: 201__

D. O. B./ Year Unknown □

Sex: Male □ Female □ indeterminate □ Not known □

No. of babies delivered: Singleton 1 □ Twin 2 □ Triplet 3 □ Quadruplet 4 □ Quintuplet 5 □ Sextuplet 6 □

Not known 9 □

Specify twin type of birth, like or unlike sex, zygosity:_____

No. of malformed (in multiple set): No. _____ Not known □

Type of birth: Live Birth (LB). □ Still Birth (SB) □ Spontaneous Abortion □

TOP □ Not known □

Civil registration status LB □ SB □ No CR □ Not known □

Birth weight (g): _____ **Confirmed** □

Length of gestation (weeks): _____ **Confirmed** □

Survival beyond one week of age:

Yes □ No □ Alive at discharge <1 Week □ Not known □

Date of death (dd/mm/yy): ____/_____/_____ Year:_____

D. O. B. Mother (dd/mm/yy): _____/____/____ Year:_____ Confirmed □

Age of mother at delivery: _____

Pattern of Malformations Study – RMH

(Baby and mother)

Local ID No _____

Mother's residence code at conception: Province _____ District _____

Mother's residence code at delivery: Province _____ District _____

Total No. of previous pregnancies: None □ Number (___) Not known □

When discovered:

At birth □ Less than 1 wk □ 1-4 wk □ 1-12 m □ >12 m □ Prenatal diagnosis □

At abortion (sp) or termination □ Not known □ Postnatal diagnosis, age not known □

Condition at discovery: Alive □ Dead □ Not known □

Gestational age at discovery (wk): _____

First positive prenatal test:

US at <14 wks □ US at 14-21 wks □ US at ≥ 22 wk □ US GA unknown □
Serum/combined screening □ CVS □ Amniocentesis □ Other tests positive □

No positive test, all results negative □

Specify 'other' prenatal test: _____

Karyotype of infant/ fetus:

Performed, result known □ Performed, result unknown □

Not performed □ Probe test performed □ Failed □ Not known □

Specify karyotype:_____

Post mortem exam:

Performed, result known □ Performed, result unknown □

Macerated fetus □ Not known □ Not performed □

First surgical procedure:

Performed (or expected) in the first year of life □

Performed (or expected) after the first year of life □

Prenatal surgery □ No surgery required □

Too sever for surgery □ Not known □

Pattern of Malformations Study – PSMMC

(Prenatal Malformations)

Local ID No _____

	Code	**Text**
Syndrome:		
Malformation 1:		
Malformation 2:		
Malformation 3:		
Malformation 4:		
Malformation 5:		
Malformation 6:		
Malformation 7:		
Malformation 8:		

Pattern of Malformations Study – RMH

(All Malformations)

Local ID No _____

	Code	**Text**
Syndrome:		
Malformation 1:		
Malformation 2:		
Malformation 3:		
Malformation 4:		
Malformation 5:		
Malformation 6:		
Malformation 7:		
Malformation 8:		

McKusick code: _____

Aetiology:

Chromosome **C** □ Familial **F** □ Isolated **I** □ Multiple **M** □

New Dominant **ND** □ Other Genomic **OG** □ Syndrome **S** □ Teratogens **T** □ Inborn Error of Metabolism**IEM** □ Control **Co** □

View anomaly subgroup(s):

Pattern of Malformations Study – RMH

Local ID No _____

Assisted conception: No □ Induced ovulation only □ Artificial insemination □

In vitro fertilization □ Gamete intrafollopian transfer □

Intracytoplasmic sperm injection □ Egg donation □ Other□

Not known □

Mother's occupation: House wife □ Teacher □ Student □ Other □

Maternal Systemic illnesses;

None □ EHT □ Hypothyroidism □ CHD □

RHD □ CRF □ Asthma □ SCA □ SLE □

IDA □Anxiety □ Depression □ Epilepsy □

Other □ (specify)_____

Weight before pregnancy (Kg) _____

Current weight (Kg) _____

Mother's height (m) _____

Body Mass Index: <18.5 □ 18.5 – 24.9 □ 25 – 29.9 □
30.0 – 34.9 □ 35.0 – 39.9 □ ≥ 40.0 □

True DM: Yes□ No □

Gestational DM on Diet (GDOD) □

Gestational DM on Insulin (GDOI) □

Diabetes screening: GTT (result) 0 time:_____ 1hour:_____ 2 hours:_____

Booking RBS:_____

HbA1c _____

Infectious disease:

Tuberculosis: Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Rubella Before pregnancy □During pregnancy □ 1st T □ 2nd T □ 3rd T □

CMV Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Toxoplasmosis Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Syphilis Before pregnancy □ During pregnancy □ 1st T □ 2ndT □ 3rd T □

UTI Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Fever Before pregnancy □ During pregnancy □1st T □ 2nd T □ 3rd T □

FLU Before pregnancy □ During pregnancy □1st T □ 2nd T □ 3rd T □

Others Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

(Specify others) _____

Previous surgical history: Obstetrical/Gynaecological □

Specify; _____

Non Obstetrical □

Specify; _____

Pattern of Malformations Study – PSMMC

Family history & sociodemographic

Local ID No _____

Folic acid supplementation:

Al least 0.4 mg folic acid supplement taken regularly, starting periconceptionally □

Folic acid supplement taken irregularly or starting post-conceptionally □

No folic acid supplement taken or not recorded □

	ATC code	Text (**only** drugs taken in the 1st trimester of pregnancy)
Drugs 1:		
Drugs 2:		
Drugs 3:		
Drugs 4:		
Drugs 5:		

Consanguinity: Not related or relationship more distant than second cousin □

Relationship of second cousin or closer □ Not known □

Specific information on consanguinity:

_____

Sibs with anomalies: Same□ Other □ Same and other □ No □ Not known □

Previous sibs notified to the Saudi Malformations Registry: Yes □ No □ Not known □

Local ID of previous sibs notified to the SMR (1):_____

Local ID of previous sibs notified to the SMR (2):_____

Local ID of previous sibs notified to the SMR (3):_____

Mother's family with anomalies: Same □ Other □ Same and other □ No □

Not known □ Specify _____

Father's family with anomalies: Same □ Other □ Same and other □ No □

Not known □ Specify _____

Maternal education: Illiterate □ Elementary and lower secondary □

Upper secondary □ Tertiary □ Not known □

Family monthly income (SR):_____

(husband or combined husband and wife income)

Nationality: Saudi □ None Saudi □ Only father Saudi □ Only mother Saudi □

General additional comments:

_____

_____

Pattern of Malformations Study – PSMMC

Local Vars. (1)

Local ID No_____

Place of birth: _____

Birth order (in multiple set), (please write as 1st, 2nd, 3rd and so on): _____

Date of discovery (dd/mm/yy): _____/____/_____ **Year**: _____

Amniocentesis: Performed result positive □ Performed result not known □

Not performed □ Performed result negative □ Failed □ Not known □

Ultrasound: Performed result positive □ Performed result not known □

Not performed □ Performed result negative □Failed □ Not known □

Chorionic villous sampling: _____

Other techniques:

Performed result positive □ Performed result not known □ Not performed □

Performed result negative □ Failed □ Not known □

Specify other technique for prenatal diagnosis: _____

(Cordocentesis,..etc)

No. of previous spontaneous abortions: None □ 1 □ 2 □ 3 □ 4 □
5 □ 6 □ 7 □ 8+ □ Not known □

No. of previous TOP: None □ 1 □ 2 □ 3 □ 4 □ 5 □
6 □ 7 □ 8+ □ Not known □

No. of previous live births: please write the exact No (1-20) _____ Unknown □

No. of previous stillbirths: None □ 1 □ 2 □ 3 □ 4 □
5 □ 6 □ 7 □ 8+ □ Not known □

Mode of transmission: Familial □ De novo □ Not known □

Habitual exposures: Smoking F179 □ Oude F159 □

Other (specify) _____

Unusual exposures: X-ray during pregnancy (any)□ Nuclear medicine during pregnancy □

(Radiation & chemical)

Date of birth of father: ____/____/_____ **Year**: _____ **Age of father**: _____

Occupation of father: Soldier □ Officer □ Civilian □

Pattern of Malformations Study – RMH

Local Vars. (2)

Local ID No_____

Date of last LMP: _____/_____/_____

Certainty of LMP: **C**ertain □ Uncertain □ No LMP □ Not known □

Labor: Spontaneous □ Induced □ No labor □

Delivery: Spontaneous □ EMLSCS □ ELSCS □ ABD □
Instrumental □

Sources of information 1:

Notes in routine scan □ Birth notification or notification of malformation at birth □

Hospital case notes □ Death or stillbirth certificate □Prenatal diagnosis □

Lab. report (cytogenetic … etc) □ Postmortem exam □ Other □ Not known □

Sources of information 2: please insert as in one _____

Sources of information 3: please insert as in one _____

Sources of information 4: please insert as in one _____

Sources of information 5: please insert as in one _____

Racial information Mother, Tribe code _____ Father, Tribe code_____

Same tribe □ Different tribe □

Otaibi 1, Mutairi 2, Shuhri 3, Asiri 4, Shamrani 5, Onazi 6, Shahrani 7, Zaharani 8, Harbi 9, Qahatni 10, Ghamdi 11,Shamari 12, Asmari 13, Ahmari 14, Amri 15, Dawsari 16, Harthi 17, Subaie 18, Ajman 19, Not known (99)

Other 20, specify: _____

Chronic illness of father (including drug abuse):_____

Confirmation of diagnosis:

Follow up needed for further confirmation □ Confirmed at <6 months □

Confirmed at 6-12 m □ Confirmed at 12-18 m □ Confirmed at 18-24 m □

Not confirmed, lost for follow up □

Source: Booked □ Un booked □ Referred □

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Observational, prospective cohort design with a nested case-control study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a BD, for an overall prevalence of 412/10000 total births, or 1 in 24 births.
		Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Birth defects (BD) are increasingly recognized as a global health priority because of their lifelong impact on health and survival.[1,2] BD affect approximately an estimated 1 in 33 newborns, contribute each year to 300,000 deaths in the first month of life, and are associated with 3·2 million birth-related disabilities.[3] Accordingly, the World Health Assembly has emphasized the urgent need for action to help prevent, diagnose, and provide timely intervention.[1]
Objectives	3	State specific objectives, including any prespecified hypotheses	4	In this study, we implemented an integrated approach to generate these data in well-defined cohort of women, tracked from mid-gestation through the second year of life of their children, to assess concurrently the burden of potentially modifiable risk factors, the occurrence of BD, and survival of affected children, as a basis for better prevention and care.[4]
		Methods		
Study design	4	Present key elements of study design early in the paper	5	Observational, prospective cohort design with a nested case-control study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution with 1250 beds and

			*15 -24	approximately 10,000 annual deliveries. PSMMC primarily serves Saudi army personnel and their families and is a referral center for the other 16 military hospitals in the Kingdom of Saudi Arabia. Study period 1 July 2010 through 30 June 2013. *Figures and tables
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case 2,3 ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5 7	All pregnant Saudi women who are eligible for their antenatal care at PSMMC were included and their pregnancy outcome. Mothers who delivered elsewhere were not included even if they have their antenatal care at PSMMC. All mothers who care pregnant with an affected foetus (birth defect) are include. For controls a random sample of women in the cohort with a normal USS. The random sample was generated daily by taking the morning list of scheduled USS and using a random number generator (http://www.random.org) to select potential controls
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	Evaluations for specific BD, Nested Case-Control Study, Follow up, Case review, coding, classification.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*n/a*
Bias	9	Describe any efforts to address potential sources of bias	5	Pregnancies referred from other hospitals because of a

				diagnosis of a fetal anomaly, and babies with BD delivered elsewhere and referred to PSMMC for evaluation and management
A	10	Explain how the study size was arrived at	5	All mother delivered at PSMMC during the study period were included

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9	Chi-square or Fisher's exact tests.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	Odd ratios for BD were computed first via univariate logistic regression, then with a multiple logistic model. The latter was developed by first including uncorrelated significant factors (p <0·05) from the univariate analysis, then reducing the number of variables by stepwise backward elimination for a more parsimonious model.
		(*b*) Describe any methods used to examine subgroups and interactions		n/a
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed		n/a
		Case-control study—If applicable, explain how matching of cases and controls was addressed	7	randomization
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy		n/a
		(*e*) Describe any sensitivity analyses		n/a
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-12	Figure 2
		(b) Give reasons for non-participation at each stage		n/a
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	23	Tables 3
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8	2 – 5 years. Follow up. Case-infants (with BD) and control-infants were examined in the dedicated study clinic at 1, 6, 12, 18 and 24 months of age
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9	1179 as cases and 1262 as controls

		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5,15-21	Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a BD, for an overall prevalence of 412/10000 total births, or 1 in 24 births. Of these 1179 cases, 38 (3.2%) were stillbirths and 18 (1.5%) were electively terminated because of lethal malformations (13 with anencephaly, 3 with severe hydrops fetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis). The antenatal detection rate among women who has had antenatal ultrasound screening examination was 70.6%(561/795), tables b 1,2,3
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		n/a
Discussion				
Key results	18	Summarise key results with reference to study objectives	1	In this cohort of women, the burden of potentially modifiable risk factors included high rates of diabetes (7.3%), maternal age >40 years (7.0%), consanguinity (54.5%), and lack of periconceptional folic acid use (90.8%). The birth prevalence of BD was 41.2/1,000 births (1179 cases / 28646 live births and stillbirths), driven mainly by congenital heart disease (14.8 per 1000), renal malformations (11.3), neural tube defects (1.9), and chromosomal anomalies (2.7). Mortality for live births with BD at 1 and 2 years of age was 14% and 15.8%, respectively.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	Single centre study, Army personnel household only
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		High prevalence of birth defects, multiple modifiable risk factors.
Generalisability	21	Discuss the generalisability (external validity) of the study results		
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3	This project was supported by King Abdul-Aziz City for Science and Technology (KACST) through the National Science, Technology and Innovation Plan (NSTIP). Project No: 09-MED748-21. The funder has no role in this study.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Congenital anomalies and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

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Congenital anomalies and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

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Abstract

Objective: To assess the three key issues for CAs prevention and care, namely, CA prevalence, risk factor prevalence, and survival, in a longitudinal cohort in Riyadh, Saudi Arabia.

Setting: Tertiary care centre, Riyadh, Saudi Arabia.

Participants: Saudi women enrolled during pregnancy over three years and their 28,646 eligible pregnancy outcomes (births, stillbirths and elective terminations of pregnancy for foetal anomalies [ETOPFAs]). The nested case-control study evaluated the CA risk factor profile of the underlying cohort. All CA cases (1,179) and unaffected controls (1,262) were followed through age 2 years. Referred mothers because of foetal anomaly and mothers who delivered outside the study centre and their pregnancy outcome were excluded.

Primary outcome measures: Prevalence and pattern of major CAs, Frequency of CA-related risk factors, and survival through age 2 years.

Results: The birth prevalence of CAs was 412/10,000 births (95% CI 388.6 to 434.9), driven mainly by congenital heart disease (148 per 10,000) (95% CI 134 to 162), renal malformations (113, 95% CI 110 to 125), neural tube defects (19, 95% CI 25.3 to 38.3), and chromosomal anomalies (27, 95% CI 21 to 33). In this study, the burden of potentially modifiable risk factors included high rates of diabetes (7.3%, OR 1.98, 95% CI 1.04 to 2.12), maternal age >40 years (7.0%, OR 2.1, 95% CI 1.35 to 3.3), consanguinity (54.5%, OR 1.5, 95% CI 1.28 to 1.81).The mortality for live births with CAs at 2 years of age was 15.8%.

Conclusions: This study documented specific opportunities to improve primary prevention and care. Specifically, folic acid fortification (the neural tube defect prevalence was >3 times that theoretically achievable by optimal fortification), preconception diabetes screening and consanguinity-related counselling could have significant and broad health benefits in this cohort and arguably in the larger Saudi population.

Strengths and limitations of this study:

- Babies with CAs are diagnosed prospectively, prenatally, and postnatally and followed up to 2 years of age.
- Involvement of multidisciplinary teams in establishing the final diagnosis.
- Inclusion of elective termination of pregnancies with lethal CAs and stillbirths.

- Single-centre study. The pregnancy cohort was mainly from families of Saudi army personnel dependents, which could be a limiting factor.

The original protocol of the study: Supplementary file.

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Competing interests statement:

All authors have completed the ICMJE uniform disclosure from www.icmje.org-coi_disclosure.pdf and declare no support from any organization for the submitted research article; no financial relationship with any organization that might have an interest in the submitted work

in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Key words: Congenital anomalies, Prevalence, Risk factors, Prevention, and Outcome

Congenital anomalies and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

Introduction

Because of their lifelong impact on health and survival, congenital anomalies (CAs) are increasingly recognized as a global health priority.[1] [2] With better control of infections and other causes of early mortality, CAs are becoming increasingly important drivers of child survival and health in low- and middle-income countries.[1] [3] CAs affect approximately an estimated 1 in 33 newborns, contribute each year to 300,000 deaths in the first month of life, and are associated with 3·2 million birth-related disabilities.[3] Accordingly, the World Health Assembly has emphasized the urgent need for action to help prevent, diagnose, and provide timely interventions.[1] Data on the prevalence and mortality associated with CAs are scarce in many low- and middle-income countries, with most reports

originating in high-income areas. For example, in a population-based study of livebirths with CAs in the United Kingdom, the 20-year survival rate was 85.5%.[4] Similarly, the 25-year survival rate among livebirths with CAs in New York state was 82.5%,[5] with a documented improvement from the 1980s (78.1% from 1983 –1988) to the early 2000s (89.3% from 2001- 2006). Among CAs, the major drivers of mortality were cardiovascular anomalies (51.1%) and chromosomal anomalies (33.1%). In Korea, infant mortality among babies with CAs was 6.8/10,000 live births, and foetal mortality was 13.5/10,000 total births.[6]

However, local action, whether focused on primary prevention or on improving care, is most effective when based on reliable information about the key indicators of the causes and outcomes of CAs in the underlying population. In this study, we implemented an integrated approach to generate these data in a systematic cohort of women, tracked from mid-gestation through the second year of life of their children, to assess the prevalence of CAs, the burden of potentially modifiable risk factors, and the survival of affected children, as a basis for better prevention and care.[7]

Methods

Setting. The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution with 1,250 beds and approximately 10,000 annual deliveries. PSMMC primarily serves Saudi army personnel and their families and is a referral centre for the other 16 military hospitals in the Kingdom of Saudi Arabia. The foetal medicine unit includes advanced imaging facilities, including 3D and 4D scanning. The paediatric department includes all major subspecialties, including medical genetics, paediatric surgery, and paediatric cardiology.

Study design This is an observational, prospective cohort study with a nested case-control study. The eligible cohort includes pregnancies of women who had their antenatal care and their routine antenatal anomaly ultrasound scan examination (USS) between 18 weeks and 22 weeks of gestation at PSMMC from 1 July 2010 through 30 June 2013 (figure 1).

In addition, Saudi women who are eligible for their antenatal care at PSMMC, but who did not have an antenatal screening ultrasound examination and later delivered at PSMMC, are also included in the study.

Inclusions and exclusions*.* Pregnancy outcomes included in the study were live births, stillbirths (foetal deaths at 20 weeks' gestation or later), and pregnancies electively terminated because of foetal anomalies (ETOPFAs). The study excluded spontaneous abortions, pregnancies

referred from other hospitals because of a diagnosis of a foetal anomaly, and babies with CAs delivered elsewhere and referred to PSMMC for evaluation and management.

Evaluations. Initial antenatal screening tests included a complete blood count, liver and kidney function tests, blood group and antibody screening, rubella and Toxoplasma status, hepatitis B screen, random blood sugar and HbA1c levels, VDRL, sickle cell screen and urine analysis. A glucose tolerance test was performed at 24-28 weeks of gestation.

When a structural birth defect was diagnosed or suspected antenatally, mothers were counselled by one of the investigators (MSR, AMK), demographic and exposure information was gathered, and both parents were scheduled within 2-4 weeks to attend a dedicated clinic developed for the study. At that time, a detailed diagnostic and care plan was developed, which may have included further blood tests and foetal imaging, or amniocentesis, chorionic villous and/or foetal blood sampling for genetic studies. Consent was requested for cord blood collection for future molecular testing.

On the first day of life, all newborns in the cohort (with and without CAs) were examined by a paediatrician as part of the first clinical screening

examination. Babies with CA, whether identified antenatally or postnatally, underwent diagnostic investigations as clinically indicated (e.g., echocardiogram, cardiac catheterization, or other imaging studies; metabolic and molecular testing) and were referred to the appropriate subspecialists. A clinical geneticist evaluated all babies with suspected syndromes or multiple CAs. A letter was distributed to all clinical departments describing the study and requesting that they inform the study team about all infants and children with CAs born at PSMMC.

Evaluations for specific congenital anomalies. If congenital heart disease (CHD) was detected or suspected antenatally on USS examination, the mother was referred to the paediatric cardiologist for a foetal echocardiogram. All these infants were also re-evaluated after birth by a paediatric cardiologist. Isolated atrial septal defects (ASDs II) were re-evaluated at 6 to 12 months of age, and if the echocardiogram showed no evidence of ASD II at the time, the infant was not considered a case. Congenital hydronephrosis (HN) was graded using the Society of Foetal Urology grading system.[8] Babies with grade one HN were given a repeat US examination within the first year of life; if HN had resolved, the baby was not considered a case. Chromosomal analysis was performed according to standard procedures, and a minimum of 20 metaphases were analysed (Applied Imaging CytoVision Karyotyping System). Reports followed the International System of Human Cytogenetic Nomenclature (ISCN 2013). Molecular studies were performed at the

Biocenthia Health Group in Germany (http://www.bioscientia.de/en/), the Mayo Medical Laboratories in the United States, and at the Developmental Genetic Laboratory at King Faisal specialist hospital and research centre in Saudi Arabia.

Nested case-control study. The nested case-control study included as cases all women in the cohort with a pregnancy diagnosed with a CA and as controls a random sample of women in the cohort with a normal USS. The random sample was generated daily by taking the morning list of scheduled USS and using a random number generator (http://www.random.org) to select potential controls so that the control sample would eventually be at least as large as the estimated total number of cases. If a woman initially selected as a control had a pregnancy diagnosed with a birth defect at the initial date or later, she was then included in the case group. Investigators administered an in-person structured interview to case and control mothers. The interview included information about age (for both parents); weight before pregnancy; height; parity; family income (father's income or combined parental income if the mother worked); maternal education level (illiterate, primary school graduate, secondary school graduate, or university graduate); parental occupation (mother; housewife, teacher, student and others, father; soldier, officer or civilian employee); folic acid (FA) supplement use (regular use before and during the 1st trimester of pregnancy; irregular or only postconception use; no use or uncertain use

as per the mother's report); parental smoking (one or both parents smoking during the current pregnancy); maternal radiation exposure during the first trimester; maternal diabetes (overt or gestational) as defined by the International Association of Diabetes and Pregnancy study groups [9] and HbA1c level; family history of CAs (in previous pregnancies and in maternal or paternal lineages); drug and medication use during the first trimester; and chronic maternal systemic illnesses (hypothyroidism, epilepsy, depression, essential hypertension, and bronchial asthma). Consanguinity was defined as women being first or second cousins to their husbands (supplementary file).

Follow-up. Case infants and control infants were examined in the dedicated study clinic at 1, 6, 12, 18 and 24 months of age. Two neonatologists and a clinical geneticist supervised the clinic. Babies with CAs also continued to be followed by the relevant subspecialty clinics. The remaining cohort (babies without CAs not selected as controls) was re-examined at 4-8 weeks by the paediatrician for a second screening examination. A head ultrasound and a postductal pulse oximetry reading were completed in all babies attending the clinics. If the O_2 saturation was below 95%, the baby was referred to the paediatric cardiologist for evaluation. If any CAs were detected at the second screening examination, the babies were referred to the genetics clinic for further evaluation and diagnosis. If the second screening examination proved to be normal, then no further follow-up was arranged. However, if CAs

were discovered later in babies up to 2 years of age, they were included in the study.

Case review, coding, classification. Congenital anomalies were coded following the International Statistical Classification of Diseases and Related Health Problems, 10th revision, (ICD10, WHO-2010) according to the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) recommended procedures.[10] We did not include isolated minor anomalies or prematurity-related conditions such as patent ductus arteriosus or hydrocephalus complicating intraventricular haemorrhage diagnosed in preterm babies (<37 completed weeks of gestation). Data were entered in a version of EUROCAT Data Management Program (EDMP) modified to include control records and the additional variables generated by the case-control study and the follow up.

Patient and public involvement: Our long-term experience with the families and their offspring has helped us to shape the research question and the study design. All families recruited were informed about the study objectives. None of the parents were involved in the study design. Consent for cord blood samples for future DNA analysis was obtained from the mothers in the nested case-control study. The study results were disseminated to the community and to the professional health care

provider through social media, newspapers, presentation at various conferences, and scientific publications.

Institutional ethics review. The study was approved by the Ethical Committee of the PSMMC (Project No. 366, series of 2009).

Statistical analysis.

Odds ratios for the association between risk factors and CAs were estimated using multiple logistic regression in a two-step process. An initial set of variables was selected by univariate logistic regression as being associated with CA risk ($p<0.05$). Variables highly correlated with other variables (e.g., insulin use) were not entered into the model. This initial variable set was then reduced by stepwise backward elimination to produce a more parsimonious model. The final model retained the following covariates: consanguinity, maternal age group, education level, diabetes and history of siblings with a congenital anomaly. The model fit was assessed with the Hosmer and Lemeshow's goodness of fit test and by calculating Nagelkerke R2. Statistical analysis was performed with SPSS for Windows, version 15 (SPSS Inc., Chicago, Illinois).

Results

Of the 31,032 birth outcomes of the 30,351 women followed since pregnancy, 30,753 (99·1%) occurred at PSMMC (figure 2). Of these,

2,107 were spontaneous abortions (6·9%) and were not included in the study, leaving 28,646 eligible births (27,726 singleton births and 920 multiple births). The overall stillbirth rate was slightly less than 1% (figure 2).

Birth defect occurrence, detection, and mortality. Of the 28,646 eligible pregnancy outcomes, 1,179 were diagnosed with a CA, for an overall prevalence of 412/10,000 (95% CI 388.6 to 434.9) total births, or 1 in 24 births. Of these 1,179 cases, 38 (3.2%) were stillbirths, and 18 (1.5%) were electively terminated because of lethal malformations (13 with anencephaly, 3 with severe hydrops foetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis) (table 1). The antenatal detection rate among women who has had an antenatal ultrasound screening examination was 70.6% (561/795). In 90% of these cases (505/561), the diagnosis was made by ultrasound scan at 22 weeks of gestation or later. Of the 618 babies diagnosed postnatally, 296 (47.9%) were diagnosed at birth, 239 (38.7%) between 1 and 7 days, 29 (4.7%) between 1 and 4 weeks, 52 (8.4%) between 1 and 12 months, and 2 (0.3%) after one year of age. Mortality among livebirths with CAs (table 1) was 14.1% in the first year, nearly half of which occurred in the first week of life, with a total mortality of 15.8% by the end of the second year of life. Mortality at two years was 0.9% in the unaffected cohort (0.24% for live births). Among the controls, there were 8 stillbirths, two deaths because of prematurity and its complications and one death at 2 years of age because of acute fulminating leukaemia.

Contribution of specific congenital anomalies.

Approximately half of the overall birth prevalence was due to congenital heart disease and central nervous system anomalies. Neural tube defects occurred at a rate of 19 per 10,000 (95% CI, 13.8 to 23.9) (1 in 526 births). Severe CHD occurred at a rate of 32 per 10,000 (95% CI, 25.3 to 38.3) (1 in 313 births) and accounted for 21.4% of all CHD cases. Chromosomal anomalies whose risk is associated with increased maternal age (trisomies 21, 18, and 13) occurred with a combined prevalence of 25 per 10,000 (95% CI, 19.6 to 31.3) (1 in 392 births). Trisomy 21 accounted for most cases of chromosomal anomalies, with a prevalence of 22 per 10,000 (95% CI, 16.7 to 27.4) or 1 in 456 births (table 2).

Two-thirds of all cases of CAs (773/1179, 65.6%) were isolated (e.g., they involved a single body system) (table 3).

Risk factors. As a proxy of risk factor prevalence in the underlying population, we used the frequency of selected maternal or parental risk factors for CAs among controls in the nested case-control study (figure 3). The most frequent potentially modifiable factors included lack of periconception folic acid supplement use, consanguinity, high body mass index, advanced maternal age, smoking (first or second-hand) and maternal diabetes. Nearly 6% of non-primiparous women had one prior child with a major CA. In the univariate analysis, the nested case-control

study (table 4) detected overall increased odds ratios for all CAs combined for consanguinity, advanced maternal age, high parity, maternal illiteracy, maternal university education, X-ray exposure during pregnancy, maternal diabetes, and positive family history of CA in a sibling. Increased odds ratios with confidence intervals, including unity, were also found for maternal depression and hypertension (table 4). In the multiple logistic regression model, only first-degree consanguinity (OR 1.5, 95% CI 1.28 to 1.81), maternal age of more than forty years (OR 2.1, 95% CI 1.35 to 3.3), maternal illiteracy (OR 1.4, 95% CI 1.17 to 1.7), maternal university level education, (OR 1.74, 95% CI 1.24 to 2.44), maternal diabetes mellitus (OR 1.98, 95% CI 1.33 to 2.95) and history of a sibling with an anomaly (OR 1.49, 95% CI 1.04 to 2.12) were retained in the model (table 5). The Hosmer and Lemeshow goodness of fit p value was 0.08, and Nagelkerke R^2 was 0.055, explaining 6% of the effect on CAs.

Of the 223 mothers with DM who had CA-affected foetuses (223/1,179, 18.9%), 36 (3%) had overt DM (ODM), and 187 (15.7%) had gestational DM (GDM). Of the mothers with GDM, 50 (26.7%) required insulin. Among the controls, 200 mothers had diabetes (200/1,179, 15.8%), of whom 12 (0.9%) had ODM, and 188 (15.9%) had GDM. Of the latter, 29 (14.5%) required insulin.

Discussion

This longitudinal study of CAs in a pregnancy cohort in Saudi Arabia, followed from mid-gestation through age 2 years, had three integrated aims: to describe the population's risk factor profile, document the associated birth prevalence of CAs, and assess survival as a critical health outcome.[7] Gathering information about these three critical areas is crucial when planning and evaluating policies and interventions, be they aimed at primary prevention (e.g., folic acid fortification to prevent neural tube defects) or at improving care.

The burden of CAs was high in this population. The study documented a remarkably high birth prevalence of CAs of 412 per 10,000 or 1 in 24 total births. This rate is higher than that reported in studies from many high-income countries, as those reported by EUROCAT (261/10,000 births),[11] BINOCAR (206/10,000 births),[12] and the Bradford (BIB) study (305/10,000).[13] This prevalence of CAs is also higher than that previously reported from Saudi Arabia (115 to 257 per 10,000 live births).[14-16] Although some studies report an even higher prevalence, e.g., such as an antenatal CA prevalence of 521/10,000 pregnancies screened, and a prevalence among livebirths of 465/10,000,[17] these figures may be overestimates of the true prevalence because of the inclusion of mothers referred from other institutions. In the current study, we strove to obtain as complete an ascertainment as possible by initiating follow-up in pregnancy and extending it through the second year of life, by including stillbirths and elective termination of

pregnancies for foetal anomalies (ETOPFAs), and by successfully including some genetic conditions that tend to be diagnosed after the newborn period.

However, the high prevalence of CAs is likely to be due not only to the completeness of the ascertainment but also to the high frequency of adverse risk factors in the underlying population, as documented in the controls of the nested case-control study. When focusing on factors that are potentially modifiable, three such factors seem to stand out. The first is insufficient folic acid use in this cohort (<10% in the periconception period). The rate of neural tube defects was 19 per 10,000/births (table 2), at least three times higher than the rate of 6 per 10,000/births, which seems achievable by providing sufficient folic acid to women of childbearing age.[18 19] Although legislation requiring the mandatory fortification of flour had been in place in Saudi Arabia for years prior to this study (Kingdom of Saudi Arabia, 2000; Food fortification initiative, 2013),[20 21] our findings suggest that there are gaps in coverage or effectiveness, which could be evaluated with nutrition or blood folate surveys. Such information would provide important evidence to improve folate sufficiency in the population, with its attendant health benefits, including a substantial reduction in the burden of neural tube defects. Because of the inclusion of stillbirths and pregnancy terminations, this study also provides a fuller estimate of the potential benefits of primary prevention than if only livebirths had been identified (representing just over half of all cases, 30/54).

The second factor is maternal diabetes (tables 4 and 5). Diabetes is an established risk factor for many CAs, and diabetes control before conception has been shown to reduce and nearly normalize CA risk.[9 22 23] Several avenues for preventing diabetes and its health effects are available, including population screening (many diabetic women are undiagnosed), health care and counselling, and education on healthy lifestyle and dietary choices starting from childhood. The current reported prevalence in Saudi Arabia of overt diabetes in women above age 40 years ranges from 7.7% – 21.7%. [24 - 26] In the study cohort, overt diabetes was observed in 2% of women and increased in women 30 years old or older. Al-Nozha and colleagues [27] reported a prevalence of overt diabetes of 11.6% in women aged 30-39 years and >22% in women aged ≥40 years compared to 2.7% and 7.1% in our study, respectively. Though lower than these estimates, the prevalence of overt diabetes in the study cohort is alarmingly high.

Third, we observed a high rate of parental consanguinity (54.5%), especially first-cousin marriages (48.0%). These marriages are common in many parts of the Middle East, Africa, and the Indian subcontinent,[28-30] with one estimate suggesting that “one billion people live in communities with a preference for consanguineous marriage” (Hamamy, 2012).[29] This preference has deep social roots. Nevertheless, education combined with preconception and premarital counselling can be important prevention strategies by focusing on increasing awareness to allow couples to make more informed choices. Close consanguinity is a known

risk factor for CAs,[30] as well as Mendelian conditions such as inborn errors of metabolism (occurring in 1 in 770 births in this study), as confirmed in prior reports from Saudi Arabia and from the world literature. [31 32]

We did not diagnose cases of congenital rubella syndrome. This is likely due to the active immunization programme in Saudi Arabia, with a measles, mumps and rubella vaccine uptake of 97%. In addition, preschool age girls are given a booster vaccine against rubella.

In a prior publication, we reported a low regular (periconception) folic acid (FA) intake (9.7%) in this study population [33] and suggested fortification of rice in addition to wheat, complemented by education programmes supporting FA supplementation, as an efficient strategy to achieve folate sufficiency in the population.

Finally, our findings emphasize the impact of CAs in this population by documenting not only birth prevalence but also the associated early mortality (table 1), which was 15.8% by the second year of life (nearly all in the first year). Further supporting the high impact of CAs are the findings by Majeed-Saidan and colleagues,[34] who reported that 36% of deaths in a large neonatal intensive care unit in Riyadh were due to lethal CAs. These findings highlight the crucial importance and urgency to improve care in addition to primary prevention.

This study demonstrated the importance of the "triple surveillance" programme, suggested by Botto and Masteroiacova,[4] for identifying the risk factors for CAs (causes), estimating the burden of the disease (prevalence), and assessing disease outcome (mortality). This will ultimately lead to disease burden reduction or prevention by instituting appropriate interventions.

The study has limitations. Because of the cohort design, the resulting sample size did not allow a more detailed analysis of specific CA groups. Estimates of some key risk factors, such as folic acid insufficiency, were based on maternal reports (e.g., reported supplement use) rather than biomarkers. Furthermore, the pregnancy cohort was mainly from families of Saudi army personnel dependents. Although the Saudi Army recruits from all sectors of Saudi society, a broader survey of the Saudi population would provide additional information to better assess gaps and opportunities for prevention and care nationwide.

Conclusion. This longitudinal surveillance programme that encompassed the causal chain from risk factors to health outcomes documented several opportunities to reduce the burden of CAs through primary prevention and better care. Folic acid fortification, preconception

diabetes screening, and consanguinity-related counselling could have significant health benefits in this cohort and arguably in the larger Saudi population, particularly if associated with a national CA monitoring programme to support and track the impact of interventions.

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References

1. World Health Organization. Sixty -Third World Health Assembly. CA Report by the Secretariat, A63/10. Geneva, Switzerland: World Health Organization, 2010.

2. World Health Organization. Global Health Observatory (GHO) data. Under-five mortality 2016. http://www.who.int/gho/child_health/mortality/mortality_under_five_text/en/ (accessed 12 December 2017).

3. Christianson AL, Howson CP, Modell B. Global report on CA: the hidden toll of dying and disabled children. White Plains (NY): March of Dimes Defects Foundation 2006.

4. Tennant PWG, Pearce MS, Bythell M, *et al.* 20-year survival of children born with congenital anomalies:

a population-based study. Lancet 2010; 375: 649–56.

5. Wang Y, Hu J, Druschel CM, *et al.* Twenty-Five–Year Survival of Children with Birth Defects in New York State: A Population-Based Study. Birth Defects Research (Part A) 201;1 91:995-1003.

6. Ko HS, Kim DJ, Chung Y, *et al*. A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea. BMJ Open 2017;7: e017963. doi:10.1136/bmjopen-2017-017963

7. Botto LD, Mastroiacovo P. Triple surveillance: a proposal for an integrated strategy to support and accelerate birth defect prevention. Ann. N. Y. Acad. Sci 2018; (1414):126-36.

8. Avni FE, Maugey-Laulom B, Cassart M, *et al*. Foetal genitourinary tract. In: Callen PW, ed. Ultrasonography in Obstetrics and Gynecology. 5th Ed. New York: W.B. Saunders 2007; 640-75.

9. Metzger BE, Gabbe SG, Persson B, *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of

hyperglycemia in pregnancy. *Diabetes Care* 2010; 33(3): 676–82. doi: 10.2337/dc09-1848.

10. EUROCAT. Eurocat Guide 1.3. Instructions for registration and surveillance of congenital anomalies. Belfast, Northern Ireland University of Ulster 2005. http://www.eurocat-network.eu/content/Section%202.4-%2027_Oct2016.pdf

11. EUROCAT. Prevalence Tables, 2011-2015 http://www.eurocat-network.eu/newprevdata/showPDF.aspx?winx=1896&winy=940&file=allsubgroups.aspx 2015. (accessed 12 December 2017).

12. Springett A, Budd J, Draper ES, *et al*. Congenital Anomaly Statistics 2012 England and Wales, London 2014. www.binocar.org/content/Annual%20report%202012_FINAL_nologo.pdf.

13. Sheridan E, Wright J, Small N, *et al*. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet 2013; 382(9901): 1350–9. doi: 10.1016/S0140-6736(13)61132-0.

14. Al Bu Ali WH, Balaha MH, Al Moghannum MS, *et al*. Risk factors and birth prevalence of CA and inborn errors of

metabolism in Al Ahsa, Saudi Arabia. Pan Afr Med J 2011; 8: 14.

15. Fida NM, Al-Aama J, Nichols W, *et al*. A prospective study of congenital malformations among live born neonates at a University Hospital in Western Saudi Arabia. Saudi Med J 2007; 28(9): 1367–73.

16. Refat MY, Al-Moghanem M, McDonald, *et al*. Major CA at King Fahd Hofuf Hospital: Prevalence, risk factors and outcome. Ann Saudi Med 1995; 15(4): 339–43.

17. Sallout B, Obedat N, Shakeel F, *et al*. Prevalence of major congenital anomalies at King Fahad Medical City in Saudi Arabia: a tertiary care centre-based study. Ann Saudi Med 2015; 35(5): 343–51.

18. Kancherla V, Oakley GP Jr, Brent RL. Urgent global opportunities to prevent CA. Semin Foetal Neonatal Med 2014; 19(3): 153–60.

19. Youngblood ME, Williamson R, Bell KN, *et al*. Update on global prevention of folic acid-preventable spina bifida and anencephaly. CA Res A Clin Mol Teratol 2013; 97(10): 658–63. doi: 10.1002/CAra.23166. Epub 2013.

20. Kingdom of Saudi Arabia, Ministry of health, Nutritional department directive. Number 652/1/26, 2000; 13/09/2000.

21. Food Fortification Initiative. (2013). http://www.ffinetwork.org/country_profiles/country.php?record=194 (accessed 12 December 2017).

22. Kitzmiller JL, Wallerstein R, Correa A, *et al.* Preconception care for women with diabetes and prevention of major congenital malformations. CA Res A Clin Mol Teratol 2010; 88(10): 791–03. doi: 10.1002/CAra.20734.

23. Simeone RM, Devine OJ, Marcinkevage JA, *et al* Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. Am J Prev Med 2014; 48(2): 195–204. doi: 10.1016/j.amepre.2014.09.002.

24. Al-Nuaim AR, Al-Rubean K, Al-Mazrou Y, *et al*. Prevalence of diabetes mellitus, obesity and hypercholesterolemia in Saudi Arabia: national chronic disease survey. Riyadh (KSA): Ministry of Health and King Saud University. ISBN: 1995; 9960-603-01-6.

25. El-Hazmi M, Warsy A, Al-Swailem AR, *et al*. Diabetes mellitus as a health problem in Saudi Arabia. East Mediterr Health J 1998 (4): 58–67.

26. Warsy AS, el-Hazmi MA. Diabetes mellitus, hypertension and obesity--common multifactorial disorders in Saudis. East Mediterr Health J 1999; 5(6): 1236–42.

27. Al-Nozha MM, Al-Maatouq M, Al-Mazrou YY. *et al*. Diabetes mellitus in Saudi Arabia. Saudi Med J 2004; 25(11): 1603–10.

28. El-Mouzan MI, Al-Salloum AA, Al-Herbish AS, *et al*. Regional variations in the prevalence of consanguinity in Saudi Arabia. Saudi Med J 2007; 28(12): 1881–4.

29. Hamamy H. Consanguineous marriages: Preconception consultation in primary health care settings. J Community Genet 2012; 3(3): 185–92.

30. Majeed-Saidan MA, Ammari AN, AlHashem AM, *et al.* Effect of consanguinity on CA in Saudi women: results from a nested case-control study. CA Res A Clin Mol Teratol 2015; 103(2): 100–4. doi: 10.1002/CAra.23331.

31. Mak CM, Lee HC, Chan AY, *et al*. Inborn errors of metabolism and expanded newborn screening: review and update. Crit Rev Clin Lab Sci 2013; 50(6): 142–62. doi: 10.3109/10408363.2013.847896.

32. Moammar H, Cheriyan G, Mathew R, *et al*. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med 2010; 30(4): 271–7. doi: 10.4103/0256-4947.65254.

33. Al Rakaf MS, Kurdi AM, Ammari AN, *et al*. Patterns of folic acid use in pregnant Saudi women and prevalence of neural tube defects — Results from a nested case–control study. Preventive Medicine Reports 2 (2015) 572–576.

34. Majeed-Saidan MA, Kashlan FT, Al-Zahrani AA, *et al*. Pattern of neonatal and postneonatal deaths over a decade (1995--2004) at a Military Hospital in Saudi Arabia. Saudi Med J 2008; 29(6):879-83.

Tables

Legend: Table 1 Distribution and rates of congenital anomalies (CA) among the cohort's pregnancy outcomes, and associated mortality.

	Total cohort		With CA			Timing of CA detection				Mortality among livebirths with CA					
						Prenatal		Postnatal		Overall (0-2 years)		1st week		Total 1st year	
Birth outcome	No	%	No.	%	Rate /10000	No.	%	No.	%	No.	%	No.	%	No.	%
Live births	28 369	99	1 123	95.3	396	505	45.0	618	55	177	15.8	64	5.7	158	14.1
Stillbirths	259	0.9	38	3.2	1467	38	100								
ETOPFA	18	0.1	18	1.5	10000	18	100								
Total	28 646		1 179		412	561	47.6	618	52.4						

Footnote:

†ETOPFA, Terminations of pregnancy for foetal anomalies.

Stillbirth (foetal death at 20 weeks of gestation or greater).

Table 2 Prevalence and distribution of congenital anomalies, overall and by pregnancy outcome.

Birth defects	Number*	%	Prevalence per 1000	Live births	Prevalence per 10000 live birth	Stillbirth	ETOPFA

			births (total births = 28646)			(total live births = 28376				
				No.	%		No.	%	No.	(%)
Any	1179	100	412	1123	95.3	396	38	3.2	18	1.5
Nervous system	160	13.6	56	129	80.6	45.7	18	11.3	13	8.1
Neural Tube Defects	54	4.6	19	30	55.5	10.6	11	20.4	13	24.1
Anencephalus	26	2.2	9	7	26.9	2.5	8	30.8	11	42.3
Encephalocele	11	0.9	4	9	81.8	3.2	1	9.1	1	9.1
Spina Bifida	17	1.4	6	14	82.4	4.9	2	11.8	1	5.9
Hydrocephaly	25	2.1	9	23	92.0	8.1	2	8.0		
Microcephaly	28	2.4	10	24	85.7	8.5	4	14.3		
Eye	33	2.8	12	33	100	11.6				
Anophthalmus/microphthalmus	11	0.9	4	11	100	3.9				
Congenital cataract	5	0.4	2	5	100	1.8				
Congenital glaucoma	9	0.8	3	9	100	3.2				
Ear, face and neck	7	0.6	2	7	100	2.5				
Anotia/microtia	7	0.6	2	7	100	2.5				
Cardiac	425	36.0	148	420	90.9	148	4	0.9		
Severe congenital heart defects *	91	7.7	32	89	97.8	31.4	2	2.2		
Common arterial truncus	3	0.3	1	3	100	1.1				
Transposition of great vessels	13	1.1	5	13	100	4.6				
Single ventricle	6	0.5	2	6	100	2.1				

Atrioventricular septal defect	17	1.4	6	15	88.2	5.3	2	11.8		
Tetralogy of Fallot	15	1.3	5	15	100	5.3				
Tricuspid atresia and stenosis	4	0.3	1	4	100	1.4				
Pulmonary valve stenosis	22	1.9	8	21	95.5	7.4	1	4.5		
Pulmonary valve atresia	9	0.8	3	9	100	3.2				
Aortic valve atresia/stenosis	5	0.4	2	5	100	1.8				
Hypoplastic left heart	15	1.3	5	15	100	5.3				
Hypoplastic right heart	5	0.4	2	5	100	1.8				
Coarctation of aorta	14	1.2	5	14	100	4.9				
Total anomalous pulmonary venous return	2	0.2	0.7	2	100	0.7				
Ventricular septal defect	171	14.5	60	171	100	60.2				
Atrial septal defect	214	18.2	74.7	214	100	75.4				
Oro-facial clefts										
Cleft lip with or without palate	42	3.6	14.7	35	83.3	12.3	5	11.9	2	4·8
Cleft palate only	11	0.9	3.8	11	100	3.9				
Respiratory	33	2.8	11.5	33	100	11.6				
Choanal atresia	5	0.4	1.7	5	100	1.8				
Digestive system	74	6.3	25.8	71	95.9	25.0	3	4.1		
Esophageal atresia with/without fistula	12	1.0	4.2	12	100	4.2				
Ano-rectal atresia and stenosis	26	2.2	9.1	25	96.2	8.8	1	3.8		
Diaphragmatic hernia	18	1.5	6.3	16	88.9	5.6	2	11.1		
Abdominal wall defects	7	0.6	2.4	6	85.7	2.1	1	14.3		
Gastroschesis	2	0.2	0.7	1	50.0	0.4	1	50.0		

Omphalocele	5	0.4	1.7	5	100	1.8				
Urinary	323	27.4	113	318	98.5	112.1	4	1.2	1	0.3
Bilateral renal agenesis	18	1.5	6.3	15	83.3	5.3	2	11.1	1	5.6
Renal dysplasia	60	5.1	21	58	96.7	20.4	2	3.3		
Congenital hydronephrosis	194	16.5	67.7	194	100	68.4				
Genital	127	10.8	44.3	126	99.2	44.4	1	0.8		
Hypospadias	108	9.2	37.7	108	100	38.1				
Indeterminate sex	3	0.3	1.0	2	66.7	0.7	1	33.3		
Limb	99	8.4	34.6	92	92.9	32.4	4	4.0	3	3.0
Limb deficiencies, all	17	1.4	5.9	17	100	6.0				
Upper limb deficiency	12	1.0	4.2	12	100	4.2				
Lower limb deficiency	7	0.6	2.4	7	100	2.5				
Club foot - talipes equinovarus	19	1.6	6.6	15	78.9	5.3	2	10.5	2	10.5
Hip dislocation and/or dysplasia	24	2.0	8.4	23	95.8	8.1			1	4.2
Polydactyly	23	2.0	8.0	23	100	8.1				
Syndactyly	9	0.8	3.1	9	100	3.2				
Musculo-skeletal	40	3.4	14	33	82.5	11.6	7	17.5		
Craniosynostosis	6	0.5	2.1	6	100	2.1				
Achondroplasia	3	0.3	1	2	66.7	0.7	1	33.3		
Thanatophoric dysplasia	2	0.2	0.7	2	100	0.7				
Jeune syndrome	2	0.2	0.7	1	50.0	0.4	1	50.5		
Other malformations	42	3.6	14.7	40	95.2	14.1	1	2.4	1	2.4
Situs inversus	10	0.8	3.5	10	100	3.5				
By underlying cause										

Chromosomal	82	7.0	8.6	79	96.3	27.8	3	3.7		
Down Syndrome/trisomy 21	63	5.3	22	62	98.4	21.8	1	1.6		
Edward syndrome/trisomy 18	8	0.7	2.8	7	87.5	2.5	1	12.5		
Patau syndrome/trisomy 13	2	0.2	0.7	2	100	0.7				
Turner syndrome	3	0.3	1	2	66.7	0.7	1	33.3		
Wolff-Hirschhorn syndrome	1	0.1	0.3	1	100	0.4				
Genetic syndromes (including microdeletions)	38	3.2	13.2	36	94.7	12.7	1	2.6	1	2.6
Teratogenic (Carbamazepine embryopathy)	1	0.1	0.3	1	100	0.4				
Conditions outside Q chapter of ICD-10										
Inborn error of metabolism	37	3.1	12.9	37	100	13.0				
Endocrine disorders	7	0.6	0.2	7	100	2.5				
Other	11	0.9	4	11	100	3.9				

Legend:

* The total number of birth defects is greater than the total umber of affected births because some had more than one major CA.

§ Severe congenital heart disease (EUROCAT definition): common arterial trunk (Q200), double outlet right ventricle (Q201), transposition of great arteries (Q203), single ventricle (Q204), atrioventricular septal defect (AVSD) (Q212), tetralogy of Fallot (Q213), pulmonary valve atresia (Q220), Ebstein anomaly (Q225), hypoplastic right heart (Q226), aortic valve atresia and stenosis (Q230), mitral valve anomalies (Q232, Q233), hypoplastic left heart (Q234), coarctation of the aorta (Q251), aortic atresia / interrupted aortic arch (Q252), total anomalous pulmonary venous return (Q262).

Legend: Table 3 Common single congenital anomalies (CA) per body system involved

Body system	Total number Of CA	Isolated CA		Common isolated anomalies
		No.	%	
Cardiovascular	424	265	62.5	ventricular septal defects in 75 (28.3%). Atrial septal defects in 67 (25.3%). Pulmonary valve atresia and stenosis in 18 (6.8%). Sever CHD in 54 (20.4%)
Urinary	323	229	70.8	Congenital hydronephrosis in 147 (64.2%). Bilateral renal agenesis in 3 (1.3%).
Central nervous	161	68	42.8	Neural tube defects in 32 (47.1%). Encephalocele in 4 (5.9%)
Gastrointestinal	74	33	44.6	Ano-rectal atresia and stenosis in 16 (48.5%). Diaphragmatic hernia in 6 (18.2).
Limb	97	31	32	Total limbs reduction in 9 (29%). Upper limb reduction in 7 (22.6%). Lower limb reduction in 3 (9.7%).
Eye	32	14	43.8	Congenital glaucoma in 6 (42.9%). Congenital cataract in 4 (28.6%).

				Anophthalmia + microphthalmia in 3 (21.4%).

Legend: Table 4 Distribution of parental socio-demographic characteristics and association with congenital anomaly risk (univariate analysis).

Variable	Cases (total n=1179)		Controls (total n=1262)		Odds Ratio‡	95% CI	
	No.	%	No.	%		Lower	Upper
Consanguinity							
Non-consanguineous	537	45.5	693	54.9	Ref	-	-
Consanguineous	642	54.5	569	45.1	1.53	1.30	1.8
Maternal age (years)							
<20	24	2.0	48	3.8	0.58	0.35	0.96
20-30	599	50.8	694	55.0	Ref	-	-
31-40	473	40.1	474	37.6	1.16	0.98	1.37
>40	83	7.0	46	3.6	2.09	1.43	3.05
Paternal age (years)							
20-30	341	28.9	403	31.9	0.92	0.76	1.10
31-40	548	46.5	593	47.0	Ref	-	-
41-50	240	20.4	225	17.8	1.15	0.93	1.43
> 50	50	4.2	41	3.2	1.32	0.86	2.03

Maternal body mass index‡							
<18·5	24	2.1	35	2.8	0.75	0.44	1.29
18·5-24·99	324	27.8	388	30.8	0.91	0.74	1.12
25·0-29·99	352	30.2	385	30.5	Ref	-	-
≥30	464	39.9	453	35.9	1.12	0.92	1.36
Previous deliveries (parity)							
Nulliparous	216	18.3	273	21.6	0.92	0.74	1.16
Para 1-2	374	31.7	436	34.5	Ref	-	-
Para 3-4	283	24.0	273	21.6	1.21	0.97	1.50
Para ≥5	306	26.0	280	22.2	1.27	1.03	1.58
Family monthly income Saudi riyals (US $)							
<3,000 SR (<800$)	19	1.9	12	1.0	1.87	0.89	3.92
10,000-14,000 SR (2667-3999$)	235	23.2	277	22.3	Ref	-	-
3,000-6,999 SR (800-1866$)	232	22.9	291	23.4	0.94	0.74	1.20
7,000-9,999 SR (1867-2666$)	367	36.3	496	39.9	0.87	0.70	1.09
≥15, 000 (≥4000$)	158	15.6	167	13.4	1.12	0.84	1.47
Maternal education							
Illiterate	391	33.2	333	26.4	1.50	1.26	1.80
Schooling up to high school	671	56.9	859	68.1	Ref	-	-
University	117	9.9	70	5.5	2.05	1.49	2.81
Folic acid intake							
Periconceptional	109	9.2	128	10.1	Ref	-	-

Improper use§	1070	90.8	1134	89.9	1.04	0.79	1.36
Parental Smoking							
Neither parent smoked	837	71.0	888	70.4	Ref	-	-
One or both parents smoked	342	29.0	374	29.6	0.97	0.82	1.16
Radiation exposure in pregnancy							
None	1161	98.5	1254	99.4	Ref	-	-
Radiation exposure in pregnancy	18	1.5	8	0.6	2.43	1.05	5.61
Diabetes mellitus (DM)							
No DM	956	81.1	1062	84.2	Ref	-	-
DM on insulin (all, overt & gestational	86	7.3	41	3.2	2.34	1.60	3.43
Gestational DM on diet only	137	11.6	157	12.6	0.91	0.62	1.16
Sibs of cases and controls (primiparous mothers excluded)							
No affected sibling	757	78.6	932	94.2	Ref-	-	-
Sibling with CA	85	8.8	58	5.7	1.61	1.14	2.27
Medication use in pregnancy							
None	792	67.2	951	75.3	-	-	-
Thyroxin	102	8.7	106	8.4	1.03	0.78	1.37
Insulin	86	7.3	40	3.2	2.34	1.59	3.45
Methyldopa	14	1.2	14	1.1	1.07	0.51	2.26

Maternal systemic illnesses							
None	808	68.5	971	76.9	Ref-	-	-
Mothers with Hypothyroidism	123	10.4	128	10.1	1.03	0.80	1.34
Mothers with Bronchial asthma	106	9.0	97	7.7	1.19	0.89	1.58
Mothers with depression	12	1.0	6	0.5	2.15	0.81	5.75
Mothers with essential hypertension	23	2.0	15	1.2	1.65	0.86	3.19

Footnote:

‡BMI not available for 15 mothers

Some families declined reporting their income.

§Improper-use includes FA taken post conception and 49 mothers (43 case mothers and 6 control mothers) who were not sure about their intake.

Legand: Table 5 multiple logistic regression model results for the significant risk factors on univariate analysis

Variable	ADJUSTED OR (from multiple logistic regression model) †			CRUDE OR (from univariate analysis)		
	OR	95% C.I.		OR	95% C.I.	
		Lower	Upper		Lower	Upper
Consanguinity, none (reference group)	-	-	-	-	-	-
Consanguinity, first degree	1.52	1.28	1.81	1.53	1.30	1.81
Maternal age, 20-30 years (reference group)	-	-	-	-	-	-
Maternal age, <20 years	0.54	0.32	0.91	0.58	0.35	0.96
Maternal age, >40 years	2.11	1.35	3.30	2.09	1.43	3.05
Maternal education, up to high school (reference group)	-	-	-	-	-	-
Maternal education, illiterate	1.41	1.17	1.70	1.50	1.26	1.80
Maternal education, university	1.74	1.24	2.44	2.05	1.49	2.81
Diabetes on insulin, overt or gestational (yes/no)	1.98	1.33	2.95	2.34	1.60	3.43
Sibling with anomalies (yes/no)	1.49	1.04	2.12	1.61	1.14	2.27

†: Adjustment for consanguinity, maternal age, maternal education, diabetes mellitus, sibling with anomalies.

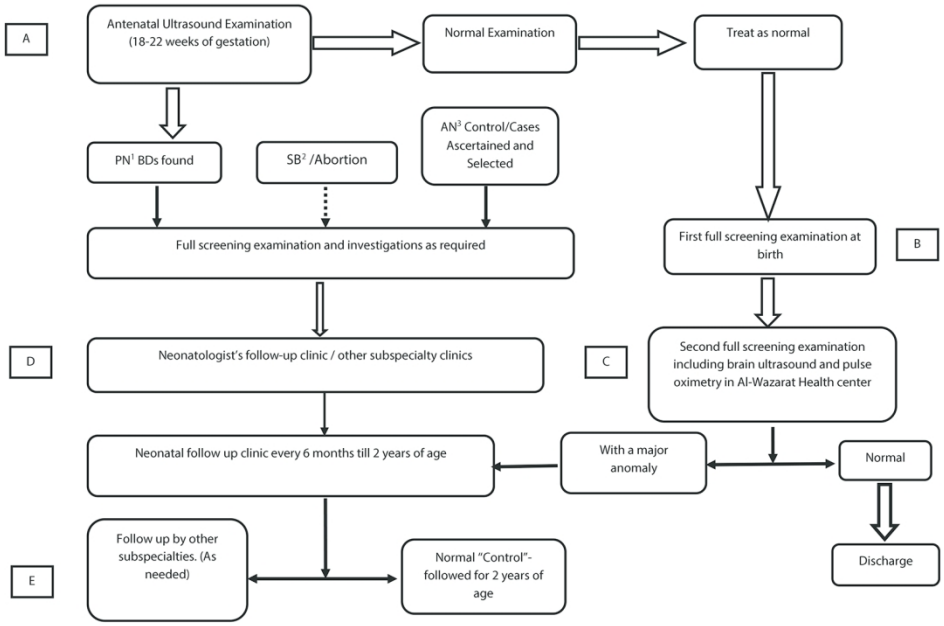
Figures legend:

Legend: Figure _1 Catchment site and the study flow chart.

Legend: Figure _2 Study population and distribution of pregnancies and their outcomes.

Legend: Figure _ 3 Frequency among control subjects of selected risk factors for CA.

Figure 1- Catchment site and the study flow chart.

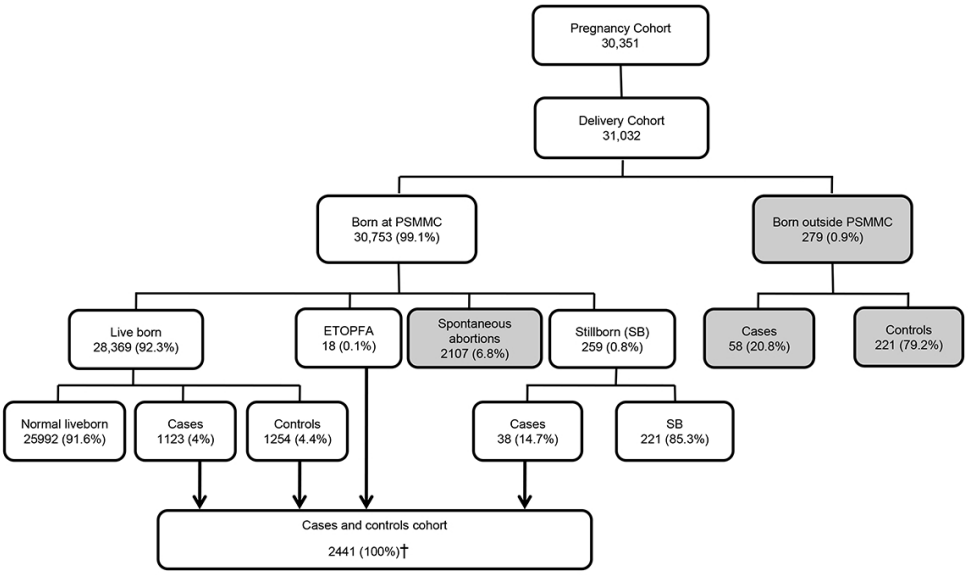


Legend: Case catchment areas (A to E). A: antenatal clinic, B: at birth, C: the "one-month clinic, D: geneticist "one-month clinic", and E: other areas. 1,2,3 are postnatal, stillbirth and antenatal respectively. BD. Birth defect

Legend: Figure _1 Catchment site and the study flow chart.

150x120mm (300 x 300 DPI)

Figure _2 Study population and distribution of pregnancies and their outcomes.

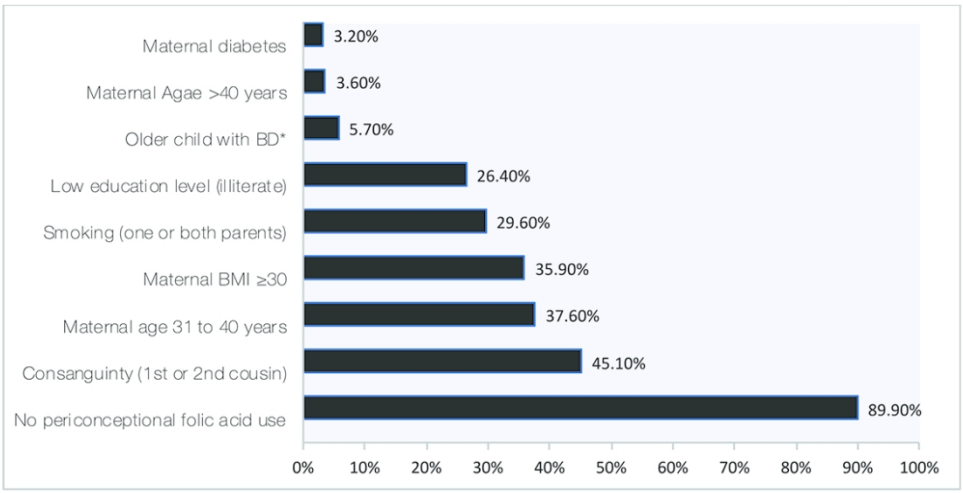


Legend:

PSMMC, Prince Sultan Military Medical City; ETOPFA, Elective termination of pregnancy for foetal anomaly.

†Eight control foetuses were stillbirth.

Figure 3. Frequency among control subjects of selected risk factors for birth defects.



Legend:
BMI, pre-pregnancy maternal body mass index
BD, birth defect
*Frequency of prior child with BD computed among non-primiparous women

Legend: Figure _ 3 Frequency among control subjects of selected risk factors for birth defects.

99x79mm (300 x 300 DPI)

Supplement file

Appendix

Confidential

PSMMC

Booklet of

"Pattern of Fetal Malformations in a Saudi Population"

☐ **Study** ☐ **Control**

Local ID No.: _____ / Year 201

Mother's Name: _____

Mother's MRN: _____

Baby's Name: _____

Baby's MRN: _____

Date of Birth: ____ / ____ / ____

Contact No: **Mobile (husband)** _____

Mobile (wife) _____

Home _____

Confidential

Keep in a safe place

Pattern of Malformations Study – PSMMC

(Baby and mother)

Local ID No _____

D.O.B. (dd/mm/yy): _____ /_____ / _____ Year: 201__

D. O. B./ Year Unknown □

Sex: Male □ Female □ indeterminate □ Not known □

No. of babies delivered: Singleton 1 □ Twin 2 □ Triplet 3 □ Quadruplet 4 □ Quintuplet 5 □ Sextuplet 6 □

Not known 9 □

Specify twin type of birth, like or unlike sex, zygosity:_____

No. of malformed (in multiple set): No. _____ Not known □

Type of birth: Live Birth (LB). □ Still Birth (SB) □ Spontaneous Abortion □

TOP □ Not known □

Civil registration status LB □ SB □ No CR □ Not known □

Birth weight (g): _____ **Confirmed** □

Length of gestation (weeks): _____ **Confirmed** □

Survival beyond one week of age:

Yes □ No □ Alive at discharge <1 Week □ Not known □

Date of death (dd/mm/yy): ____/_____/_____ Year:_____

D. O. B. Mother (dd/mm/yy): _____/____/____ Year:_____ Confirmed □

Age of mother at delivery: _____

Pattern of Malformations Study – RMH

(Baby and mother)

Local ID No _____

Mother's residence code at conception: Province _____ District _____

Mother's residence code at delivery: Province _____ District _____

Total No. of previous pregnancies: None □ Number (___) Not known □

When discovered:

At birth □ Less than 1 wk □ 1-4 wk □ 1-12 m □ >12 m □ Prenatal diagnosis □

At abortion (sp) or termination □ Not known □ Postnatal diagnosis, age not known □

Condition at discovery: Alive □ Dead □ Not known □

Gestational age at discovery (wk): _____

First positive prenatal test:

US at <14 wks □ US at 14-21 wks □ US at ≥ 22 wk □ US GA unknown □
Serum/combined screening □ CVS □ Amniocentesis □ Other tests positive □

No positive test, all results negative □

Specify 'other' prenatal test: _____

Karyotype of infant/ fetus:

Performed, result known □ Performed, result unknown □

Not performed □ Probe test performed □ Failed □ Not known □

Specify karyotype:_____

Post mortem exam:

Performed, result known □ Performed, result unknown □

Macerated fetus □ Not known □ Not performed □

First surgical procedure:

Performed (or expected) in the first year of life □

Performed (or expected) after the first year of life □

Prenatal surgery □ No surgery required □

Too sever for surgery □ Not known □

Pattern of Malformations Study – PSMMC

(Prenatal Malformations)

Local ID No _____

	Code	**Text**
Syndrome:		
Malformation 1:		
Malformation 2:		
Malformation 3:		
Malformation 4:		
Malformation 5:		
Malformation 6:		
Malformation 7:		
Malformation 8:		

Pattern of Malformations Study – RMH

(All Malformations)

Local ID No _____

	Code	**Text**
Syndrome:		
Malformation 1:		
Malformation 2:		
Malformation 3:		
Malformation 4:		
Malformation 5:		
Malformation 6:		
Malformation 7:		
Malformation 8:		

McKusick code: _____

Aetiology:

Chromosome **C** □ Familial **F** □ Isolated **I** □ Multiple **M** □

New Dominant **ND** □ Other Genomic **OG** □ Syndrome **S** □ Teratogens **T** □ Inborn Error of Metabolism**IEM** □ Control **Co** □

View anomaly subgroup(s):

Pattern of Malformations Study – RMH

Local ID No _____

Assisted conception: No □ Induced ovulation only □ Artificial insemination □

In vitro fertilization □ Gamete intrafollopian transfer □

Intracytoplasmic sperm injection □ Egg donation □ Other□

Not known □

Mother's occupation: House wife □ Teacher □ Student □ Other □

Maternal Systemic illnesses;

None □ EHT □ Hypothyroidism □ CHD □

RHD □ CRF □ Asthma □ SCA □ SLE □

IDA □Anxiety □ Depression □ Epilepsy □

Other □ (specify)_____

Weight before pregnancy (Kg) _____

Current weight (Kg) _____

Mother's height (m) _____

Body Mass Index: <18.5 □ 18.5 – 24.9 □ 25 – 29.9 □
30.0 – 34.9 □ 35.0 – 39.9 □ ≥ 40.0 □

True DM: Yes□ No □

Gestational DM on Diet (GDOD) □

Gestational DM on Insulin (GDOI) □

Diabetes screening: GTT (result) 0 time:_____ 1hour:_____ 2 hours:_____

Booking RBS:_____

HbA1c _____

Infectious disease:

Tuberculosis: Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Rubella Before pregnancy □During pregnancy □ 1st T □ 2nd T □ 3rd T □

CMV Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Toxoplasmosis Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Syphilis Before pregnancy □ During pregnancy □ 1st T □ 2ndT □ 3rd T □

UTI Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Fever Before pregnancy □ During pregnancy □1st T □ 2nd T □ 3rd T □

FLU Before pregnancy □ During pregnancy □1st T □ 2nd T □ 3rd T □

Others Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

(Specify others) _____

Previous surgical history: Obstetrical/Gynaecological □

Specify; _____

Non Obstetrical □

Specify; _____

Pattern of Malformations Study – PSMMC

Family history & sociodemographic

Local ID No _____

Folic acid supplementation:

Al least 0.4 mg folic acid supplement taken regularly, starting periconceptionally □

Folic acid supplement taken irregularly or starting post-conceptionally □

No folic acid supplement taken or not recorded □

ATC code Text (**only** drugs taken in the 1st trimester of pregnancy)

Drugs 1:		
Drugs 2:		
Drugs 3:		
Drugs 4:		
Drugs 5:		

Consanguinity: Not related or relationship more distant than second cousin □

Relationship of second cousin or closer □ Not known □

Specific information on consanguinity:

_____

Sibs with anomalies: Same□ Other □ Same and other □ No □ Not known □

Previous sibs notified to the Saudi Malformations Registry: Yes □ No □ Not known □

Local ID of previous sibs notified to the SMR (1):_____

Local ID of previous sibs notified to the SMR (2):_____

Local ID of previous sibs notified to the SMR (3):_____

Mother's family with anomalies: Same □ Other □ Same and other □ No □

Not known □ Specify _____

Father's family with anomalies: Same □ Other □ Same and other □ No □

Not known □ Specify _____

Maternal education: Illiterate □ Elementary and lower secondary □

Upper secondary □ Tertiary □ Not known □

Family monthly income (SR):_____

(husband or combined husband and wife income)

Nationality: Saudi □ None Saudi □ Only father Saudi □ Only mother Saudi □

General additional comments:

_____

_____

Pattern of Malformations Study – PSMMC

Local Vars. (1)

Local ID No_____

Place of birth: _____

Birth order (in multiple set), (please write as 1st, 2nd, 3rd and so on): _____

Date of discovery (dd/mm/yy): _____/____/_____ **Year**: _____

Amniocentesis: Performed result positive □ Performed result not known □

Not performed □ Performed result negative □ Failed □ Not known □

Ultrasound: Performed result positive □ Performed result not known □

Not performed □ Performed result negative □Failed □ Not known □

Chorionic villous sampling: _____

Other techniques:

Performed result positive □ Performed result not known □ Not performed □

Performed result negative □ Failed □ Not known □

Specify other technique for prenatal diagnosis: _____

(Cordocentesis,..etc)

No. of previous spontaneous abortions: None □ 1 □ 2 □ 3 □ 4 □
5 □ 6 □ 7 □ 8+ □ Not known □

No. of previous TOP: None □ 1 □ 2 □ 3 □ 4 □ 5 □
6 □ 7 □ 8+ □ Not known □

No. of previous live births: please write the exact No (1-20) _____ Unknown □

No. of previous stillbirths: None □ 1 □ 2 □ 3 □ 4 □
5 □ 6 □ 7 □ 8+ □ Not known □

Mode of transmission: Familial □ De novo □ Not known □

Habitual exposures: Smoking F179 □ Oude F159 □

Other (specify) _____

Unusual exposures: X-ray during pregnancy (any)□ Nuclear medicine during pregnancy □

(Radiation & chemical)

Date of birth of father: ____/____/_____ **Year**: _____ **Age of father**: _____

Occupation of father: Soldier □ Officer □ Civilian □

Pattern of Malformations Study – RMH

Local Vars. (2)

Local ID No_____

Date of last LMP: _____/_____/_____

Certainty of LMP: **C**ertain □ Uncertain □ No LMP □ Not known □

Labor: Spontaneous □ Induced □ No labor □

Delivery: Spontaneous □ EMLSCS □ ELSCS □ ABD □
Instrumental □

Sources of information 1:

Notes in routine scan □ Birth notification or notification of malformation at birth □

Hospital case notes □ Death or stillbirth certificate □Prenatal diagnosis □

Lab. report (cytogenetic … etc) □ Postmortem exam □ Other □ Not known □

Sources of information 2: please insert as in one _____

Sources of information 3: please insert as in one _____

Sources of information 4: please insert as in one _____

Sources of information 5: please insert as in one _____

Racial information Mother, Tribe code _____ Father, Tribe code_____

Same tribe □ Different tribe □

Otaibi 1, Mutairi 2, Shuhri 3, Asiri 4, Shamrani 5, Onazi 6, Shahrani 7, Zaharani 8, Harbi 9, Qahatni 10, Ghamdi 11,Shamari 12, Asmari 13, Ahmari 14, Amri 15, Dawsari 16, Harthi 17, Subaie 18, Ajman 19, Not known (99)

Other 20, specify: _____

Chronic illness of father (including drug abuse):_____

Confirmation of diagnosis:

Follow up needed for further confirmation □ Confirmed at <6 months □

Confirmed at 6-12 m □ Confirmed at 12-18 m □ Confirmed at 18-24 m □

Not confirmed, lost for follow up □

Source: Booked □ Un booked □ Referred □

Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Observational, prospective cohort design with a nested case-control study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a CA, for an overall prevalence of 412/10000 total births, or 1 in 24 births.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Congenital anomalies(CA) are increasingly recognized as a global health priority because of their lifelong impact on health and survival.[1,2] CA affect approximately an estimated 1 in 33 newborns, contribute each year to 300,000 deaths in the first month of life, and are associated with 3·2 million birth-related disabilities.[3] Accordingly, the World Health Assembly has emphasized the urgent need for action to help prevent, diagnose, and provide timely intervention.[1]
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5	In this study, we implemented an integrated approach to generate these data in well-defined cohort of women, tracked from mid-gestation through the second year of life of their children, to assess concurrently the burden of potentially modifiable risk factors, the occurrence of CA, and survival of affected children, as a basis for better prevention and care.[4]
Methods				
Study design	4	Present key elements of study design early in the paper	5	Observational, prospective cohort design with a nested case-control study.

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 *8-15	The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution with 1250 beds and approximately 10,000 annual deliveries. PSMMC primarily serves Saudi army personnel and their families and is a referral center for the other 16 military hospitals in the Kingdom of Saudi Arabia. Study period 1 July 2010 through 30 June 2013. *Figures and tables
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case 2,3 ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5 7,8 n/a	All pregnant Saudi women who are eligible for their antenatal care at PSMMC were included and their pregnancy outcome. Mothers who delivered elsewhere were not included even if they have their antenatal care at PSMMC. All mothers who care pregnant with an affected foetus (birth defect) are include. For controls a random sample of women in the cohort with a normal USS. The random sample was generated daily by taking the morning list of scheduled USS and using a random number generator (http://www.random.org) to select potential controls
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	Evaluations for specific congenital anomaly. Table 4 and 5. Nested Case-Control Study, Follow up, Case review, coding, classification.

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*n/a*
Bias	9	Describe any efforts to address potential sources of bias	5,6	Pregnancies referred from other hospitals because of a diagnosis of a foetal anomaly, and babies with CA delivered elsewhere and referred to PSMMC for evaluation and management
Study size	10	Explain how the study size was arrived at	5	All mother delivered at PSMMC during the study period were included
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10	Odd ratios for CA were computed first via univariate logistic regression, then with a multiple logistic model. The latter was developed by first including uncorrelated significant factors (p <0·05) from the univariate analysis, then reducing the number of variables by stepwise backward elimination for a more parsimonious model.
		(*b*) Describe any methods used to examine subgroups and interactions		n/a
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7	n/a randomization n/a

		(*e*) Describe any sensitivity analyses		n/a
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 -11	All mothers and their offspring were included. For details see Figure 2.
		(b) Give reasons for non-participation at each stage		n/a
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	29 - 32	All demographic data were shown in Tables 4 and 5
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	2 – 5 years. Follow up. Case-infants (with CA) and control-infants were examined in the dedicated study clinic at 1, 6, 12, 18 and 24 months of age
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9	1179 as cases and 1262 as controls
		Cross-sectional study—Report numbers of outcome events or summarymeasures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	9-11	Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a CA, for an overall prevalence of 412/10000 total births, or 1 in 24 births. Of these 1179 cases, 38 (3.2%) were stillbirths and 18 (1.5%) were electively terminated because of lethal malformations

		which confounders were adjusted for and why they were included		(13 with anencephaly, 3 with severe hydrops foetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis). The antenatal detection rate among women who has had antenatal ultrasound screening examination was 70.6%(561/795), tables b 1,2,3
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		n/a
Discussion				
Key results	18	Summarise key results with reference to study objectives	2	In this cohort of women, the burden of potentially modifiable risk factors included high rates of diabetes (7.3%), maternal age >40 years (7.0%), consanguinity (54.5%), and lack of periconceptional folic acid use (90.8%). The birth prevalence of CA was 41.2/1,000 births (1179 cases / 28646 live births and stillbirths), driven mainly by congenital heart disease (14.8 per 1000), renal malformations (11.3), neural tube defects (1.9), and chromosomal anomalies (2.7). Mortality for live births with CA at 1 and 2 years of age was 14% and 15.8%, respectively.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15	Single centre study, Army personnel household only
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15	High prevalence of CA, multiple modifiable risk factors.

Generalizability	21	Discuss the generalizability (external validity) of the study results	15	Since it's a single centre study, it should be generalized with caution as mentioned in the discussion.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2	This project was supported by King Abdul-Aziz City for Science and Technology (KACST) through the National Science, Technology and Innovation Plan (NSTIP). Project No: 09-MED748-21. The funder has no role in this study.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Congenital anomalies and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

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Primary Subject Heading:	Epidemiology
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Keywords:	Prevalence, Risk factors, Prevention, Outcome, Congenital anomaly

Congenital anomalies and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

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Running title: Congenital anomalies and Risk Factors in a Saudi population

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Abstract

Objective: To assess the three key issues for CAs prevention and care, namely, CA prevalence, risk factor prevalence, and survival, in a longitudinal cohort in Riyadh, Saudi Arabia.

Setting: Tertiary care centre, Riyadh, Saudi Arabia.

Participants: Saudi women enrolled during pregnancy over three years and their 28,646 eligible pregnancy outcomes (births, stillbirths and elective terminations of pregnancy for foetal anomalies [ETOPFAs]). The nested case-control study evaluated the CA risk factor profile of the underlying cohort. All CA cases (1,179) and unaffected controls (1,262) were followed through age 2 years. Referred mothers because of foetal anomaly and mothers who

delivered outside the study centre and their pregnancy outcome were excluded.

Primary outcome measures: Prevalence and pattern of major CAs, Frequency of CA-related risk factors, and survival through age 2 years.

Results: The birth prevalence of CAs was 412/10,000 births (95% CI 388.6 to 434.9), driven mainly by congenital heart disease (148 per 10,000) (95% CI 134 to 162), renal malformations (113, 95% CI 110 to 125), neural tube defects (19, 95% CI 25.3 to 38.3), and chromosomal anomalies (27, 95% CI 21 to 33). In this study, the burden of potentially modifiable risk factors included high rates of diabetes (7.3%, OR 1.98, 95% CI 1.04 to 2.12), maternal age >40 years (7.0%, OR 2.1, 95% CI 1.35 to 3.3), consanguinity (54.5%, OR 1.5, 95% CI 1.28 to 1.81).The mortality for live births with CAs at 2 years of age was 15.8%.

Conclusions: This study documented specific opportunities to improve primary prevention and care. Specifically, folic acid fortification (the neural tube defect prevalence was >3 times that theoretically achievable by optimal fortification), preconception diabetes screening and consanguinity-related counselling could have significant and broad health benefits in this cohort and arguably in the larger Saudi population.

Strengths and limitations of this study:

- Babies with CAs are diagnosed prospectively, prenatally, and postnatally and followed up to 2 years of age.

- Involvement of multidisciplinary teams in establishing the final diagnosis.
- Inclusion of elective termination of pregnancies with lethal CAs and stillbirths.
- Single-centre study. The pregnancy cohort was mainly from families of Saudi army personnel dependents, which could be a limiting factor.

Funding statement: This project was supported by a generous grant from King Abdul-Aziz City for Science and Technology (KACST) through the National Science, Technology and Innovation Plan (NSTIP). Project No: 09-MED748-21.

Disclaimer: The funding institution had no role in the study design, data collection, analysis, interpretation of data, the writing of the various reports or the decision for submission for publication. All authors have full independence from the funder, have full access to the data in the study and take full responsibility for the integrity of the data and the accuracy of the analysis.

Competing interests statement: None declared

All authors have completed the ICMJE uniform disclosure from www.icmje.org-coi_disclosure.pdf and declare no support from any organization for the submitted research article; no financial

relationship with any organization that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Key words: Congenital anomalies, Prevalence, Risk factors, Prevention, and Outcome

Congenital anomalies and associated risk factors in a Saudi population: a cohort study from pregnancy to age 2 years

Introduction

Because of their lifelong impact on health and survival, congenital anomalies (CAs) are increasingly recognized as a global health priority.[1 2] With better control of infections and other causes of early mortality, CAs are becoming increasingly important drivers of child survival and health in low- and middle-income countries.[1 3] CAs affect approximately an estimated 1 in 33 newborns, contribute each year to 300,000 deaths in the first month of life, and are associated with 3·2 million birth-related disabilities.[3] Accordingly, the World Health Assembly has emphasized the urgent need for action to help prevent,

diagnose, and provide timely interventions.[1] Data on the prevalence and mortality associated with CAs are scarce in many low- and middle-income countries, with most reports originating in high-income areas. For example, in a population-based study of livebirths with CAs in the United Kingdom, the 20-year survival rate was 85.5%.[4] Similarly, the 25-year survival rate among livebirths with CAs in New York state was 82.5%,[5] with a documented improvement from the 1980s (78.1% from 1983 –1988) to the early 2000s (89.3% from 2001-2006). Among CAs, the major drivers of mortality were cardiovascular anomalies (51.1%) and chromosomal anomalies (33.1%). In Korea, infant mortality among babies with CAs was 6.8/10,000 live births, and foetal mortality was 13.5/10,000 total births.[6]

However, local action, whether focused on primary prevention or on improving care, is most effective when based on reliable information about the key indicators of the causes and outcomes of CAs in the underlying population. In this study, we implemented an integrated approach to generate these data in a systematic cohort of women, tracked from mid-gestation through the second year of life of their children, to assess the prevalence of CAs, the burden of potentially modifiable risk factors, and the survival of affected children, as a basis for better prevention and care.[7]

Methods

Setting. The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution with 1,250 beds and approximately 10,000 annual deliveries. PSMMC primarily serves Saudi army personnel and their families and is a referral centre for the other 16 military hospitals in the Kingdom of Saudi Arabia. The foetal medicine unit includes advanced imaging facilities, including 3D and 4D scanning. The paediatric department includes all major subspecialties, including medical genetics, paediatric surgery, and paediatric cardiology.

Study design This is an observational, prospective cohort study with a nested case-control study. The eligible cohort includes pregnancies of women who had their antenatal care and their routine antenatal anomaly ultrasound scan examination (USS) between 18 weeks and 22 weeks of gestation at PSMMC from 1 July 2010 through 30 June 2013 (figure 1).

In addition, Saudi women who are eligible for their antenatal care at PSMMC, but who did not have an antenatal screening ultrasound examination and later delivered at PSMMC, are also included in the study.

Inclusions and exclusions. Pregnancy outcomes included in the study were live births, stillbirths (foetal deaths at 20 weeks' gestation or

later), and pregnancies electively terminated because of foetal anomalies (ETOPFAs). The study excluded spontaneous abortions, pregnancies referred from other hospitals because of a diagnosis of a foetal anomaly, and babies with CAs delivered elsewhere and referred to PSMMC for evaluation and management.

Evaluations. Initial antenatal screening tests included a complete blood count, liver and kidney function tests, blood group and antibody screening, rubella and Toxoplasma status, hepatitis B screen, random blood sugar and HbA1c levels, VDRL, sickle cell screen and urine analysis. A glucose tolerance test was performed at 24-28 weeks of gestation.

When a structural birth defect was diagnosed or suspected antenatally, mothers were counselled by one of the investigators (MSR, AMK), demographic and exposure information was gathered, and both parents were scheduled within 2-4 weeks to attend a dedicated clinic developed for the study. At that time, a detailed diagnostic and care plan was developed, which may have included further blood tests and foetal imaging, or amniocentesis, chorionic villous and/or foetal blood sampling for genetic studies. Consent was requested for cord blood collection for future molecular testing.

On the first day of life, all newborns in the cohort (with and without CAs) were examined by a paediatrician as part of the first clinical screening examination. Babies with CA, whether identified antenatally or postnatally, underwent diagnostic investigations as clinically indicated (e.g., echocardiogram, cardiac catheterization, or other imaging studies; metabolic and molecular testing) and were referred to the appropriate subspecialists. A clinical geneticist evaluated all babies with suspected syndromes or multiple CAs. A letter was distributed to all clinical departments describing the study and req uesting that they inform the study team about all infants and children with CAs born at PSMMC.

Evaluations for specific congenital anomalies. If congenital heart disease (CHD) was detected or suspected antenatally on USS examination, the mother was referred to the paediatric cardiologist for a foetal echocardiogram. All these infants were also re-evaluated after birth by a paediatric cardiologist. Isolated atrial septal defects (ASDs II) were re-evaluated at 6 to 12 months of age, and if the echocardiogram showed no evidence of ASD II at the time, the infant was not considered a case. Congenital hydronephrosis (HN) was graded using the Society of Foetal Urology grading system.[8] Babies with grade one HN were given a repeat US examination within the first year of life; if HN had resolved, the baby was not considered a case. Chromosomal analysis was performed according to standard

procedures, and a minimum of 20 metaphases were analysed (Applied Imaging CytoVision Karyotyping System). Reports followed the International System of Human Cytogenetic Nomenclature (ISCN 2013). Molecular studies were performed at the Biocenthia Health Group in Germany (http://www.bioscientia.de/en/), the Mayo Medical Laboratories in the United States, and at the Developmental Genetic Laboratory at King Faisal specialist hospital and research centre in Saudi Arabia.

Nested case-control study. The nested case-control study included as cases all women in the cohort with a pregnancy diagnosed with a CA and as controls a random sample of women in the cohort with a normal USS. The random sample was generated daily by taking the morning list of scheduled USS and using a random number generator (http://www.random.org) to select potential controls so that the control sample would eventually be at least as large as the estimated total number of cases. If a woman initially selected as a control had a pregnancy diagnosed with a birth defect at the initial date or later, she was then included in the case group. Investigators administered an in-person structured interview to case and control mothers. The interview included information about age (for both parents); weight before pregnancy; height; parity; family income (father's income or combined parental income if the mother worked); maternal education level (illiterate, primary school graduate, secondary school graduate,

or university graduate); parental occupation (mother; housewife, teacher, student and others, father; soldier, officer or civilian employee); folic acid (FA) supplement use (regular use before and during the 1st trimester of pregnancy; irregular or only postconception use; no use or uncertain use as per the mother's report); parental smoking (one or both parents smoking during the current pregnancy); maternal radiation exposure during the first trimester; maternal diabetes (overt or gestational) as defined by the International Association of Diabetes and Pregnancy study groups [9] and HbA1c level; family history of CAs (in previous pregnancies and in maternal or paternal lineages); drug and medication use during the first trimester; and chronic maternal systemic illnesses (hypothyroidism, epilepsy, depression, essential hypertension, and bronchial asthma). Consanguinity was defined as women being first or second cousins to their husbands (supplementary file).

Follow-up. Case infants and control infants were examined in the dedicated study clinic at 1, 6, 12, 18 and 24 months of age. Two neonatologists and a clinical geneticist supervised the clinic. Babies with CAs also continued to be followed by the relevant subspecialty clinics. The remaining cohort (babies without CAs not selected as controls) was re-examined at 4-8 weeks by the paediatrician for a second screening examination. A head ultrasound and a postductal pulse oximetry reading were completed in all babies attending the

clinics. If the O_2 saturation was below 95%, the baby was referred to the paediatric cardiologist for evaluation. If any CAs were detected at the second screening examination, the babies were referred to the genetics clinic for further evaluation and diagnosis. If the second screening examination proved to be normal, then no further follow-up was arranged. However, if CAs were discovered later in babies up to 2 years of age, they were included in the study.

Case review, coding, classification. Congenital anomalies were coded following the International Statistical Classification of Diseases and Related Health Problems, 10th revision, (ICD10, WHO-2010) according to the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) recommended procedures.[10] We did not include isolated minor anomalies or prematurity-related conditions such as patent ductus arteriosus or hydrocephalus complicating intraventricular haemorrhage diagnosed in preterm babies (<37 completed weeks of gestation). Data were entered in a version of EUROCAT Data Management Program (EDMP) modified to include control records and the additional variables generated by the case-control study and the follow up.

Institutional ethics review. The study and the consent procedure were approved by the Ethical Committee of the PSMMC (Project No. 366, series of 2009).

Statistical analysis.

The data collected and used in this study was part of our routine care and was anonymised.

Odds ratios for the association between risk factors and CAs were estimated using multiple logistic regression in a two-step process. An initial set of variables was selected by univariate logistic regression as being associated with CA risk ($p<0.05$). Variables highly correlated with other variables (e.g., insulin use) were not entered into the model. This initial variable set was then reduced by stepwise backward elimination to produce a more parsimonious model. The final model retained the following covariates: consanguinity, maternal age group, education level, diabetes and history of siblings with a congenital anomaly. The model fit was assessed with the Hosmer and Lemeshow's goodness of fit test and by calculating Nagelkerke R2. Statistical analysis was performed with SPSS for Windows, version 15 (SPSS Inc., Chicago, Illinois).

Patient and public involvement: Our long-term experience with the families and their offspring has helped us to shape the research question and the study design. All families recruited were informed about the study objectives. None of the parents were involved in the study design, recruitment to and conduct of the study. The study results were disseminated to the community and to the professional

health care provider through social media, newspapers, presentation at various conferences, and scientific publications.

Results

Of the 31,032 birth outcomes of the 30,351 women followed since pregnancy, 30,753 (99·1%) occurred at PSMMC (figure 2). Of these, 2,107 were spontaneous abortions (6·9%) and were not included in the study, leaving 28,646 eligible births (27,726 singleton births and 920 multiple births). The overall stillbirth rate was slightly less than 1% (figure 2).

Birth defect occurrence, detection, and mortality. Of the 28,646 eligible pregnancy outcomes, 1,179 were diagnosed with a CA, for an overall prevalence of 412/10,000 (95% CI 388.6 to 434.9) total births, or 1 in 24 births. Of these 1,179 cases, 38 (3.2%) were stillbirths, and 18 (1.5%) were electively terminated because of lethal malformations (13 with anencephaly, 3 with severe hydrops foetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis) (table 1). The antenatal detection rate among women who has had an antenatal ultrasound screening examination was 70.6% (561/795). In 90% of these cases (505/561), the diagnosis was made by ultrasound scan at 22 weeks of gestation or later. Of the 618 babies diagnosed postnatally, 296 (47.9%) were diagnosed at birth,

239 (38.7%) between 1 and 7 days, 29 (4.7%) between 1 and 4 weeks, 52 (8.4%) between 1 and 12 months, and 2 (0.3%) after one year of age. Mortality among livebirths with CAs (table 1) was 14.1% in the first year, nearly half of which occurred in the first week of life, with a total mortality of 15.8% by the end of the second year of life. Mortality at two years was 0.9% in the unaffected cohort (0.24% for live births). Among the controls, there were 8 stillbirths, two deaths because of prematurity and its complications and one death at 2 years of age because of acute fulminating leukaemia.

Contribution of specific congenital anomalies.

Approximately half of the overall birth prevalence was due to congenital heart disease and central nervous system anomalies. Neural tube defects occurred at a rate of 19 per 10,000 (95% CI, 13.8 to 23.9) (1 in 526 births). Severe CHD occurred at a rate of 32 per 10,000 (95% CI, 25.3 to 38.3) (1 in 313 births) and accounted for 21.4% of all CHD cases. Chromosomal anomalies whose risk is associated with increased maternal age (trisomies 21, 18, and 13) occurred with a combined prevalence of 25 per 10,000 (95% CI, 19.6 to 31.3) (1 in 392 births). Trisomy 21 accounted for most cases of chromosomal anomalies, with a prevalence of 22 per 10,000 (95% CI, 16.7 to 27.4) or 1 in 456 births (table 2).

Two-thirds of all cases of CAs (773/1179, 65.6%) were isolated (e.g., they involved a single body system) (table 3).

Risk factors. As a proxy of risk factor prevalence in the underlying population, we used the frequency of selected maternal or parental risk factors for CAs among controls in the nested case-control study (figure 3). The most frequent potentially modifiable factors included lack of periconception folic acid supplement use, consanguinity, high body mass index, advanced maternal age, smoking (first or second-hand) and maternal diabetes. Nearly 6% of non-primiparous women had one prior child with a major CA. In the univariate analysis, the nested case-control study (table 4) detected overall increased odds ratios for all CAs combined for consanguinity, advanced maternal age, high parity, maternal illiteracy, maternal university education, X-ray exposure during pregnancy, maternal diabetes, and positive family history of CA in a sibling. Increased odds ratios with confidence intervals, including unity, were also found for maternal depression and hypertension (table 4). In the multiple logistic regression model, only first-degree consanguinity (OR 1.5, 95% CI 1.28 to 1.81), maternal age of more than forty years (OR 2.1, 95% CI 1.35 to 3.3), maternal illiteracy (OR 1.4, 95% CI 1.17 to 1.7), maternal university level education, (OR 1.74, 95% CI 1.24 to 2.44), maternal diabetes mellitus (OR 1.98, 95% CI 1.33 to 2.95) and history of a sibling with an anomaly (OR 1.49, 95% CI 1.04 to 2.12) were retained in the model (table 5). The Hosmer and Lemeshow goodness of fit p value was 0.08, and Nagelkerke R^2 was 0.055, explaining 6% of the effect on CAs.

Of the 223 mothers with DM who had CA-affected foetuses (223/1,179, 18.9%), 36 (3%) had overt DM (ODM), and 187 (15.7%) had gestational DM (GDM). Of the mothers with GDM, 50 (26.7%) required insulin. Among the controls, 200 mothers had diabetes (200/1,179, 15.8%), of whom 12 (0.9%) had ODM, and 188 (15.9%) had GDM. Of the latter, 29 (14.5%) required insulin.

Maternal age over 40 years was high at 7% among mothers of babies with CA compared to 3.6% among controls mothers (OR 2.09, 95% CI 1.43 to 3.05, p=0.0002) (table 4). This was mainly due to chromosomal aneuploidy. Further subgroup analysis showed non-chromosomal anomalies (NCA) was found in 55 mothers (4.6%) compared to 3.6% among the controls mothers (OR 1.29, 95% CI 0.86 to 1.9, p= 0.2). The main NCA found were CHD in 22 (40%), 7 (12.7%) were severe CHD and neural tube defects in 5 (9.1%).

Discussion

This longitudinal study of CAs in a pregnancy cohort in Saudi Arabia, followed from mid-gestation through age 2 years, had three integrated aims: to describe the population's risk factor profile, document the associated birth prevalence of CAs, and assess survival

as a critical health outcome.[7] Gathering information about these three critical areas is crucial when planning and evaluating policies and interventions, be they aimed at primary prevention (e.g., folic acid fortification to prevent neural tube defects) or at improving care.

The burden of CAs was high in this population. The study documented a remarkably high birth prevalence of CAs of 412 per 10,000 or 1 in 24 total births. This rate is higher than that reported in studies from many high-income countries, as those reported by EUROCAT (261/10,000 births),[11] BINOCAR (206/10,000 births),[12] and the Bradford (BIB) study (305/10,000).[13] This prevalence of CAs is also higher than that previously reported from Saudi Arabia (115 to 257 per 10,000 live births).[14-16] Although some studies report an even higher prevalence, e.g., such as an antenatal CA prevalence of 521/10,000 pregnancies screened, and a prevalence among livebirths of 465/10,000,[17] these figures may be overestimates of the true prevalence because of the inclusion of mothers referred from other institutions. In the current study, we strove to obtain as complete an ascertainment as possible by initiating follow-up in pregnancy and extending it through the second year of life, by including stillbirths and elective termination of pregnancies for foetal anomalies (ETOPFAs), and by successfully including some genetic conditions that tend to be diagnosed after the newborn period.

However, the high prevalence of CAs is likely to be due not only to the completeness of the ascertainment but also to the high frequency

of adverse risk factors in the underlying population, as documented in the controls of the nested case-control study. When focusing on factors that are potentially modifiable, three such factors seem to stand out. The first is insufficient folic acid use in this cohort (<10% in the periconception period). The rate of neural tube defects was 19 per 10,000/births (table 2), at least three times higher than the rate of 6 per 10,000/births, which seems achievable by providing sufficient folic acid to women of childbearing age.[18 19] Although legislation requiring the mandatory fortification of flour had been in place in Saudi Arabia for years prior to this study (Kingdom of Saudi Arabia, 2000; Food fortification initiative, 2013),[20 21] our findings suggest that there are gaps in coverage or effectiveness, which could be evaluated with nutrition or blood folate surveys. Such information would provide important evidence to improve folate sufficiency in the population, with its attendant health benefits, including a substantial reduction in the burden of neural tube defects. Because of the inclusion of stillbirths and pregnancy terminations, this study also provides a fuller estimate of the potential benefits of primary prevention than if only livebirths had been identified (representing just over half of all cases, 30/54).

The second factor is maternal diabetes (tables 4 and 5). Diabetes is an established risk factor for many CAs, and diabetes control before conception has been shown to reduce and nearly normalize CA risk.[9 22 23] Several avenues for preventing diabetes and its health effects are

available, including population screening (many diabetic women are undiagnosed), health care and counselling, and education on healthy lifestyle and dietary choices starting from childhood. The current reported prevalence in Saudi Arabia of overt diabetes in women above age 40 years ranges from 7.7% – 21.7%. [24 - 26] In the study cohort, overt diabetes was observed in 2% of women and increased in women 30 years old or older. Al-Nozha and colleagues [27] reported a prevalence of overt diabetes of 11.6% in women aged 30-39 years and >22% in women aged ≥40 years compared to 2.7% and 7.1% in our study, respectively. Though lower than these estimates, the prevalence of overt diabetes in the study cohort is alarmingly high.

Third, we observed a high rate of parental consanguinity (54.5%), especially first-cousin marriages (48.0%). These marriages are common in many parts of the Middle East, Africa, and the Indian subcontinent,[28-30] with one estimate suggesting that "one billion people live in communities with a preference for consanguineous marriage" (Hamamy, 2012).[29] This preference has deep social roots. Nevertheless, education combined with preconception and premarital counselling can be important prevention strategies by focusing on increasing awareness to allow couples to make more informed choices. Close consanguinity is a known risk factor for CAs,[30] as well as Mendelian conditions such as inborn errors of metabolism (occurring in 1 in 770 births in this study), as confirmed in prior reports from Saudi Arabia and from the world literature. [31 32]

Advanced maternal age (>40 years) was high (7%) among mothers of babies affected with CA in the cohort studied. This is comparable to 6% among French mothers but higher than mothers from other 14 European countries (Loane et.al., 2009). [33] Advanced maternal age is increasing over the last two decades [33,34] and is affecting the prevalence of aneuploidy. The risk for NCA were similar to controls and recent reports suggest that it has a protective effect. [35] Several reports have shown a higher prevalence of specific CA among babies of mothers at this age group like neural tube defects, cleft lip, oesophageal atresia with or without tracheal fistula. We found a high prevalence of CHD and neural tube defects.

Structured health education programs at several levels should emphasize the importance of planed pregnancies at the optimal age (20-30 years), ensure adequate periconceptional folic acid intake (400 to 800 µg daily) [36] and detailed fetal anomaly scan. A nation-wide CA registry will help to give a fuller picture and monitor the trends and the results of any intervention.

We did not diagnose cases of congenital rubella syndrome. This is likely due to the active immunization programme in Saudi Arabia, with a measles, mumps and rubella vaccine uptake of 97%. In

addition, preschool age girls are given a booster vaccine against rubella.

In a prior publication, we reported a low regular (periconception) folic acid (FA) intake (9.7%) in this study population [37] and suggested fortification of rice in addition to wheat, complemented by education programmes supporting FA supplementation, as an efficient strategy to achieve folate sufficiency in the population.

Finally, our findings emphasize the impact of CAs in this population by documenting not only birth prevalence but also the associated early mortality (table 1), which was 15.8% by the second year of life (nearly all in the first year). Further supporting the high impact of CAs are the findings by Majeed-Saidan and colleagues [38] who reported that 36% of deaths in a large neonatal intensive care unit in Riyadh were due to lethal CAs. These findings highlight the crucial importance and urgency to improve care in addition to primary prevention.

This study demonstrated the importance of the "triple surveillance" programme, suggested by Botto and Masteroiacova,[4] for identifying the risk factors for CAs (causes), estimating the burden of the disease (prevalence), and assessing disease outcome (mortality). This will ultimately lead to disease

burden reduction or prevention by instituting appropriate interventions.

The study has limitations. Because of the cohort design, the resulting sample size did not allow a more detailed analysis of specific CA groups. Estimates of some key risk factors, such as folic acid insufficiency, were based on maternal reports (e.g., reported supplement use) rather than biomarkers. Furthermore, the pregnancy cohort was mainly from families of Saudi army personnel dependents. Although the Saudi Army recruits from all sectors of Saudi society, a broader survey of the Saudi population would provide additional information to better assess gaps and opportunities for prevention and care nationwide.

Conclusion. This longitudinal surveillance programme that encompassed the causal chain from risk factors to health outcomes documented several opportunities to reduce the burden of CAs through primary prevention and better care. Folic acid fortification, preconception diabetes screening, and consanguinity-related counselling could have significant health benefits in this cohort and arguably in the larger Saudi population, particularly if associated with a national CA monitoring programme to support and track the impact of interventions.

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Author's statement:

AMK study conception and design, revised the manuscript. **MAMS**, study conception and design, drafting and revising the manuscript., **MSR**, study design, data collection. **AMH**, data collection, revised the manuscript. **LDB**, study design, critically revised the manuscript for intellectual content. **HSB**, statistical analysis and revised the manuscript. **ANA**, study design, data collection, revised the manuscript. All authors approved the submission of the manuscript.

Written informed consent:

Consent for cord blood samples for future DNA analysis was obtained from the mothers in the nested case-control study only.

Data sharing statement:

Dataset can be obtained on request through a third party "King AbdulAziz city for science and technology".

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References

1. World Health Organization. Sixty -Third World Health Assembly. CA Report by the Secretariat, A63/10. Geneva, Switzerland: World Health Organization, 2010.

2. World Health Organization. Global Health Observatory (GHO) data. Under-five mortality 2016. http://www.who.int/gho/child_health/mortality/mortality_under_five_text/en/ (accessed 12 December 2017).

3. Christianson AL, Howson CP, Modell B. Global report on CA: the hidden toll of dying and disabled children. White Plains (NY): March of Dimes Defects Foundation 2006.

4. Tennant PWG, Pearce MS, Bythell M, *et al.* 20-year survival of children born with congenital anomalies:

a population-based study. Lancet 2010; 375: 649–56.

5. Wang Y, Hu J, Druschel CM, *et al.* Twenty-Five–Year Survival of Children with Birth Defects in New York State: A Population-Based Study. Birth Defects Research (Part A) 201;1 91:995-1003.

6. Ko HS, Kim DJ, Chung Y, *et al*. A national cohort study evaluating infant and fetal mortality caused by birth defects in Korea. BMJ Open 2017;7: e017963. doi:10.1136/bmjopen-2017-017963

7. Botto LD, Mastroiacovo P. Triple surveillance: a proposal for an integrated strategy to support and accelerate birth defect prevention. Ann. N. Y. Acad. Sci 2018; (1414):126-36.

8. Avni FE, Maugey-Laulom B, Cassart M, *et al.* Foetal genitourinary tract. In: Callen PW, ed. Ultrasonography in Obstetrics and Gynecology. 5th Ed. New York: W.B. Saunders 2007; 640-75.

9. Metzger BE, Gabbe SG, Persson B, *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of

hyperglycemia in pregnancy. *Diabetes Care* 2010; 33(3): 676–82. doi: 10.2337/dc09-1848.

10. EUROCAT. Eurocat Guide 1.3. Instructions for registration and surveillance of congenital anomalies. Belfast, Northern Ireland University of Ulster 2005. http://www.eurocat-network.eu/content/Section%202.4-%2027_Oct2016.pdf

11. EUROCAT. Prevalence Tables, 2011-2015 http://www.eurocat-network.eu/newprevdata/showPDF.aspx?winx=1896&winy=940&file=allsubgroups.aspx 2015. (accessed 12 December 2017).

12. Springett A, Budd J, Draper ES, *et al*. Congenital Anomaly Statistics 2012 England and Wales, London 2014. www.binocar.org/content/Annual%20report%202012_FINAL_nologo.pdf.

13. Sheridan E, Wright J, Small N, *et al*. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet 2013; 382(9901): 1350–9. doi: 10.1016/S0140-6736(13)61132-0.

14. Al Bu Ali WH, Balaha MH, Al Moghannum MS, *et al*. Risk factors and birth prevalence of CA and inborn errors of

metabolism in Al Ahsa, Saudi Arabia. Pan Afr Med J 2011; 8: 14.

15. Fida NM, Al-Aama J, Nichols W, *et al*. A prospective study of congenital malformations among live born neonates at a University Hospital in Western Saudi Arabia. Saudi Med J 2007; 28(9): 1367–73.

16. Refat MY, Al-Moghanem M, McDonald, *et al*. Major CA at King Fahd Hofuf Hospital: Prevalence, risk factors and outcome. Ann Saudi Med 1995; 15(4): 339–43.

17. Sallout B, Obedat N, Shakeel F, *et al*. Prevalence of major congenital anomalies at King Fahad Medical City in Saudi Arabia: a tertiary care centre-based study. Ann Saudi Med 2015; 35(5): 343–51.

18. Kancherla V, Oakley GP Jr, Brent RL. Urgent global opportunities to prevent CA. Semin Foetal Neonatal Med 2014; 19(3): 153–60.

19. Youngblood ME, Williamson R, Bell KN, *et al*. Update on global prevention of folic acid-preventable spina bifida and anencephaly. CA Res A Clin Mol Teratol 2013; 97(10): 658–63. doi: 10.1002/CAra.23166. Epub 2013.

20. Kingdom of Saudi Arabia, Ministry of health, Nutritional department directive. Number 652/1/26, 2000; 13/09/2000.

21. Food Fortification Initiative. (2013). http://www.ffinetwork.org/country_profiles/country.php?record=194 (accessed 12 December 2017).

22. Kitzmiller JL, Wallerstein R, Correa A, *et al.* Preconception care for women with diabetes and prevention of major congenital malformations. CA Res A Clin Mol Teratol 2010; 88(10): 791–03. doi: 10.1002/CAra.20734.

23. Simeone RM, Devine OJ, Marcinkevage JA, *et al* Diabetes and congenital heart defects: a systematic review, meta-analysis, and modeling project. Am J Prev Med 2014; 48(2): 195–204. doi: 10.1016/j.amepre.2014.09.002.

24. Al-Nuaim AR, Al-Rubean K, Al-Mazrou Y, *et al*. Prevalence of diabetes mellitus, obesity and hypercholesterolemia in Saudi Arabia: national chronic disease survey. Riyadh (KSA): Ministry of Health and King Saud University. ISBN: 1995; 9960-603-01-6.

25. El-Hazmi M, Warsy A, Al-Swailem AR, *et al*. Diabetes mellitus as a health problem in Saudi Arabia. East Mediterr Health J 1998 (4): 58–67.

26. Warsy AS, el-Hazmi MA. Diabetes mellitus, hypertension and obesity--common multifactorial disorders in Saudis. East Mediterr Health J 1999; 5(6): 1236–42.

27. Al-Nozha MM, Al-Maatouq M, Al-Mazrou YY. *et al*. Diabetes mellitus in Saudi Arabia. Saudi Med J 2004; 25(11): 1603–10.

28. El-Mouzan MI, Al-Salloum AA, Al-Herbish AS, *et al*. Regional variations in the prevalence of consanguinity in Saudi Arabia. Saudi Med J 2007; 28(12): 1881–4.

29. Hamamy H. Consanguineous marriages: Preconception consultation in primary health care settings. J Community Genet 2012; 3(3): 185–92.

30. Majeed-Saidan MA, Ammari AN, AlHashem AM, *et al.* Effect of consanguinity on CA in Saudi women: results from a nested case-control study. CA Res A Clin Mol Teratol 2015; 103(2): 100–4. doi: 10.1002/CAra.23331.

31. Mak CM, Lee HC, Chan AY, *et al*. Inborn errors of metabolism and expanded newborn screening: review and update. Crit Rev Clin Lab Sci 2013; 50(6): 142–62. doi: 10.3109/10408363.2013.847896.

32. Moammar H, Cheriyan G, Mathew R, *et al*. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med 2010; 30(4): 271–7. doi: 10.4103/0256-4947.65254.

33. Loane M, Dolk H, Morris JK, a EUROCATE working group. Maternal age-specific risk of non-chromosomal anomalies. BJOG 2009; 116:1111-19.

34. Nabukrea S, Wingate MS, Alexander GR, et al. First -time births among women 30 years and older in the United States: patterns and risk of adverse outcome. J Reprod Med 2006; 9:676-82.

35. Goetzinger KR, Shanks AL, Odibo AO, st al. Advanced maternal age and the risk of major congenital anomalies. Am J Perinatol. 2017; 34(3):217-22.

36. U.S. Preventive Task force. Folic acid for the prevention of neural tube defects: US preventive services task force recommendation statement. Ann Intern Med. 2009; 150:626-31.

37. Al Rakaf MS, Kurdi AM, Ammari AN, *et al*. Patterns of folic acid use in pregnant Saudi women and prevalence of neural tube defects — Results from a nested case–control study. Preventive Medicine Reports 2 (2015) 572–576.

38. Majeed-Saidan MA, Kashlan FT, Al-Zahrani AA, *et al*. Pattern of neonatal and postneonatal deaths over a decade (1995--2004) at a Military Hospital in Saudi Arabia. Saudi Med J 2008; 29(6):879-83.

Tables

Legend: Table 1 Distribution and rates of congenital anomalies (CA) among the cohort's pregnancy outcomes, and associated mortality.

	Total cohort		With CA			Timing of CA detection				Mortality among livebirths with CA					
						Prenatal		Postnatal		Overall (0-2 years)		1st week		Total 1st year	
Birth outcome	No	%	No.	%	Rate /10000	No.	%	No.	%	No.	%	No.	%	No.	%
Live births	28 369	99	1 123	95.3	396	505	45.0	618	55	177	15.8	64	5.7	158	14.1
Stillbirths	259	0.9	38	3.2	1467	38	100								
ETOPFA	18	0.1	18	1.5	10000	18	100								
Total	28 646		1 179		412	561	47.6	618	52.4						

Footnote:

†ETOPFA, Terminations of pregnancy for foetal anomalies.

Stillbirth (foetal death at 20 weeks of gestation or greater).

Table 2 Prevalence and distribution of congenital anomalies, overall and by pregnancy outcome.

Birth defects	Number*	%	Prevalence per 1000 births (total births = 28646)	Live births		Prevalence per 10000 live birth (total live births = 28376	Stillbirth		ETOPFA	
				No.	%		No.	%	No.	(%)
Any	1179	100	412	1123	95.3	396	38	3.2	18	1.5
Nervous system	160	13.6	56	129	80.6	45.7	18	11.3	13	8.1
Neural Tube Defects	54	4.6	19	30	55.5	10.6	11	20.4	13	24.1
Anencephalus	26	2.2	9	7	26.9	2.5	8	30.8	11	42.3
Encephalocele	11	0.9	4	9	81.8	3.2	1	9.1	1	9.1
Spina Bifida	17	1.4	6	14	82.4	4.9	2	11.8	1	5.9
Hydrocephaly	25	2.1	9	23	92.0	8.1	2	8.0		
Microcephaly	28	2.4	10	24	85.7	8.5	4	14.3		
Eye	33	2.8	12	33	100	11.6				
Anophthalmus/microphthalmus	11	0.9	4	11	100	3.9				
Congenital cataract	5	0.4	2	5	100	1.8				
Congenital glaucoma	9	0.8	3	9	100	3.2				
Ear, face and neck	7	0.6	2	7	100	2.5				

Anotia/microtia	7	0.6	2	7	100	2.5				
Cardiac	425	36.0	148	420	90.9	148	4	0.9		
Severe congenital heart defects *	91	7.7	32	89	97.8	31.4	2	2.2		
Common arterial truncus	3	0.3	1	3	100	1.1				
Transposition of great vessels	13	1.1	5	13	100	4.6				
Single ventricle	6	0.5	2	6	100	2.1				
Atrioventricular septal defect	17	1.4	6	15	88.2	5.3	2	11.8		
Tetralogy of Fallot	15	1.3	5	15	100	5.3				
Tricuspid atresia and stenosis	4	0.3	1	4	100	1.4				
Pulmonary valve stenosis	22	1.9	8	21	95.5	7.4	1	4.5		
Pulmonary valve atresia	9	0.8	3	9	100	3.2				
Aortic valve atresia/stenosis	5	0.4	2	5	100	1.8				
Hypoplastic left heart	15	1.3	5	15	100	5.3				
Hypoplastic right heart	5	0.4	2	5	100	1.8				
Coarctation of aorta	14	1.2	5	14	100	4.9				
Total anomalous pulmonary venous return	2	0.2	0.7	2	100	0.7				
Ventricular septal defect	171	14.5	60	171	100	60.2				
Atrial septal defect	214	18.2	74.7	214	100	75.4				
Oro-facial clefts										
Cleft lip with or without palate	42	3.6	14.7	35	83.3	12.3	5	11.9	2	4·8
Cleft palate only	11	0.9	3.8	11	100	3.9				
Respiratory	33	2.8	11.5	33	100	11.6				
Choanal atresia	5	0.4	1.7	5	100	1.8				

Digestive system	74	6.3	25.8	71	95.9	25.0	3	4.1		
Esophageal atresia with/without fistula	12	1.0	4.2	12	100	4.2				
Ano-rectal atresia and stenosis	26	2.2	9.1	25	96.2	8.8	1	3.8		
Diaphragmatic hernia	18	1.5	6.3	16	88.9	5.6	2	11.1		
Abdominal wall defects	7	0.6	2.4	6	85.7	2.1	1	14.3		
Gastroschesis	2	0.2	0.7	1	50.0	0.4	1	50.0		
Omphalocele	5	0.4	1.7	5	100	1.8				
Urinary	323	27.4	113	318	98.5	112.1	4	1.2	1	0.3
Bilateral renal agenesis	18	1.5	6.3	15	83.3	5.3	2	11.1	1	5.6
Renal dysplasia	60	5.1	21	58	96.7	20.4	2	3.3		
Congenital hydronephrosis	194	16.5	67.7	194	100	68.4				
Genital	127	10.8	44.3	126	99.2	44.4	1	0.8		
Hypospadias	108	9.2	37.7	108	100	38.1				
Indeterminate sex	3	0.3	1.0	2	66.7	0.7	1	33.3		
Limb	99	8.4	34.6	92	92.9	32.4	4	4.0	3	3.0
Limb deficiencies, all	17	1.4	5.9	17	100	6.0				
Upper limb deficiency	12	1.0	4.2	12	100	4.2				
Lower limb deficiency	7	0.6	2.4	7	100	2.5				
Club foot - talipes equinovarus	19	1.6	6.6	15	78.9	5.3	2	10.5	2	10.5
Hip dislocation and/or dysplasia	24	2.0	8.4	23	95.8	8.1			1	4.2
Polydactyly	23	2.0	8.0	23	100	8.1				
Syndactyly	9	0.8	3.1	9	100	3.2				
Musculo-skeletal	40	3.4	14	33	82.5	11.6	7	17.5		

Craniosynostosis	6	0.5	2.1	6	100	2.1				
Achondroplasia	3	0.3	1	2	66.7	0.7	1	33.3		
Thanatophoric dysplasia	2	0.2	0.7	2	100	0.7				
Jeune syndrome	2	0.2	0.7	1	50.0	0.4	1	50.5		
Other malformations	42	3.6	14.7	40	95.2	14.1	1	2.4	1	2.4
Situs inversus	10	0.8	3.5	10	100	3.5				
By underlying cause										
Chromosomal	82	7.0	8.6	79	96.3	27.8	3	3.7		
Down Syndrome/trisomy 21	63	5.3	22	62	98.4	21.8	1	1.6		
Edward syndrome/trisomy 18	8	0.7	2.8	7	87.5	2.5	1	12.5		
Patau syndrome/trisomy 13	2	0.2	0.7	2	100	0.7				
Turner syndrome	3	0.3	1	2	66.7	0.7	1	33.3		
Wolff-Hirschhorn syndrome	1	0.1	0.3	1	100	0.4				
Genetic syndromes (including microdeletions)	38	3.2	13.2	36	94.7	12.7	1	2.6	1	2.6
Teratogenic (Carbamazepine embryopathy)	1	0.1	0.3	1	100	0.4				
Conditions outside Q chapter of ICD-10										
Inborn error of metabolism	37	3.1	12.9	37	100	13.0				
Endocrine disorders	7	0.6	0.2	7	100	2.5				
Other	11	0.9	4	11	100	3.9				

Legend:

* The total number of birth defects is greater than the total umber of affected births because some had more than one major CA.

§ Severe congenital heart disease (EUROCAT definition): common arterial trunk (Q200), double outlet right ventricle (Q201), transposition of great arteries (Q203), single ventricle (Q204), atrioventricular septal defect (AVSD) (Q212), tetralogy of Fallot (Q213), pulmonary valve atresia (Q220), Ebstein anomaly (Q225), hypoplastic right heart (Q226), aortic valve atresia and stenosis (Q230), mitral valve anomalies (Q232, Q233), hypoplastic left heart (Q234), coarctation of the aorta (Q251), aortic atresia / interrupted aortic arch (Q252), total anomalous pulmonary venous return (Q262).

Legend: Table 3 Common single congenital anomalies (CA) per body system involved

Body system	Total number Of CA	Isolated CA		Common isolated anomalies
		No.	%	
Cardiovascular	424	265	62.5	ventricular septal defects in 75 (28.3%). Atrial septal defects in 67 (25.3%). Pulmonary valve atresia and stenosis in 18 (6.8%). Sever CHD in 54 (20.4%)
Urinary	323	229	70.8	Congenital hydronephrosis in 147 (64.2%). Bilateral renal agenesis in 3 (1.3%).
Central nervous	161	68	42.8	Neural tube defects in 32 (47.1%). Encephalocele in 4 (5.9%)
Gastrointestinal	74	33	44.6	Ano-rectal atresia and stenosis in 16 (48.5%).

				Diaphragmatic hernia in 6 (18.2).
Limb	97	31	32	Total limbs reduction in 9 (29%). Upper limb reduction in 7 (22.6%). Lower limb reduction in 3 (9.7%).
Eye	32	14	43.8	Congenital glaucoma in 6 (42.9%). Congenital cataract in 4 (28.6%). Anophthalmia + microphthalmia in 3 (21.4%).

Legend: Table 4 Distribution of parental socio-demographic characteristics and association with congenital anomaly risk (univariate analysis).

Variable	Cases (total n=1179)		Controls (total n=1262)		Odds Ratio‡	95% CI	
	No.	%	No.	%		Lower	Upper
Consanguinity							
Non-consanguineous	537	45.5	693	54.9	Ref	-	-
Consanguineous	642	54.5	569	45.1	1.53	1.30	1.8
Maternal age (years)							

<20	24	2.0	48	3.8	0.58	0.35	0.96
20-30	599	50.8	694	55.0	Ref	-	-
31-40	473	40.1	474	37.6	1.16	0.98	1.37
>40	83	7.0	46	3.6	2.09	1.43	3.05
Paternal age (years)							
20-30	341	28.9	403	31.9	0.92	0.76	1.10
31-40	548	46.5	593	47.0	Ref	-	-
41-50	240	20.4	225	17.8	1.15	0.93	1.43
> 50	50	4.2	41	3.2	1.32	0.86	2.03
Maternal body mass index‡							
<18·5	24	2.1	35	2.8	0.75	0.44	1.29
18·5-24·99	324	27.8	388	30.8	0.91	0.74	1.12
25·0-29·99	352	30.2	385	30.5	Ref	-	-
≥30	464	39.9	453	35.9	1.12	0.92	1.36
Previous deliveries (parity)							
Nulliparous	216	18.3	273	21.6	0.92	0.74	1.16
Para 1-2	374	31.7	436	34.5	Ref	-	-
Para 3-4	283	24.0	273	21.6	1.21	0.97	1.50
Para ≥5	306	26.0	280	22.2	1.27	1.03	1.58
Family monthly income Saudi riyals (US $)							
<3,000 SR (<800$)	19	1.9	12	1.0	1.87	0.89	3.92
10,000-14,000 SR (2667-3999$)	235	23.2	277	22.3	Ref	-	-

3,000-6,999 SR (800-1866$)	232	22.9	291	23.4	0.94	0.74	1.20
7,000-9,999 SR (1867-2666$)	367	36.3	496	39.9	0.87	0.70	1.09
≥15, 000 (≥4000$)	158	15.6	167	13.4	1.12	0.84	1.47
Maternal education							
Illiterate	391	33.2	333	26.4	1.50	1.26	1.80
Schooling up to high school	671	56.9	859	68.1	Ref	-	-
University	117	9.9	70	5.5	2.05	1.49	2.81
Folic acid intake							
Periconceptional	109	9.2	128	10.1	Ref	-	-
Improper use§	1070	90.8	1134	89.9	1.04	0.79	1.36
Parental Smoking							
Neither parent smoked	837	71.0	888	70.4	Ref	-	-
One or both parents smoked	342	29.0	374	29.6	0.97	0.82	1.16
Radiation exposure in pregnancy							
None	1161	98.5	1254	99.4	Ref	-	-
Radiation exposure in pregnancy	18	1.5	8	0.6	2.43	1.05	5.61
Diabetes mellitus (DM)							
No DM	956	81.1	1062	84.2	Ref	-	-
DM on insulin (all, overt & gestational	86	7.3	41	3.2	2.34	1.60	3.43
Gestational DM on diet only	137	11.6	157	12.6	0.91	0.62	1.16

Sibs of cases and controls (primiparous mothers excluded)							
No affected sibling	757	78.6	932	94.2	Ref-	-	-
Sibling with CA	85	8.8	58	5.7	1.61	1.14	2.27
Medication use in pregnancy							
None	792	67.2	951	75.3	-	-	-
Thyroxin	102	8.7	106	8.4	1.03	0.78	1.37
Insulin	86	7.3	40	3.2	2.34	1.59	3.45
Methyldopa	14	1.2	14	1.1	1.07	0.51	2.26
Maternal systemic illnesses							
None	808	68.5	971	76.9	Ref-	-	-
Mothers with Hypothyroidism	123	10.4	128	10.1	1.03	0.80	1.34
Mothers with Bronchial asthma	106	9.0	97	7.7	1.19	0.89	1.58
Mothers with depression	12	1.0	6	0.5	2.15	0.81	5.75
Mothers with essential hypertension	23	2.0	15	1.2	1.65	0.86	3.19

Footnote:

[‡]BMI not available for 15 mothers

Some families declined reporting their income.

§Improper-use includes FA taken post conception and 49 mothers (43 case mothers and 6 control mothers) who were not sure about their intake.

Legand: Table 5 multiple logistic regression model results for the significant risk factors on univariate analysis

Variable	ADJUSTED OR (from multiple logistic regression model) †			CRUDE OR (from univariate analysis)		
	OR	95% C.I.		OR	95% C.I.	
		Lower	Upper		Lower	Upper
Consanguinity, none (reference group)	-	-	-	-	-	-
Consanguinity, first degree	1.52	1.28	1.81	1.53	1.30	1.81
Maternal age, 20-30 years (reference group)	-	-	-	-	-	-
Maternal age, <20 years	0.54	0.32	0.91	0.58	0.35	0.96
Maternal age, >40 years	2.11	1.35	3.30	2.09	1.43	3.05

Maternal education, up to high school (reference group)	-	-	-	-	-	-
Maternal education, illiterate	1.41	1.17	1.70	1.50	1.26	1.80
Maternal education, university	1.74	1.24	2.44	2.05	1.49	2.81
Diabetes on insulin, overt or gestational (yes/no)	1.98	1.33	2.95	2.34	1.60	3.43
Sibling with anomalies (yes/no)	1.49	1.04	2.12	1.61	1.14	2.27

†: Adjustment for consanguinity, maternal age, maternal education, diabetes mellitus, sibling with anomalies.

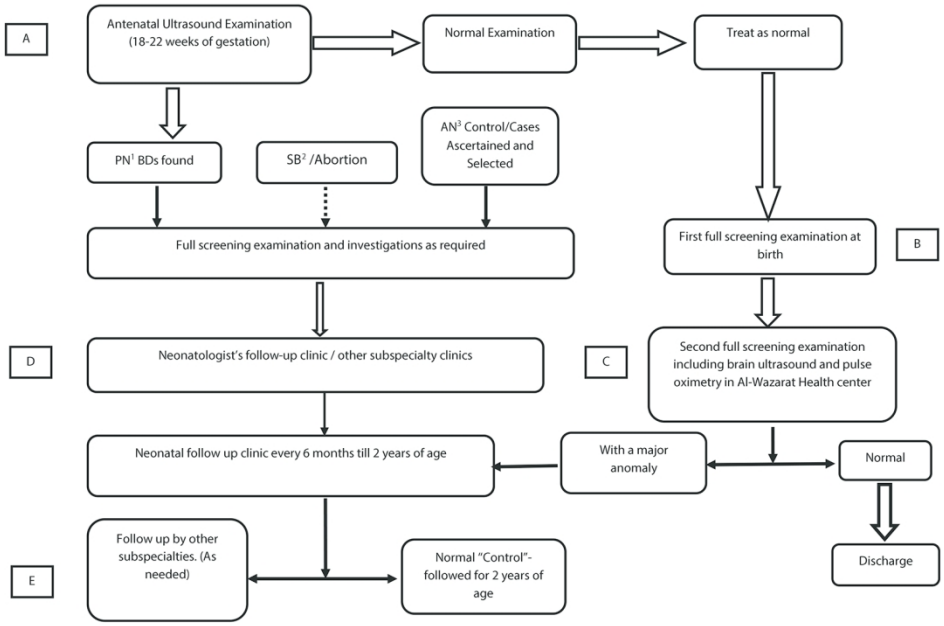
Figures legend:

Legend: Figure _1 Catchment site and the study flow chart.

Legend: Figure _2 Study population and distribution of pregnancies and their outcomes.

Legend: Figure _ 3 Frequency among control subjects of selected risk factors for CA.

Figure 1- Catchment site and the study flow chart.

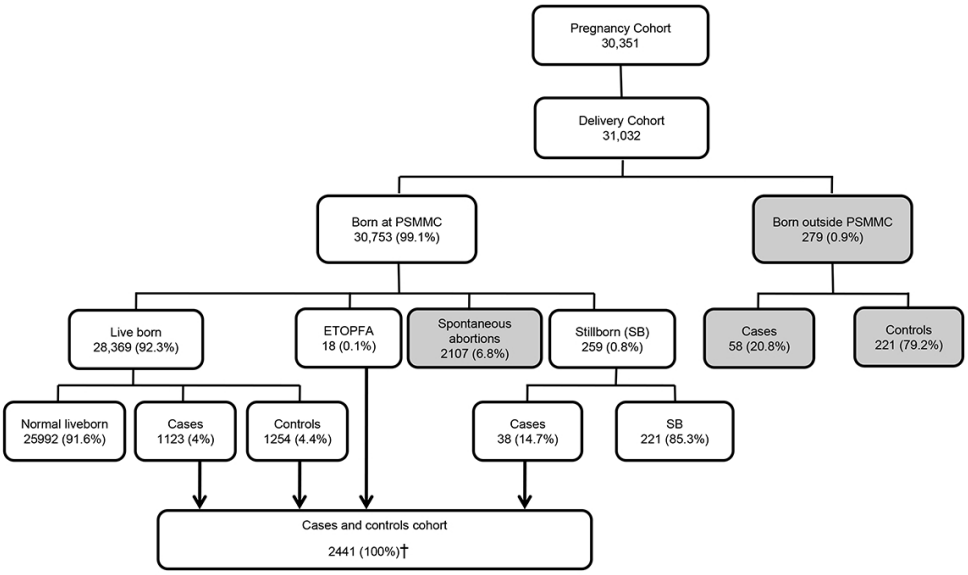


Legend: Case catchment areas (A to E). A: antenatal clinic, B: at birth, C: the "one-month clinic, D: geneticist "one-month clinic", and E: other areas. 1,2,3 are postnatal, stillbirth and antenatal respectively. BD. Birth defect

Legend: Figure _1 Catchment site and the study flow chart.

150x120mm (300 x 300 DPI)

Figure _2 Study population and distribution of pregnancies and their outcomes.

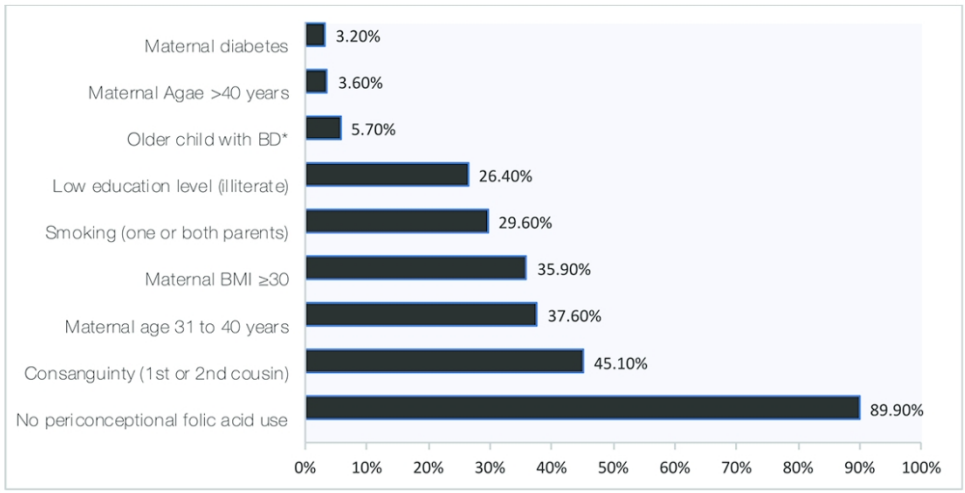


Legend:

PSMMC, Prince Sultan Military Medical City; ETOPFA, Elective termination of pregnancy for foetal anomaly.

†Eight control foetuses were stillbirth.

Figure 3. Frequency among control subjects of selected risk factors for birth defects.



Legend:
BMI, pre-pregnancy maternal body mass index
BD, birth defect
*Frequency of prior child with BD computed among non-primiparous women

Legend: Figure _ 3 Frequency among control subjects of selected risk factors for birth defects.

99x79mm (300 x 300 DPI)

Supplement file

Appendix

Confidential

PSMMC

Booklet of

"Pattern of Fetal Malformations in a Saudi Population"

☐ **Study** ☐ **Control**

Local ID No.: _____ / Year 201

Mother's Name: _____

Mother's MRN: _____

Baby's Name: _____

Baby's MRN: _____

Date of Birth: ____ / ____ / ____

Contact No: **Mobile (husband)** _____

Mobile (wife) _____

Home _____

Confidential

Keep in a safe place

Pattern of Malformations Study – PSMMC

(Baby and mother)

Local ID No _____

D.O.B. (dd/mm/yy): _____ /_____ / _____ Year: 201__

D. O. B./ Year Unknown □

Sex: Male □ Female □ indeterminate □ Not known □

No. of babies delivered: Singleton 1 □ Twin 2 □ Triplet 3 □ Quadruplet 4 □ Quintuplet 5 □ Sextuplet 6 □

Not known 9 □

Specify twin type of birth, like or unlike sex, zygosity:_____

No. of malformed (in multiple set): No. _____ Not known □

Type of birth: Live Birth (LB). □ Still Birth (SB) □ Spontaneous Abortion □

TOP □ Not known □

Civil registration status LB □ SB □ No CR □ Not known □

Birth weight (g): _____ **Confirmed** □

Length of gestation (weeks): _____ **Confirmed** □

Survival beyond one week of age:

Yes □ No □ Alive at discharge <1 Week □ Not known □

Date of death (dd/mm/yy): ____/_____/_____ Year:_____

D. O. B. Mother (dd/mm/yy): _____/____/____ Year:_____ Confirmed □

Age of mother at delivery: _____

Pattern of Malformations Study – RMH

(Baby and mother)

Local ID No _____

Mother's residence code at conception: Province _____ District _____

Mother's residence code at delivery: Province _____ District _____

Total No. of previous pregnancies: None □ Number (___) Not known □

When discovered:

At birth □ Less than 1 wk □ 1-4 wk □ 1-12 m □ >12 m □ Prenatal diagnosis □

At abortion (sp) or termination □ Not known □ Postnatal diagnosis, age not known □

Condition at discovery: Alive □ Dead □ Not known □

Gestational age at discovery (wk): _____

First positive prenatal test:

US at <14 wks □ US at 14-21 wks □ US at ≥ 22 wk □ US GA unknown □
Serum/combined screening □ CVS □ Amniocentesis □ Other tests positive □

No positive test, all results negative □

Specify 'other' prenatal test: _____

Karyotype of infant/ fetus:

Performed, result known □ Performed, result unknown □

Not performed □ Probe test performed □ Failed □ Not known □

Specify karyotype:_____

Post mortem exam:

Performed, result known □ Performed, result unknown □

Macerated fetus □ Not known □ Not performed □

First surgical procedure:

Performed (or expected) in the first year of life □

Performed (or expected) after the first year of life □

Prenatal surgery □ No surgery required □

Too sever for surgery □ Not known □

Pattern of Malformations Study – PSMMC

(Prenatal Malformations)

Local ID No _____

	Code	**Text**
Syndrome:		
Malformation 1:		
Malformation 2:		
Malformation 3:		
Malformation 4:		
Malformation 5:		
Malformation 6:		
Malformation 7:		
Malformation 8:		

Pattern of Malformations Study – RMH

(All Malformations)

Local ID No _____

	Code	**Text**
Syndrome:		
Malformation 1:		
Malformation 2:		
Malformation 3:		
Malformation 4:		
Malformation 5:		
Malformation 6:		
Malformation 7:		
Malformation 8:		

McKusick code: _____

Aetiology:

Chromosome **C** □ Familial **F** □ Isolated **I** □ Multiple **M** □

New Dominant **ND** □ Other Genomic **OG** □ Syndrome **S** □ Teratogens **T** □ Inborn Error of Metabolism**IEM** □ Control **Co** □

View anomaly subgroup(s):

Pattern of Malformations Study – RMH

Local ID No _____

Assisted conception: No □ Induced ovulation only □ Artificial insemination □

In vitro fertilization □ Gamete intrafollopian transfer □

Intracytoplasmic sperm injection □ Egg donation □ Other□

Not known □

Mother's occupation: House wife □ Teacher □ Student □ Other □

Maternal Systemic illnesses;

None □ EHT □ Hypothyroidism □ CHD □

RHD □ CRF □ Asthma □ SCA □ SLE □

IDA □Anxiety □ Depression □ Epilepsy □

Other □ (specify)_____

Weight before pregnancy (Kg) _____

Current weight (Kg) _____

Mother's height (m) _____

Body Mass Index: <18.5 □ 18.5 – 24.9 □ 25 – 29.9 □
30.0 – 34.9 □ 35.0 – 39.9 □ ≥ 40.0 □

True DM: Yes□ No □

Gestational DM on Diet (GDOD) □

Gestational DM on Insulin (GDOI) □

Diabetes screening: GTT (result) 0 time:_____ 1hour:_____ 2 hours:_____

Booking RBS:_____

HbA1c _____

Infectious disease:

Tuberculosis: Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Rubella Before pregnancy □During pregnancy □ 1st T □ 2nd T □ 3rd T □

CMV Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Toxoplasmosis Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Syphilis Before pregnancy □ During pregnancy □ 1st T □ 2ndT □ 3rd T □

UTI Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

Fever Before pregnancy □ During pregnancy □1st T □ 2nd T □ 3rd T □

FLU Before pregnancy □ During pregnancy □1st T □ 2nd T □ 3rd T □

Others Before pregnancy □ During pregnancy □ 1st T □ 2nd T □ 3rd T □

(Specify others) _____

Previous surgical history: Obstetrical/Gynaecological □

Specify; _____

Non Obstetrical □

Specify; _____

Pattern of Malformations Study – PSMMC

Family history & sociodemographic

Local ID No _____

Folic acid supplementation:

Al least 0.4 mg folic acid supplement taken regularly, starting periconceptionally □

Folic acid supplement taken irregularly or starting post-conceptionally □

No folic acid supplement taken or not recorded □

ATC code	Text (**only** drugs taken in the 1st trimester of pregnancy)	
Drugs 1:		
Drugs 2:		
Drugs 3:		
Drugs 4:		
Drugs 5:		

Consanguinity: Not related or relationship more distant than second cousin □

Relationship of second cousin or closer □ Not known □

Specific information on consanguinity:

_____

Sibs with anomalies: Same□ Other □ Same and other □ No □ Not known □

Previous sibs notified to the Saudi Malformations Registry: Yes □ No □ Not known □

Local ID of previous sibs notified to the SMR (1):_____

Local ID of previous sibs notified to the SMR (2):_____

Local ID of previous sibs notified to the SMR (3):_____

Mother's family with anomalies: Same □ Other □ Same and other □ No □

Not known □ Specify _____

Father's family with anomalies: Same □ Other □ Same and other □ No □

Not known □ Specify _____

Maternal education: Illiterate □ Elementary and lower secondary □

Upper secondary □ Tertiary □ Not known □

Family monthly income (SR):_____

(husband or combined husband and wife income)

Nationality: Saudi □ None Saudi □ Only father Saudi □ Only mother Saudi □

General additional comments:

_____

_____

Pattern of Malformations Study – PSMMC

Local Vars. (1)

Local ID No_____

Place of birth: _____

Birth order (in multiple set), (please write as 1st, 2nd, 3rd and so on): _____

Date of discovery (dd/mm/yy): _____/____/_____ **Year**: _____

Amniocentesis: Performed result positive □ Performed result not known □

Not performed □ Performed result negative □ Failed □ Not known □

Ultrasound: Performed result positive □ Performed result not known □

Not performed □ Performed result negative □Failed □ Not known □

Chorionic villous sampling: _____

Other techniques:

Performed result positive □ Performed result not known □ Not performed □

Performed result negative □ Failed □ Not known □

Specify other technique for prenatal diagnosis: _____

(Cordocentesis,..etc)

No. of previous spontaneous abortions: None □ 1 □ 2 □ 3 □ 4 □
5 □ 6 □ 7 □ 8+ □ Not known □

No. of previous TOP: None □ 1 □ 2 □ 3 □ 4 □ 5 □
6 □ 7 □ 8+ □ Not known □

No. of previous live births: please write the exact No (1-20) _____ Unknown □

No. of previous stillbirths: None □ 1 □ 2 □ 3 □ 4 □
5 □ 6 □ 7 □ 8+ □ Not known □

Mode of transmission: Familial □ De novo □ Not known □

Habitual exposures: Smoking F179 □ Oude F159 □

Other (specify) _____

Unusual exposures: X-ray during pregnancy (any)□ Nuclear medicine during pregnancy □

(Radiation & chemical)

Date of birth of father: ____/____/_____ **Year**: _____ **Age of father**: _____

Occupation of father: Soldier □ Officer □ Civilian □

Pattern of Malformations Study – RMH

Local Vars. (2)

Local ID No_____

Date of last LMP: _____/_____/_____

Certainty of LMP: **C**ertain □ Uncertain □ No LMP □ Not known □

Labor: Spontaneous □ Induced □ No labor □

Delivery: Spontaneous □ EMLSCS □ ELSCS □ ABD □
Instrumental □

Sources of information 1:

Notes in routine scan □ Birth notification or notification of malformation at birth □

Hospital case notes □ Death or stillbirth certificate □Prenatal diagnosis □

Lab. report (cytogenetic … etc) □ Postmortem exam □ Other □ Not known □

Sources of information 2: please insert as in one _____

Sources of information 3: please insert as in one _____

Sources of information 4: please insert as in one _____

Sources of information 5: please insert as in one _____

Racial information Mother, Tribe code _____ Father, Tribe code_____

Same tribe □ Different tribe □

Otaibi 1, Mutairi 2, Shuhri 3, Asiri 4, Shamrani 5, Onazi 6, Shahrani 7, Zaharani 8, Harbi 9, Qahatni 10, Ghamdi 11,Shamari 12, Asmari 13, Ahmari 14, Amri 15, Dawsari 16, Harthi 17, Subaie 18, Ajman 19, Not known (99)

Other 20, specify: _____

Chronic illness of father (including drug abuse):_____

Confirmation of diagnosis:

Follow up needed for further confirmation □ Confirmed at <6 months □

Confirmed at 6-12 m □ Confirmed at 12-18 m □ Confirmed at 18-24 m □

Not confirmed, lost for follow up □

Source: Booked □ Un booked □ Referred □

Checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Observational, prospective cohort design with a nested case-control study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a CA, for an overall prevalence of 412/10000 total births, or 1 in 24 births.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Congenital anomalies(CA) are increasingly recognized as a global health priority because of their lifelong impact on health and survival.[1,2] CA affect approximately an estimated 1 in 33 newborns, contribute each year to 300,000 deaths in the first month of life, and are associated with 3·2 million birth-related disabilities.[3] Accordingly, the World Health Assembly has emphasized the urgent need for action to help prevent, diagnose, and provide timely intervention.[1]
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5	In this study, we implemented an integrated approach to generate these data in well-defined cohort of women, tracked from mid-gestation through the second year of life of their children, to assess concurrently the burden of potentially modifiable risk factors, the occurrence of CA, and survival of affected children, as a basis for better prevention and care.[4]
Methods				
Study design	4	Present key elements of study design early in the paper	5	Observational, prospective cohort design with a nested case-control study.

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 *8-15	The Prince Sultan Military Medical City (PSMMC) is a tertiary teaching institution with 1250 beds and approximately 10,000 annual deliveries. PSMMC primarily serves Saudi army personnel and their families and is a referral center for the other 16 military hospitals in the Kingdom of Saudi Arabia. Study period 1 July 2010 through 30 June 2013. *Figures and tables
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case 2,3 ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5 7,8 n/a	All pregnant Saudi women who are eligible for their antenatal care at PSMMC were included and their pregnancy outcome. Mothers who delivered elsewhere were not included even if they have their antenatal care at PSMMC. All mothers who care pregnant with an affected foetus (birth defect) are include. For controls a random sample of women in the cohort with a normal USS. The random sample was generated daily by taking the morning list of scheduled USS and using a random number generator (http://www.random.org) to select potential controls
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	Evaluations for specific congenital anomaly. Table 4 and 5. Nested Case-Control Study, Follow up, Case review, coding, classification.

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*n/a*
Bias	9	Describe any efforts to address potential sources of bias	5,6	Pregnancies referred from other hospitals because of a diagnosis of a foetal anomaly, and babies with CA delivered elsewhere and referred to PSMMC for evaluation and management
Study size	10	Explain how the study size was arrived at	5	All mother delivered at PSMMC during the study period were included
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10	Odd ratios for CA were computed first via univariate logistic regression, then with a multiple logistic model. The latter was developed by first including uncorrelated significant factors (p <0·05) from the univariate analysis, then reducing the number of variables by stepwise backward elimination for a more parsimonious model.
		(*b*) Describe any methods used to examine subgroups and interactions		n/a
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7	n/a randomization n/a

		(*e*) Describe any sensitivity analyses		n/a
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 -11	All mothers and their offspring were included. For details see Figure 2.
		(b) Give reasons for non-participation at each stage		n/a
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	29 - 32	All demographic data were shown in Tables 4 and 5
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	2 – 5 years. Follow up. Case-infants (with CA) and control-infants were examined in the dedicated study clinic at 1, 6, 12, 18 and 24 months of age
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9	1179 as cases and 1262 as controls
		Cross-sectional study—Report numbers of outcome events or summarymeasures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	9-11	Of the 28 646 eligible pregnancy outcomes, 1179 were diagnosed with a CA, for an overall prevalence of 412/10000 total births, or 1 in 24 births. Of these 1179 cases, 38 (3.2%) were stillbirths and 18 (1.5%) were electively terminated because of lethal malformations

		which confounders were adjusted for and why they were included		(13 with anencephaly, 3 with severe hydrops foetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis). The antenatal detection rate among women who has had antenatal ultrasound screening examination was 70.6%(561/795), tables b 1,2,3
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		n/a
Discussion				
Key results	18	Summarise key results with reference to study objectives	2	In this cohort of women, the burden of potentially modifiable risk factors included high rates of diabetes (7.3%), maternal age >40 years (7.0%), consanguinity (54.5%), and lack of periconceptional folic acid use (90.8%). The birth prevalence of CA was 41.2/1,000 births (1179 cases / 28646 live births and stillbirths), driven mainly by congenital heart disease (14.8 per 1000), renal malformations (11.3), neural tube defects (1.9), and chromosomal anomalies (2.7). Mortality for live births with CA at 1 and 2 years of age was 14% and 15.8%, respectively.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15	Single centre study, Army personnel household only
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15	High prevalence of CA, multiple modifiable risk factors.

Generalizability	21	Discuss the generalizability (external validity) of the study results	15	Since it's a single centre study, it should be generalized with caution as mentioned in the discussion.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2	This project was supported by King Abdul-Aziz City for Science and Technology (KACST) through the National Science, Technology and Innovation Plan (NSTIP). Project No: 09-MED748-21. The funder has no role in this study.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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