ABSTRACT

Objective To assess the three key issues for congenital anomalies (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 3 years and their 28 646 eligible pregnancy outcomes (births, stillbirths and elective terminations of pregnancy for foetal anomalies). The nested case-control study evaluated the CA risk factor profile of the underlying cohort. All CA cases (1179) and unaffected controls (1262) 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 morality 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.

INTRODUCTION

Because of their lifelong impact on health and survival, congenital anomalies (CAs) are increasingly recognised as a global health priority. 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. 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. Accordingly, the World Health Assembly has emphasised the urgent need for action to help prevent, diagnose and provide timely interventions. 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 live births with CAs in the UK, the 20-year survival rate was 85.5%. Similarly, the 25-year survival rate among live births with CAs in New York state was 82.5%, with a documented improvement from the 1980s (78.1% from 1983 to 1988) to the early 2000s (89.3% from 2001 to 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.
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 1250 beds and approximately 10000 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 three-dimensional and four-dimensional scanning. The paediatric department includes all major subspecialities, 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 (USS) examination 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 elective terminations of pregnancy for 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

Figure 1 Catchment site and the study flow chart. 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. AN, antenatal; BD, birth defect; PN, postnatal; SB, stillbirth.
and antibody screening, rubella and Toxoplasma status, hepatitis B screen, random blood sugar and glycated haemoglobin (HbA1c) levels, Venereal Disease Research Laboratory (VDRL, sickle cell screen and urine analysis. A glucose tolerance test was performed at 24 to 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 to 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 (eg, echocardiogram, cardiac catheterisation 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 hydrencephrosis (HN) was graded using the Society of Foetal Urology grading system. Babies with grade 1 HN were given a repeat USS 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 USA 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 first 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 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 (online 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 subspeciality clinics. The remaining cohort (babies without CAs not selected as controls) was re-examined at 4 to 8 weeks by the paediatrician for a second screening examination. A head ultrasound and a postdactal pulse oximetry reading were completed in all babies attending the clinics. If the oxygen 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, 10⁰ revision, (ICD10, WHO-2010) according to the European Concerted Action on Congenital Anomalies and Twins (EUROCAT) recommended procedures.' 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 modified to include control records and the additional variables generated by the case-control study and the follow-up.

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

ORs 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 (eg, 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 $R^2$. Statistical analysis was performed with SPSS for Windows, V.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 healthcare 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, 2107 were spontaneous abortions (6.8%) 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, 1179 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 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 foetalis and cystic hygroma, 1 with Meckel-Gruber syndrome and 1 with bilateral renal agenesis) (table 1). The antenatal detection rate among women who 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 1 year of age. Mortality among live births with CA (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 2 years was 0.9% in the unaffected cohort (0.24% for live births). Among the controls, there were eight 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 CA (773/1179, 65.6%) were isolated (eg, 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 CA among controls in the nested case-control study (figure 3). The most frequent potentially modifiable factors included lack of preconception folic acid supplement use, consanguinity, high body mass index, advanced maternal age, smoking (first or secondhand) 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 ORs 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 ORs with CIs, 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

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**Table 1** Distribution and rates of congenital anomalies (CA) among the cohort’s pregnancy outcomes and associated mortality

| CA outcome | Total cohort | With CA | Mortality among live births with CA |
|------------|--------------|---------|---------------------------------|
| Birth      | 28 646       | 28 369  | 28 646                           |
| No.        | 1179         | 99      | 99                               |
| No. %     | 99.9%        | 3.4%    | 3.4%                            |
| Rate/10 000| 39.5/10 000  | 36.0/10 000 | 32.0/10 000 |
| Postnatal  | 618          | 52.4%   | 618                              |
| Total      | 618          | 618     | 618                              |
| Total first year | 52.4% | 14.1% | 14.1% |

ETOPFA, elective terminations of pregnancy for foetal anomalies.

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**Table 2** Contribution of specific congenital anomalies

| Category                  | Rate/10 000 | No. % | No. | %  |
|---------------------------|-------------|-------|-----|----|
| Neural tube defects       | 19/10 000   | 13.8% | 953 | 31.3% |
| Severe CHD                | 32/10 000   | 21.4% | 1123| 38.3% |
| Chromosomal anomalies     | 25/10 000   | 19.6% | 1123| 38.3% |
| Trisomy 21                | 22/10 000   | 16.7% | 1123| 38.3% |

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**Table 3** Distribution and rates of congenital anomalies (CA) among the cohort’s pregnancy outcomes and associated mortality

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| Birth      | 28 646       | 28 369  | 28 646                           |
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| Rate/10 000| 39.5/10 000  | 36.0/10 000 | 32.0/10 000 |
| Postnatal  | 618          | 52.4%   | 618                              |
| Total      | 618          | 618     | 618                              |
| Total first year | 52.4% | 14.1% | 14.1% |

ETOPFA, elective terminations of pregnancy for foetal anomalies.

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**Table 4** Risk factors

| Risk factor          | OR   | 95% CI     |
|----------------------|------|------------|
| Consanguinity        | 1.5  | 1.28 to 1.81|
| Advanced maternal age| 2.1  | 1.76 to 2.49|
| High parity          | 1.7  | 1.31 to 2.19|
| Maternal illiteracy  | 1.8  | 1.48 to 2.16|
| Maternal university education | 1.7 | 1.34 to 2.16|
| X-ray exposure during pregnancy | 1.6 | 1.25 to 2.07|
| Maternal diabetes    | 1.5  | 1.21 to 1.83|
| Positive family history of CA in a sibling | 1.5 | 1.21 to 1.83|
| Maternal depression  | 1.5  | 1.21 to 1.83|
| Maternal hypertension| 1.5  | 1.21 to 1.83|
Table 2  Prevalence and distribution of congenital anomalies, overall and by pregnancy outcome

| Birth defects                             | Number | %   | Prevalence per 10 000 births | Live births | Prevalence per 10 000 live birth | Stillbirth | ETOPFA |
|------------------------------------------|--------|-----|------------------------------|-------------|----------------------------------|------------|--------|
|                                          | (total births=28 646) | No. | %   | (total live births=28376) | 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 |

Continued
| Birth defects                                      | Number | %   | Prevalence per 10 000 births (total births=28 646) | Live births | %   | No. | %   | Prevalence per 10 000 live birth (total live births=28 376) | Stillbirth | No. | %   | ETOPFA |
|---------------------------------------------------|--------|-----|---------------------------------------------------|-------------|-----|-----|-----|---------------------------------------------------------------|------------|-----|-----|--------|
| Oro-facial clefts                                  | 42     | 3.6 | 14.7                                              | 35          | 83.3| 12.3| 5   | 11.9                                                         | 2          | 4.8 |
| Cleft lip with or without palate                   | 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                                                         |
| Gastrochisis                                      | 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 hydrenephrosis                         | 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 |
| Clubfoot - 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 |
| Musculoskeletal                                   | 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 |

Table 2 Continued
| Birth defects                      | Number | %   | Prevalence per 10 000 births (total births=28 646) | Live births | Prevalence per 10 000 live birth (total live births=28 376) | Stillbirth | ETOPFA |
|-----------------------------------|--------|-----|--------------------------------------------------|-------------|-------------------------------------------------------------|------------|--------|
|                                   |        |     | No. %                                           |             | No. %                                                       |            | No. %  |
| Thanatophoric dysplasia           | 2      | 0.2 | 0.7                                             | 2           | 100                                                         | 0.7        |        |
| Jeune syndrome                    | 2      | 0.2 | 0.7                                             | 1           | 50.0                                                        | 0.4        | 1      |
| Other malformations               | 42     | 3.6 | 14.7                                            | 40          | 95.2                                                        | 14.1       | 1      |
| 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      |
| Down syndrome/trisomy 21          | 63     | 5.3 | 22                                              | 62          | 98.4                                                        | 21.8       | 1      |
| Edward syndrome/trisomy 18        | 8      | 0.7 | 2.8                                             | 7           | 87.5                                                        | 2.5        | 1      |
| 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      |
| 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      |
| 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        |        |

*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), coartation of the aorta (Q251), aortic atresia / interrupted aortic arch (Q232), total anomalous pulmonary venous return (Q262).

ETOPFA, elective terminations of pregnancy for foetal anomalies; ICD10, International Statistical Classification of Diseases and Related Health Problems, 10th revision.
Table 3 Common single congenital anomalies (CA) per body system involved

| Body system       | Total number Of CA | Isolated CA No. | Isolated CA % | Common isolated anomalies                                                                 |
|-------------------|--------------------|-----------------|---------------|--------------------------------------------------------------------------------------------|
| 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%). Severe 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%). |

CHD, congenital heart disease.

Maternal age over 40 years was high at 7% among mothers of babies with CA compared with 3.6% among controls mothers (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 4). The Hosmer and Lemeshow goodness of fit p value was 0.08, and Nagelkerke R² was 0.055, explaining 6% of the effect on CAs.

Of the 223 mothers with diabetes mellitus (DM) who had CA-affected foetuses (223/1179, 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 (200/1179, 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 (eg, 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 British Isles Network of Congenital Anomaly Registers (BINOCAR) (206/10 000 births)12 and the Bradford 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
### Table 4  Distribution of parental sociodemographic characteristics and association with congenital anomaly risk (univariate analysis)

| Variable                        | Cases (total n=1179) | Controls (total n=1262) | OR* | 95%CI Lower | 95%CI 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$)** |               |                         |     |             |             |
| <3000 SR (<800$)               | 19 1.9                | 12 1.0                  | 1.87| 0.89        | 3.92        |
| 10 000–14 000 SR (2667–3999$)   | 235 23.2              | 277 22.3                | Ref | –           | –           |
| 3000–6999 SR (800–1866$)        | 232 22.9              | 291 23.4                | 0.94| 0.74        | 1.20        |
| 7000–9999 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        |

Continued
Table 4  Continued

| Variable                                                                 | Cases (total n=1179) | Controls (total n=1262) | OR* | 95%CI Lower | 95%CI Upper |
|--------------------------------------------------------------------------|-----------------------|-------------------------|-----|-------------|-------------|
| Diabetes mellitus                                                        |                       |                         |     |             |             |
| 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        |
| Siblings 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        |

Some families declined reporting their income.
*BMI not available for 15 mothers.
†Improper-use includes FA taken post conception in 49 mothers (43 case mothers and 6 six control mothers) who were not sure about their intake.
CA, congenital anomalies; DM, diabetes mellitus; SR, Saudi riyals.

prevalence, for example, such as an antenatal CA prevalence of 521/10 000 pregnancies screened, and a prevalence among live births 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

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. Lower | 95% C.I. Upper | OR          | 95% C.I. Lower | 95% C.I. 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.
ascertaintion as possible by initiating follow-up in pregnancy and extending it through the second year of life, by including stillbirths and 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 live births 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 normalise CA risk.9 22 23 Several avenues for preventing diabetes and its health effects are available, including population screening (many diabetic women are undiagnosed), healthcare 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% to 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 colleagues27 reported a prevalence of overt diabetes of 11.6% in women aged 30 to 39 years and ≥22% in women aged ≥40 years compared with 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).31 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,32 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 decades33 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.25 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 programmes at several levels should emphasise the importance of planned pregnancies at the optimal age (20 to 30 years), ensure adequate periconceptional folic acid intake (400 to 800 µg daily)26 and detailed foetal 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 immunisation 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 (peri-conception) folic acid (FA) intake (9.7%) in this study population 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 emphasise 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 colleagues38 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 Mastroiacovo,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 (eg, 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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