www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2017;6(1):e060121
doi: 10.7363/060121
Received: 2016 Mar 20; revised: 2016 Apr 09; accepted: 2016 Apr 10; published online: 2017 Jan 06

Original article

Congenital anomalies: 15 years of experience in a level III hospital

Carolina Félix[1], Filipa Flor-de-Lima[1,2], Susana Pissarra[1,2], Fátima Clemente[1,2], Paulo Soares[1,2], Manuela Rodrigues[2], Gustavo Rocha[1,2], Maria Beatriz Guedes[2], Carla Ramalho[2,3,4], Hercília Guimarães[1,2]

[1]Department of Pediatrics, Faculty of Medicine, Porto University, Porto, Portugal
[2]Neonatal Intensive Care Unit, Centro Hospitalar de São João, Porto, Portugal
[3]Department of Obstetrics and Gynecology, Centro Hospitalar de São João, Porto, Portugal
[4]Institute of Investigation and Innovation in Health, Porto University, Porto, Portugal

Abstract

Background: Congenital anomalies (CAs) are a leading cause of fetal and infant mortality and morbidity worldwide. They may be identified prenatally, at the moment of birth or later in life.

Purpose: To describe the cases of CAs registered over the last 15 years at a level III hospital, comparing individuals who were detected through prenatal (preN) diagnosis with those detected through postnatal (postN) diagnosis.

Methods: All records were collected from the Registo Nacional de Anomalias Congénitas (RENAC) online platform between 1st January 2000 to 31st December 2014, in a level III hospital, where cases of CAs were notified voluntarily (n = 1,222). We tested differences for selected variables between the years in study. A multivariate analysis was performed to identify potential factors associated to preN diagnosis.

Results: We observed a total of 1,510 anomalies, being 493 (40.3%) circulatory, 252 (20.6%) chromosomal, 187 (15.3%) musculoskeletal, 138 (11.3%) digestive, 133 (10.9%) urinary, 117 (9.6%) nervous, 37 (3.0%) respiratory, 35 (2.9%) genital, 25 (2%) anomalies of the eye, ear, face and neck, 20 (1.6%) cleft lip/cleft palate and 73 (6.0%) others. Time of diagnosis was known for all subjects: 770 (63.0%) were diagnosed prenatally and 452 (37.0%) were diagnosed at birth or during the first month of life. We found statistically significant differences between groups for several variables. Assisted reproduction techniques ($p = 0.023$), maternal medications during the first trimester of pregnancy ($p = 0.004$) and the number of anomalies per individual ($p \leq 0.001$) had a statistically significant impact on receiving preN diagnosis.

Conclusion: Our data confirm the importance of both RENAC national database and preN diagnosis in improving perinatal healthcare. However, in order to determine the national prevalence of CAs and understand any

involved factors, it is desirable to enhance the notification in the whole country, facilitating the adjustment of national protocols to achieve a better perinatal counseling and surveillance.

Keywords

Congenital abnormalities, prenatal diagnosis, pregnancy outcome, infant mortality, risk factors, maternal health, maternal exposure, consanguinity.

Corresponding author

Carolina Félix, Department of Pediatrics, Faculty of Medicine, Porto University, Porto, Portugal; email: carolinamaralfelix@gmail.com.

How to cite

Félix C, Flor-de-Lima F, Pissarra S, Clemente F, Soares P, Rodrigues M, Rocha G, Guedes MB, Ramalho C, Guimarães H. Congenital anomalies: 15 years of experience in a level III hospital. J Pediatr Neonat Individual Med. 2017;6(1):e060121. doi: 10.7363/060121.

Introduction

Congenital anomalies (CAs), congenital malformations, congenital disorders and birth defects can be defined as structural or functional anomalies arising during intrauterine life that may be identified prenatally (prenatal [preN] diagnosis), at the moment of birth or later in life (postnatal [postN] diagnosis) [1]. Worldwide, CAs are a leading cause of fetal and infant mortality and morbidity, often resulting in long-term disability, which may have relevant repercussions on individual and family life, as well as on health-care systems and costs [2]. These anomalies represent nowadays a major issue for health services, in terms of the number of resources that are needed because of their increasing life expectancy [3].

According to the World Health Organization (WHO; http://www.who.int/en/), CAs are the cause of 4.4% (276,000) of global deaths during the neonatal period, and they are associated to a mortality rate of 1 per 1,000 live births in children aged 1-59 months [4].

The European Surveillance of Congenital Anomalies (EUROCAT; http://www.eurocat-network.eu/) collects data from several European countries. EUROCAT reports that approximately 2% (104,000) of the 5.2 million births each year were affected by CAs. CAs also caused 25% of all neonatal deaths in the considered regions [2]. In Portugal the mortality rate is 1.5 per 100,000 habitants [5], and in 2013 10% of deaths under 1 year of life in our country were attributable to heart defects, whereas other malformations caused 8% of deaths in this age group [6].

The most common severe CAs worldwide are heart anomalies, neural tube anomalies and Down syndrome [1]. A considerable number of birth defects cannot be associated to an exact cause or a known etiology [7]. About 25% are due to a chromosomal anomaly, 20% to single gene disorder, 5% to an environmental factor and approximately 50% are caused by multiple factors [8]. Previous studies demonstrated an association between CAs and male sex, low birth weight, advanced maternal age and other important factors such as maternal infection and drug exposure [9, 10]. Recently, pregnancy obesity, smoking and assisted conception have been suspected as risk factors for CAs [11], and these factors are all relevant in our national setting.

In 2010 the WHO announced new strategies in order to prevent CAs, including family planning, preconceptional and antenatal screening with enhanced preN diagnosis techniques, optimization of maternal diet before and throughout pregnancy and treatment for possible teratogen-induced infections [1]. PreN diagnosis comprehends an important assembly of resources targeted to detect these anomalies, thus allowing an optimized management of the pregnancy and planning of postnatal treatment. Many European countries provide screening in the first trimester of pregnancy, which consists in ultrasound to measure nuchal translucency and specific blood tests. Although some major anomalies may be detected at the 12 week scan, most cannot be seen at this gestational age, whereby supplementary tests are provided between 18 and 22 weeks. An amniocentesis may be performed in case of detection of one or more CAs in order to investigate underlying genetic alterations. In most European countries, parents may opt for termination if one or more severe CAs are diagnosed in the fetus.

The events involving the use of thalidomide in the 1960s [12] warned for the need to control tendencies of CAs, whereby many countries provide this information to surveillance organizations, thus allowing a prompt detection of alterations of patterns and an explanation for the change, in order to develop mechanisms of prevention. Within our country, an organization founded in

1985 and called Registo Nacional de Anomalias Congénitas (RENAC; http://www.insa-rios.net/renac/) collects this data from several obstetrics and neonatology health services that accept to cooperate, both in public and private practice [13].

The purpose of this study was to retrospectively describe the registered cases of CAs in the last 15 years in a level III hospital and to assess the trends during this period.

Material and methods

All records were collected from RENAC's online platform by selecting the period between 1st January 2000 to 31st December 2014 (n = 1,222) at Centro Hospitalar São João (CHSJ – Porto, Portugal), a level III hospital, referral center for pediatric surgery and congenital heart diseases. The prenatal consultation service in our center follows pregnancies from the North of Portugal (five districts: Viana do Castelo, Braga, Porto, Vila Real and Bragança; estimated population of 3.6 million).

Data related to CAs cases were notified by professionals that completed an online default questionnaire.

For the purpose of this study, isolated anomalies were considered to be cases of single CAs, and those with more than one were categorized as multiple. Where a CA included two or more CAs with the same ICD-10 classification (Q00 – Q99), we considered the case as having only one of each type.

The CAs were categorized according to the ICD-10 classification, as chapter XVII includes: congenital malformations of the nervous system; congenital malformations of eye, ear, face and neck; congenital malformations of the circulatory system; congenital malformations of the respiratory system; cleft lip and cleft palate; other congenital malformations of the digestive system; congenital malformations of genital organs; congenital malformations of the urinary system; congenital malformations and deformations of the musculoskeletal system; other congenital malformations; chromosomal abnormalities, not elsewhere classified.

Maternal occupation was grouped according to the Classificação Nacional das Profissões (CNP; http://www.cdp.portodigital.pt), our national classification.

The Ethics Committee of our institution approved this retrospective study.

Data collection was performed using Microsoft® Excel® v.14.0.0 and the statistical analysis was performed with IBM® SPSS® statistics v.23. Categorical variables were characterized by absolute and relative frequencies, whereas continuous variables by mean (± standard deviation) if they had symmetric distribution, and by median (minimum-maximum) if they had asymmetric distribution. Fisher's exact test and Chi-squared test were used to compare categorical variables and Independent t test or Mann-Whitney U test for continuous variables, when they had symmetric or asymmetric distribution, respectively. Finally, a multivariate analysis was performed by logistic regression to identify potential factors associated to preN diagnosis. A p-value lower than 0.05 was considered statistically significant.

Results

From 1st January 2000 to 31st December 2014, 1,222 cases of CAs were notified to RENAC by our institution. Over this 15 year's period, about 2,800 newborns were delivered in the obstetric department yearly, and 450 were admitted in our neonatal intensive care unit every year. During the year of 2015, 2,052 consultations of preN diagnosis were held in our hospital.

All our data was collected from the RENAC national database, which depends on physicians' initiative to notify cases of CAs and provide all of the requested information. Therefore, some variables have missing values.

Annual distribution of notifications and total number of anomalies are presented in **Fig. 1**.

Fetus or newborn characteristics are listed in **Tab. 1**. Gestational age at the moment of birth was registered as being calculated through ultrasound in 1,114 (93.7%) cases and by the date of the last menstrual period in 75 (6.3%) cases. Pregnancy outcomes during the period in study are represented in **Fig. 2**. A total of 333 (30.7%) cases failed to survive during the first week after birth (46.3% preN vs 7.6% postN; $p < 0.001$). Multiple pregnancies had one affected fetus in 168 (90.3%) cases (92.5% preN vs 77.8% postN) and two in 18 (9.7%) cases (7.5% preN vs 22.2% postN); $p = 0.017$. Karyotype testing was performed in a total of 853 (71.2%) cases: 533 (44.5%) normal; 253 (21.1%) pathologic; 66 (5.5%) unknown results; in 1 case (0.1%) it was inconclusive. Fetal products sampling methods included 417 (82.2%) amniocentesis (81.1% preN vs 100% postN), 86 (17%) chorionic villus sampling (CVS) (18% preN vs 0 postN) and 4 (0.8%) cordocentesis (0.8% preN vs 0 postN); $p = 0.032$.

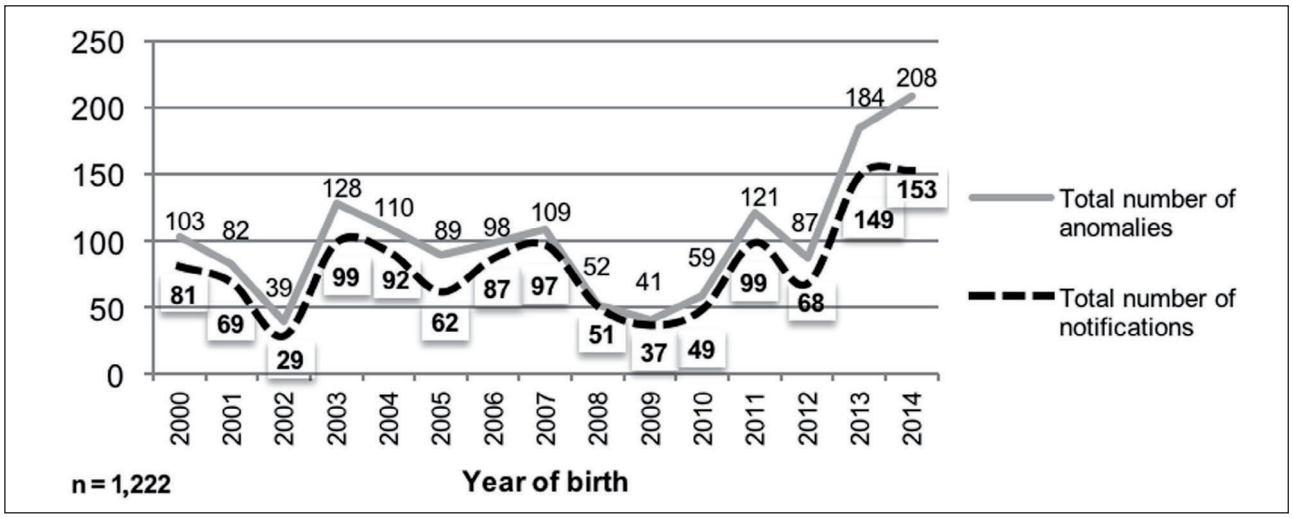

Figure 1. Annual distribution of notifications and total number of anomalies.

Table 1. Fetus/newborn characteristics within the total sample and according to the moment of diagnosis (prenatal [preN] versus postnatal [postN]).

	Total (n = 1,222)	With preN diagnosis (n = 770)	With postN diagnosis (n = 452)	p-value
Gender, n (%)				
Male	679 (56.3)	401 (53.1)	278 (61.6)	
Female	525 (43.5)	352 (46.6)	173 (38.4)	
Ambiguous	2 (0.2)	2 (0.3)	0	**0.01** [c]
Gestational age at birth, median (min-max)	37 (9-42)	31 (9-42)	38 (11-41)	**< 0.001** [d]
Birth weight, grams, median (min-max)	2,912.5 (380-5,230)	2,815 (380-4,355)	3,000 (600-5,230)	**< 0.001** [d]
Pregnancy outcome, n (%)				
Live birth	797 (65.4)	376 (49.0)	421 (93.3)	
Termination of pregnancy	352 (28.9)	351 (45.7)	1 (0.2)	**< 0.001** [c]
Spontaneous abortion (< 20 weeks)	50 (4.1)	22 (2.9)	28 (6.2)	
Fetal death	20 (1.6)	19 (2.5)	1 (0.2)	
First week survival, n (%) [a]	752 (69.3)	348 (53.7)	404 (92.4)	**< 0.001** [c]
Autopsy, n (%)	435 (91.4)	399 (93.0)	36 (76.6)	**0.001** [c]
Inborn, n (%)	1,210 (99.3)	761 (99.2)	449 (99.6)	0.545
Assisted reproduction techniques, n (%)	38 (3.1)	32 (4.2)	6 (1.3)	**0.006** [c]
Intracytoplasmic sperm injection	8 (66.7)	7 (63.6)	1 (100.0)	
***In vitro* fertilization**	3 (25.0)	3 (27.3)	0	0.761 [c]
Induction of ovulation	1 (8.3)	1 (9.1)	0	
Obstetric ultrasound, n (%)				
1st and 2nd trimesters	330 (62.0)	234 (56.5)	96 (81.4)	**< 0.001** [c]
1st trimester only	181 (34.0)	169 (40.8)	12 (10.2)	
2nd trimester only	7 (1.3)	5 (1.2)	2 (1.7)	
Fetal fluid sampling, n (%) [b]				
Not proposed	653 (54.0)	251 (32.8)	402 (90.5)	
Yes, because of ecographic marker	404 (33.4)	400 (52.3)	4 (0.9)	
Yes, because of maternal age	88 (7.3)	66 (8.6)	22 (5.0)	
Yes, because of positive biochemical screening	31 (2.6)	31 (4.1)	0	**< 0.001** [c]
Yes, because of other reason	13 (1.1)	8 (1.0)	5 (1.1)	
Proposed but rejected	20 (1.7)	9 (1.2)	11 (2.5)	
Karyotype testing, n (%)				
Yes, normal	533 (44.5)	366 (48.4)	167 (37.8)	**< 0.001** [c]
Yes, pathologic	253 (21.1)	222 (29.4)	31 (7.0)	

preN: prenatal; postN: postnatal.
All our data was collected from the RENAC national database, which depends on physicians' initiative to notify cases of CAs and provide all of the requested information. Therefore, some variables have missing values.
[a]This question was only to be filled if the pregnancy outcome was live birth.
[b]Two different questions about fetal products sampling were asked in the questionnaire. In the Results section of the text, the analyzed variable is "fetal products sampling method", with registered cases of performed amniocentesis/chorionic villus samplings (CVS)/cordocentesis. Here in the Table the analyzed variable is "fetal fluid sampling", which is related to the reason why the mother performed the test. The absence of mandatory filling led to different number of answers for the two variables.
[c]Chi-square test; [d]Mann-Whitney U test.

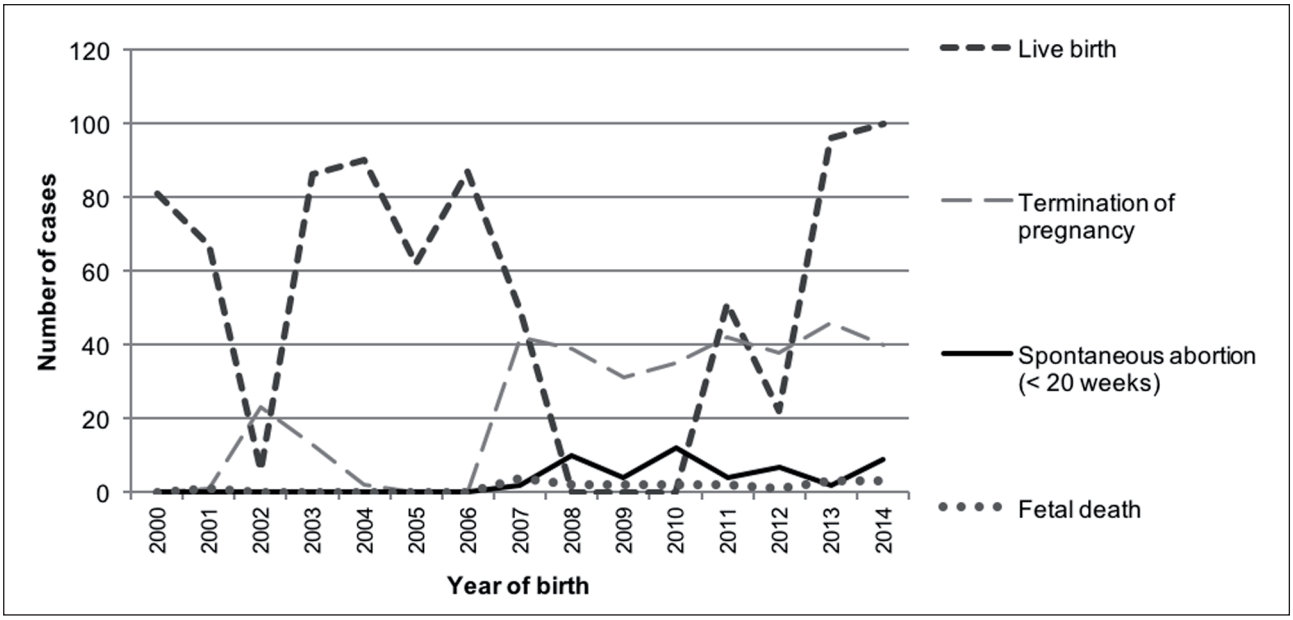

Figure 2. Pregnancy outcomes during the period in study.
During the period 2008-2010 the cases were registered by a reduced number of professionals, factor that explains the missing data about live births.

The time of diagnosis was known for all subjects: 770 (63.0%) were diagnosed prenatally and the remaining 452 (37.0%) were diagnosed at birth or during the first month of life. Individuals in latest group were diagnosed at birth in 186 (15.2%) cases; during the first week of life in 183 (15.0%) cases; between the first and fourth week of life in 53 (4.3%) cases, or after autopsy was performed in 29 (2.4%) cases. The evolution of the moment of anomaly detection through the years is represented in **Fig. 3**.

When detected through preN diagnosis testing, the median gestational age at that time was 22 weeks (min-max: 10-39). Ultrasound was the first altered exam in 701 (59.5%) cases: 166 (14.1%) detections were carried out during the first trimester; 195 (16.6%) detections during the second trimester; 189 (16.0%) identifications within the last trimester of pregnancy and 151 (19.8%) at unknown gestational age. Amniocentesis or CVS were the first altered prenatal exam in 35 (3.0%) cases and biochemical screening in 25 (2.1%) cases. Normal results were registered in 398 (33.8%) cases.

All 1,222 cases had a total of 1,510 anomalies, described in **Tab. 2**. The most common CAs are summarized in **Tab. 3**. Changes in the number of cases of CAs of the circulatory, musculo-skeletal and nervous system and chromosomal abnormalities through the years are represented in **Fig. 4**.

Maternal characteristics are described in **Tab. 4**. Maternal age was not registered in 6% of the cases among preN diagnoses and in 21% of the cases among postN diagnoses. Concerning their obstetric history, we found statistically significant differences for the number of previous live births: 320 (72.7%) mothers had one (77% preN vs 65% postN), 85 (19.3%) had two (17% preN vs 23.6% postN) and 35 (7.9%) had three or more (6% preN vs 11.5% postN); p = 0.005. Although we did not verify differences among groups for these variables, smoking was recorded in 35 (3.9%) cases and drug abuse in 4 (0.4%). Drinking was registered in 17 (1.9%) cases (1% preN vs 3.6% postN; p = 0.006). There were statistically significant differences for folic acid intake: 141 (37.5%) started during the preconception period (41.8% preN vs 22.6% postN); 184 (48.9%) started during the first trimester of pregnancy (46.6% preN vs 57.1% postN); and in 51 (13.6%) cases the mothers denied the intake of folic acid (11.6% preN vs 20.2% postN; p = 0.003).

Maternal CA was present in 22 (2.0%) of all cases and 39 (5.0%) had history of CAs within the maternal side of the family.

Paternal age was registered in 341 (27.9%) cases: 33.77 years (± 6.79) in prenatally diagnosed cases vs 32.04 (± 6.24) in postnatally diagnosed cases; p = 0.028. Paternal CA was notified in 10 (1.4%) cases and 23 (4.0%) individuals had paternal familiar history of CAs.

Tab. 5 describes the multivariate analysis of factors associated to preN diagnosis.

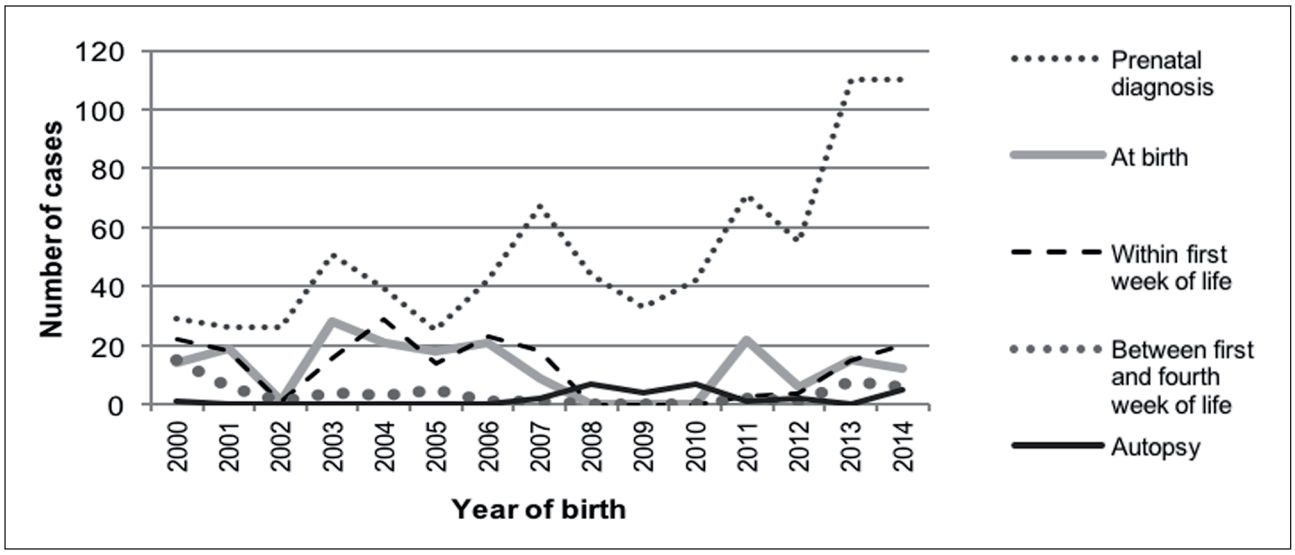

Figure 3. Evolution of the moment of anomaly detection through the years.

Table 2. Fetus/newborn's CA (congenital anomaly) characteristics within the total sample and according to the moment of diagnosis (prenatal [preN] versus postnatal [postN]).

	Total (n = 1,222)	With preN diagnosis (n = 770)	With postN diagnosis (n = 452)	p-value
Status at diagnosis, n (%)				
Alive	1,177 (97.1)	756 (99.3)	421 (93.3)	**< 0.001**[a]
Deceased	35 (2.9)	5 (0.7)	30 (6.7)	
Number of anomalies per individual, n (%)				
Isolated	845 (69.1)	526 (68.3)	319 (70.6)	0.476[a]
Multiple	377 (30.9)	244 (31.7)	133 (29.4)	
CA classification, n (%)				
Congenital malformations of the circulatory system	493 (40.3)	226 (29.4)	267 (59.1)	**< 0.001**[a]
Chromosomal abnormalities, not elsewhere classified	252 (20.6)	220 (28.6)	32 (7.1)	**< 0.001**[a]
Congenital malformations and deformations of the musculoskeletal system	187 (15.3)	132 (17.1)	55 (12.2)	**0.020**[a]
Other congenital malformations of the digestive system	138 (11.3)	65 (8.4)	73 (16.2)	**< 0.001**[a]
Congenital malformations of the urinary system	133 (10.9)	112 (14.5)	21 (4.6)	**< 0.001**[a]
Congenital malformations of the nervous system	117 (9.6)	98 (12.7)	19 (4.2)	**< 0.001**[a]
Congenital malformations of the respiratory system	37 (3.0)	26 (3.4)	11 (2.4)	0.353[a]
Congenital malformations of the genital organs	35 (2.9)	24 (3.1)	11 (2.4)	0.459[a]
Congenital malformations of the eye, ear, face and neck	25 (2.0)	15 (1.9)	10 (2.2)	0.753[a]
Cleft lip and cleft palate	20 (1.6)	11 (1.4)	9 (2.0)	0.454[a]
Other congenital malformations	73 (6.0)	47 (6.1)	26 (5.8)	0.802[a]

preN: prenatal; postN: postnatal; CA: congenital anomaly.
All our data was collected from the RENAC national database, which depends on physicians' initiative to notify cases of CAs and provide all of the requested information. Therefore, some variables have missing values.
The CAs were categorized according to the ICD-10 classification (chapter XVII).
[a]Chi-square test.

Discussion

Considering the 15-year period of this study, the lowest number of notifications of fetus or newborn with CAs occurred in 2002. Notifications doubled from 2012 to 2013 (68 in 2012, 149 in 2013). This was probably the reflection of an increased effort to register cases among professionals in our institution and not necessarily because of an increased occurrence. In fact, all information included in the RENAC national database depends on voluntary notification of CAs cases by healthcare professionals.

CAs were more common in males than in females, as verified nationally according to RENAC

Table 3. Most common CAs (congenital anomalies) within specific groups.

Circulatory
- Interventricular communication (16.4%)
- Coarctation of the aorta (12%)
- Discordant ventriculoarterial connection (11.6%)
- Tetralogy of Fallot (7.7%)

Chromosomal
- Down syndrome (40%)
- Edwards syndrome (12.2%)
- Triploidy and polyploidy (7.7%)
- Turner syndrome (3.8%)

Musculoskeletal
- Congenital diaphragmatic hernia (26.3%)
- Gastroschisis (12.5%)
- Exomphalos (8.6%)

Other digestive
- Atresia of esophagus with tracheo-esophageal fistula (23.4%)
- Congenital absence, atresia and stenosis of duodenum (12.3%)

Urinary
- Congenital hydronephrosis (32.7%)
- Renal dysplasia (17.6%)

Nervous
- Lumbar spina bifida with hydrocephalus (18.6%)
- Arnold-Chiari syndrome (14.5%)
- Congenital hydrocephalus, unspecified (13.1%)

Respiratory
- Congenital hypoplasia and dysplasia of lung (18.9%)
- Congenital cystic lung (13.5%)

Genital
- Hypospadias (11.5%)

Eye, ear, face and neck
- Congenital glaucoma (4%)

Other
- Pierre Robin deformity or syndrome (9%)

The CAs were categorized according to the ICD-10 classification (chapter XVII).

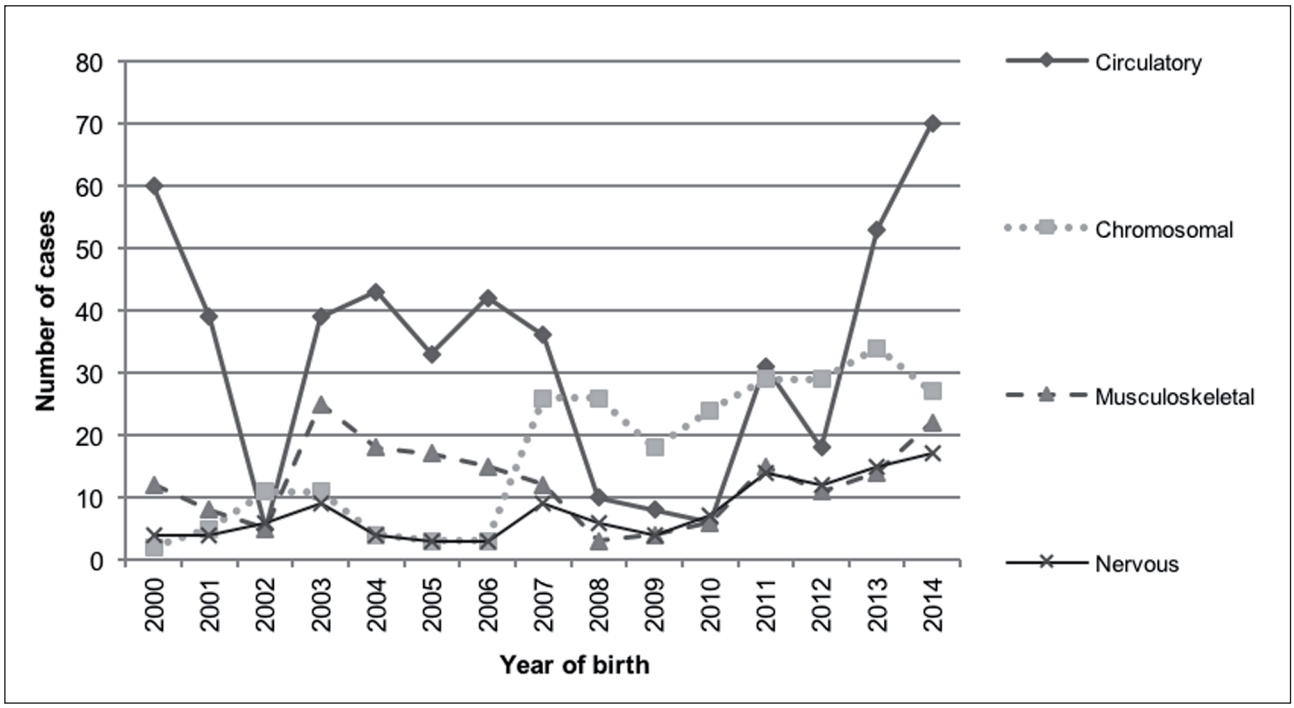

Figure 4. Changes in the number of cases of CAs (congenital anomalies) of the circulatory, musculoskeletal and nervous system and chromosomal abnormalities through the years.

latest report [14]. We found differences in gestational age at birth and birth weight for pre- and postnatally diagnosed individuals. Both were higher in the latest group, due to the influence of terminations of pregnancy and indications to induce birth [15].

According to recorded data, about 70% of all cases survived through the first week after birth and

Table 4. Maternal characteristics within the total sample and according to the moment of diagnosis (prenatal [preN] versus postnatal [postN]).

	Total (n = 1,222)	With preN diagnosis (n = 770)	With postN diagnosis (n = 452)	p-value
Maternal age, mean (± SD)[a]	31.09 (± 6.13)	31.70 (± 6.17)	29.87 (± 5.87)	**< 0.001**[e]
Maternal ethnicity, n (%)				
Caucasian	1,114 (98.4)	694 (98.7)	420 (97.9)	
Black	4 (0.4)	2 (0.3)	2 (0.5)	0.456[f]
Gypsy	9 (0.8)	3 (0.4)	6 (1.4)	
Asian	3 (0.3)	2 (0.3)	1 (0.2)	
Maternal occupation, n (%)				
Specialists of intellectual and scientific areas	145 (27.8)	127 (29.6)	18 (19.4)	
Services personnel and sellers	69 (13.2)	57 (13.3)	12 (12.9)	
Administrative personnel and similar	65 (12.5)	51 (11.9)	14 (15.1)	
Industrial workers, craftsmen and similar	63 (12.1)	42 (9.8)	21 (22.6)	
Technicians and intermediate level professionals	47 (9.0)	43 (10.0)	4 (4.3)	**0.018**[f]
Senior managers of public administration, company CEOs and senior executives	18 (3.4)	16 (3.7)	2 (2.2)	
Unqualified workers	16 (3.1)	14 (3.3)	2 (2.2)	
Unemployed	51 (9.8)	44 (10.3)	7 (7.5)	
Domestic	32 (6.1)	23 (5.4)	9 (9.7)	
Student	15 (2.9)	11 (2.6)	4 (4.3)	
Disease during pregnancy, n (%)[b]	69 (8.6)	47 (9.0)	22 (7.9)	0.581[f]
Maternal medications during first trimester, n (%)[c]	109 (16.1)	79 (18.8)	30 (11.7)	**0.015**[f]
Maternal chronic illness, n (%)[d]	174 (15.6)	125 (17.9)	49 (11.8)	**0.007**[f]
Inbreeding, n (%)	7 (0.9)	4 (0.9)	3 (1.0)	0.999[f]

preN: prenatal; postN: postnatal.
All our data was collected from the RENAC national database, which depends on physicians' initiative to notify cases of CAs and provide all of the requested information. Therefore, some variables have missing values.
[a]Maternal age was not registered in 6% of the cases among preN diagnoses and in 21% of the cases among postN diagnoses.
[b]Diseases included: gestational diabetes – 29 (2.4%); urinary infection – 17 (1.4%); hypertension during pregnancy – 7 (0.6%); cytomegalovirus (CMV) infection – 2 (0.2%); flu – 2 (0.2%); human immunodeficiency virus (HIV) infection, herpes simplex virus infection, lysteria and syphilis – 1 (0.1%) each; other pregnancy diseases – 9 (0.7%).
[c]Medications included: insulin and oral antidiabetics – 17 (1.4%); antiseptics, antibiotics, antiparasitics, antiviral and antifungal agents – 16 (1.3%); hypnotics, sedatives and psychotropics – 13 (1.1%); vitamins – 13 (1.1%); anticoagulants and antithrombotics – 11 (0.9%); antiarrhythmics, antihypertensives – 10 (0.8%); antithyroid agents – 10 (0.8%); antiasthmatics – 6 (0.5%); estrogens, progestogens, androgens or oral contraceptives – 6 (0.5%); antiepileptics – 4 (0.3%); adrenocortical steroids – 3 (0.2%); antiproliferatives and immunosuppressives – 2 (0.2%); analgesics, antipyretics and anti-inflammatories – 1 (0.1%); diuretics – 1 (0.1%); other medication – 9 (0.7%).
[d]Chronic illnesses included: asthma – 23 (1.9%); obesity – 22 (1.8%); thyroid disease – 21 (1.7%); hypertension – 17 (1.4%); diabetes mellitus – 12 (1.0%); epilepsy – 10 (0.8%); other chronic illness - 80 (6.5%).
[e]Independent t test; [f]Chi-square test.

Table 5. Multivariate analysis of selected factors possibly leading to prenatal diagnosis.

	OR[a]	95% CI	p-value
Assisted reproduction techniques	11.89	1.41-00.18	**0.023**
Maternal medications during first trimester	2.18	1.27-3.74	**0.004**
Congenital malformations of the circulatory system	0.10	0.07-0.15	**< 0.001**
Other congenital malformations of the digestive system	0.19	0.11-0.35	**< 0.001**
Number of anomalies per individual	1.73	1.38-2.16	**< 0.001**

95% CI: 95% confidence interval.
The CAs were categorized according to the ICD-10 classification (chapter XVII).
[a]Logistic regression.

survival was higher among postnatally diagnosed. However, this question was only to be filled if the pregnancy outcome was live birth, meaning that survival among prenatally diagnosed cases is probably underestimated in our series. A previous study concerning EUROCAT public health indicators for CAs in Europe showed that Portugal was one of the countries with the lowest perinatal

mortality rate (< 0.25/1,000 births), whereas EUROCAT average was more than the double (1.0/1,000 births) [16].

Assisted reproductive techniques (ART) have been associated to a higher risk of CAs [17, 18] and our multivariate analysis showed an important impact of that factor on antenatal detection, probably because of higher pregnancy surveillance. However, other studies [19] verified that ART conception was not significantly associated with the probability of having preN diagnosis.

We found differences in pregnancy ultrasound rates between groups. Amniocentesis, CVS or cordocentesis were mostly performed because of an ultrasound marker (33%) and maternal age (33.4%). These tests were not proposed by the physician in 54% of all cases and in 90% of cases diagnosed postnatally. Moreover, these questions were only introduced by RENAC in 2008. Our findings are comparable to RENAC report concerning the period between 2000 and 2010 [13].

About 65% of the notified cases were live births. Live birth was the pregnancy outcome in 93% of postnatally diagnosed individuals (versus 49% among prenatally detected). Cases of termination of pregnancy represented approximately 29% of total notifications. Virtually all of these cases had preN diagnosis, showing the contribution of antenatal findings on perinatal mortality, which is also reported in other studies [20]. Moreover, 4% were spontaneous abortions before 20 weeks of gestation and 1.6% were fetal deaths. Live birth was globally the most frequent pregnancy outcome throughout the period studied, followed by termination of pregnancy with a roughly constant number of notifications since 2007. This can be associated to earlier detection of CAs due to enhanced preN diagnosis centers activity, higher availability of differentiated ultrasonography and optimized screening test implementation [21]. These results are comparable to those verified by RENAC [13, 14].

More than half of the cases of CAs notified by our institution were detected through preN diagnosis (63%), which was the most frequent moment of detection throughout the fifteen years, followed by delivery (15%) and the first week of life (15%). RENAC latest reports showed an increase in prenatally diagnosed cases of CAs: 44% between 2000 and 2010; 56% between 2011 and 2013 [13, 14]. According to EUROCAT information, about 31% of non-chromosomal anomalies in Europe from 2008 to 2012 were diagnosed during gestation [22]. A study in West Africa showed a preN diagnosis detection of 1.5% [23]. Although not all notifications included the first altered prenatal test (8/770 cases), obstetric ultrasound detected primarily the CAs in about 60% of the cases, whereas amniocentesis/CVS or biochemical screening were the detection point for 5% of the individuals. Importantly, about 34% of the cases had normal prenatal testing results, but it would be necessary to analyze specific anomalies in order to understand their level of detection and compare this result to other studies. In Portugal, from 2011 to 2013 obstetric ultrasound allowed the detection of CAs in 48% of the cases. The uneven quality and effectiveness across the country is possibly at least in part responsible of some of the difference from our results [14]. The characteristics of CAs appear to have played a role in the time of diagnosis, and some types such as anencephaly are detectable earlier than others [24].

Almost 70% of all registered anomalies were isolated and there were no statistically significant differences among pre- and postnatally diagnosed cases for the number of anomalies per individual, although other studies verified differences [25]. Nevertheless, our multivariate analysis showed that the number of CAs in each case influenced antenatal detection, whereby the presence of more than one anomaly facilitated preN diagnosis.

The most common type of CAs was circulatory (40%), as verified worldwide [1] and in Europe [26], followed by chromosomal abnormalities (21%) and those related to the musculoskeletal system (15%). Similar studies in India [27], Iran [28] and Colombia [29] demonstrated a predominance of CAs of the musculoskeletal or nervous system. Different ethnic, social and environmental factors within distinct parts of the world explain the divergence among studies, whereby developed countries have an higher accessibility and resources for diagnosis and treatment (particularly if surgical) [28, 30]. Our results were different from those included in the RENAC report concerning the period between 2000 to 2010, where 27% of the cases had circulatory anomalies, 20% had musculoskeletal, 13% had urinary, 9% had chromosomal and 7% had nervous system related defects [13].

We verified statistically significant differences to notifications on selected types of CAs throughout the 15 years. Importantly, notifications of chromosomal abnormalities rose since 2007. This was probably associated to more notifications and/or older mothers with more frequent referral to specialized centers and assistance, since this type of CAs has been demonstrated to be more common

at more advanced maternal ages [31]. A RENAC study showed an association between the age of the mother and CAs, especially in chromosomal and circulatory types (for older mothers) [10]. Furthermore, we verified a higher frequency of congenital malformations of the circulatory system and other congenital malformations of the digestive system among postnatally diagnosed individuals, and our multivariate analysis demonstrated that having these type of anomalies did not increase the probability of antenatal diagnosis, since OR is less than 1 (**Tab. 5**). This can be explained by the increased difficulty of detecting specific types of these kind of CAs, as it has been shown in other studies [32-34].

We verified differences in maternal age among pre- and postnatally diagnosed individuals, with a higher median of age in the first group. Although this could be explained in part by higher pregnancy surveillance and therefore more antenatal testing in more advanced ages, this could not be confirmed by this series, as about 21% of postnatally diagnosed individuals lacked this information.

Previous studies found that smoking was a risk factor for CAs [11]. In 2013, a birth cohort study assembled at public maternity units of Porto showed that 25% of mothers smoked during pregnancy [35]. It is very likely that a relevant number of cases included in our study omitted this information. Alcohol has also been associated to CAs, especially those related to central nervous system [36]. Differences for drinking mothers were found among groups. Given our national social context, it is possible that the higher frequency of drinking mothers among postnatally diagnosed cases was due to lower socio-economic and educational levels, in which pregnancy was not monitored at all.

Only 16% of all cases had notification of maternal medications during the first trimester of pregnancy. Multivariate analysis showed that this factor increased the probability of preN diagnosis, however, it is possible that mothers with preN diagnosis recalled better this type of information and/or had better surveillance due to a situation that required medical treatment. Previous studies suggested a higher risk of CAs with pregnancy drug exposure [37], but the study of specific class effects goes beyond our purposes.

The diseases that were most frequently notified during pregnancy were gestational diabetes, urinary infection and hypertension, whereas the medications that were reportedly most used during gestation were insulin and oral diabetics. A previous cohort study demonstrated a higher antenatal detection of cardiovascular anomalies in women with gestational diabetes [38].

Maternal chronic disease has been associated to a higher risk of CAs [39]. About 15% of all mothers notified a chronic disease, mostly asthma, obesity, and thyroid disease. We verified statistically significant differences between pre- and postnatally detected cases of CAs, with a higher number of occurrences among the first group. These women were probably better monitored due to their previously known condition. A case-control study conducted between 1998 and 2012 suggested an association between CAs and maternal chronic hypertensive disorders, regardless of pharmacological treatment [40]. Another study showed a reduction in antenatal ultrasound detection of CAs in obese women [41], which is a relevant finding considering our national health context [42]. RENAC reported that 9% of mothers had at least one pregnancy disease between 2000 and 2011 (predominantly urinary infections), and other 9% had chronic disease (40% asthma) [13].

Almost 100 cases had familiar history of CAs and other studies found that CAs were more prevalent in cases with a family history of an anomaly [43]. Consanguinity has been considered as a major risk factor for CAs [44].

As mentioned above, all our data was collected from the RENAC national database, which depends on physicians' initiative to notify cases of CAs and provide all of the requested information. Therefore, we had a relevant number of variables with missing values that may have altered some results. More importantly, it is very likely that the real number of occurrences is higher than we verified. Furthermore, it is also possible that our hospital characteristics, as an important referral center for congenital heart defects and other CAs requiring surgical treatment, affected the proportion of cases with preN diagnosis and the types of anomaly.

Since CAs are currently an important cause of fetal and infant morbidity and mortality, it is important to determine whether preN diagnosis centers are capable of effectively detect and manage these cases according to their severity. It would be necessary to study specific CAs to understand if long-term prognosis had an impact on the decision to carry on the gestation.

Conclusion

Our data confirms the importance of both the RENAC national database and preN diagnosis in

improving perinatal health care. However, in order to determine the national prevalence of CAs and understand any involved factors, it is desirable to improve notification of cases throughout the country, facilitating the adjustment of national protocols to achieve a better perinatal counseling and surveillance.

Acknowledgements

We would like to express our gratitude to the people that contributed to the reporting of cases with congenital anomaly during the 15-year period.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. World Health Organization. Birth Defects – report by the secretariat. 2010.
2. EUROCAT Central Registry. EUROCAT Statistical Monitoring Report – 2012. 2015.
3. Corsello G, Giuffre M. Congenital malformations. J Matern Fetal Neonatal Med. 2012;25(Suppl 1):25-9.
4. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, Cousens S, Mathers C, Black RE. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430-40.
5. Instituto Nacional de Estatística. Causas de Mortem 2013. 2015.
6. Instituto Nacional de Estatística. Dia Mundial da Saúde: 2002-2013. 2015.
7. Nussbaum R, McInnes R, Willard H. Thompson & Thompson Genetics in Medicine – 8th edition. Canada: Elsevier, 2015.
8. Lee NC, Chien YH, Hwu WL. Congenital malformations in newborns – a challenge unmet for decades. Pediatr Neonatol. 2015;56(1):5-6.
9. Correa C, Mallarino C, Pena R, Rincon LC, Gracia G, Zarante I. Congenital malformations of pediatric surgical interest: prevalence, risk factors, and prenatal diagnosis between 2005 and 2012 in the capital city of a developing country. Bogotá, Colombia. J Pediatr Surg. 2014;49(7):1099-103.
10. Braz P, Machado A, Dias CM. Risco fetal de anomalias congénitas com base na idade materna em Portugal. Registo Nacional de Anomalias Congénitas – Instituto Nacional de Saúde Dr. Ricardo Jorge, 2012.
11. Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: Established teratogens and risk factors. Birth Defects Res A Clin Mol Teratol. 2015;103(8):652-5.
12. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease. Toxicol Sci. 2011;122(1):1-6.
13. Braz P, Machado A, Roquette R, Dias CM. Registo Nacional de Anomalias Congénitas: 11 anos de vigilância em Portugal. Registo Nacional de Anomalias Congénitas – Instituto Nacional de Saúde Dr Ricardo Jorge, 2015.
14. Instituto Nacional de Saúde Dr. Ricardo Jorge. Boletim informativo do Registo Nacional de Anomalias Congénitas. 2015.
15. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, Stoll C, Gener B, Pierini A, Nelen V, Rosch C, Gillerot Y, Feijoo M, Tincheva R, Queisser-Luft A, Addor MC, Mosquera C, Gatt M, Barisic I. Prenatal diagnosis of severe structural congenital malformations in Europe. Ultrasound Obstet Gynecol. 2005;25(1):6-11.
16. Khoshnood B, Greenlees R, Loane M, Dolk H. Paper 2: EUROCAT public health indicators for congenital anomalies in Europe. Birth Defects Res A Clin Mol Teratol. 2011;91(Suppl 1):S16-22.
17. El-Chaar D, Yang Q, Gao J, Bottomley J, Leader A, Wen SW, Walker M. Risk of birth defects increased in pregnancies conceived by assisted human reproduction. Fertil Steril. 2009;92(5):1557-61.
18. Farhi A, Reichman B, Boyko V, Mashiach S, Hourvitz A, Margalioth EJ, Levran D, Calderon I, Orvieto R, Ellenbogen A, Meyerovitch J, Ron-El R, Lerner-Geva L. Congenital malformations in infants conceived following assisted reproductive technology in comparison with spontaneously conceived infants. J Matern Fetal Neonatal Med. 2013; 26(12):1171-9.
19. Tararbit K, Lelong N, Jouannic JM, Goffinet F, Khoshnood B. Is the probability of prenatal diagnosis or termination of pregnancy different for fetuses with congenital anomalies conceived following assisted reproductive techniques? A population-based evaluation of fetuses with congenital heart defects. BJOG. 2015;122(7):924-31.
20. Boyd PA, Rounding C, Chamberlain P, Wellesley D, Kurinczuk JJ. The evolution of prenatal screening and diagnosis and its impact on an unselected population over an 18-year period. BJOG. 2012;119(9):1131-40.
21. Ministério da Saúde. Despacho n.º 10325/99 (2.ª Série), de 3 de maio. Orientações reguladoras dos centros de diagnóstico pré-natal. DR n.º 122/1999, Série II de 1999-05-26, p. 7785-86.
22. http://www.eurocat-network.eu/prenatalscreeninganddiagnosis/prenataldetection(pd)rates, last access: December 2015.
23. Kouame BD, N'Guetta-Brou IA, Kouame GS, Sounkere M, Koffi M, Yaokreh JB, Odehouri-Koudou T, Tembely S, Dieth GA, Ouattara O, Dick R. Epidemiology of congenital abnormalities in West Africa: Results of a descriptive study in teaching hospitals in Abidjan: Cote d'Ivoire. Afr J Paediatr Surg. 2015;12(1):51-5.
24. Boyd PA, Tonks AM, Rankin J, Rounding C, Wellesley D, Draper ES. Monitoring the prenatal detection of structural fetal congenital anomalies in England and Wales: register-based study. J Med Screen. 2011;18(1):2-7.

25. Calzolari E, Barisic I, Loane M, Morris J, Wellesley D, Dolk H, Addor M-C, Arriola L, Bianchi F, Neville AJ, Budd JLS, Klungsoyr K, Khoshnood B, McDonnell B, Nelen V, Queisser-Luft A, Rankin J, Rissmann A, Rounding C, Tucker D, Verellen-Dumoulin C, de Walle H, Garne E. Epidemiology of multiple congenital anomalies in Europe: a EUROCAT population-based registry study. Birth Defects Res A Clin Mol Teratol. 2014;100(4):270-6.
26. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol. 2010;686:349-64.
27. Sarkar S, Patra C, Dasgupta MK, Nayek K, Karmakar PR. Prevalence of Congenital Anomalies in Neonates and Associated Risk Factors in a Tertiary Care Hospital in Eastern India. J Clin Neonatol. 2013;2(3):131-4.
28. Hossein MA, Kargar Maher MH, Afsharnia F, Dastgiri S. Prevalence of Congenital Anomalies: A Community-Based Study in the Northwest of Iran. ISRN Pediatrics. 2014.
29. García MA, Imbachí L, Hurtado PM, Gracia G, Zarante I. [Ultrasound detection of congenital anomalies in 76,155 births in the cities of Bogotá and Cali, 2011-2012]. [Article in Spanish]. Biomedica. 2014;34(3):379-86.
30. Sitkin NA, Ozgediz D, Donkor P, Farmer DL. Congenital Anomalies in Low- and Middle-Income Countries: The Unborn Child of Global Surgery. World J Surg. 2014;39(1):36-40.
31. Zile I, Villerusa A. Maternal age-associated congenital anomalies among newborns: a retrospective study in Latvia. Medicina (Kaunas). 2013;49(1):29-35.
32. Allan LD. Diagnosis of cardiac anomalies in offspring of women with congenital heart disease: is fetal echocardiography enough? Nat Clin Pract Cardiovasc Med. 2008;5(9):522-3.
33. Manganaro L, Saldari M, Bernardo S, Vinci V, Aliberti C, Sollazzo P, Giancotti A, Capozza F, Porpora MG, Cozzi DA, Catalano C. Role of magnetic resonance imaging in the prenatal diagnosis of gastrointestinal fetal anomalies. Radiol Med. 2015;120(4):393-403.
34. Virgone C, D'Antonio F, Khalil A, Jonh R, Manzoli L, Giuliani S. Accuracy of prenatal ultrasound in detecting jejunal and ileal atresia: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;45(5):523-9.
35. Alves E, Henriques A, Correia S, Santos AC, Azevedo A, Barros H. Cardiovascular risk profile of mothers of a Portuguese birth cohort: a survey 4 years after delivery. Prev Med. 2013;57(5):494-9.
36. Viteri OA, Soto EE, Bahado-Singh RO, Christensen CW, Chauhan SP, Sibai BM. Fetal anomalies and long-term effects associated with substance abuse in pregnancy: a literature review. Am J Perinatol. 2015;32(5):405-16.
37. Bunn TL, Ouyang BJ, Slavova S. Newborn Congenital Malformations Associated With Prenatal Exposure to Drugs in Kentucky, 2009-2013. South Med J. 2016;109(2):124-9.
38. Newham JJ, Glinianaia SV, Tennant PW, Rankin J, Bell R. Improved antenatal detection of congenital anomalies in women with pre-gestational diabetes: population-based cohort study. Diabet Med. 2013;30(12):1442-8.
39. Ordonez MP, Nazer J, Aguila A, Cifuentes L. Congenital malformations and chronic diseases of the mother. Latin American Collaborative Study of Congenital Malformations (ECLAMC) 1971-1999. Rev Med Chil. 2003;131(4):404-11.
40. van Gelder MM, Van Bennekom CM, Louik C, Werler MM, Roeleveld N, Mitchell AA. Maternal hypertensive disorders, antihypertensive medication use, and the risk of birth defects: a case-control study. BJOG. 2015;122(7):1002-9.
41. Best KE, Tennant PW, Bell R, Rankin J. Impact of maternal body mass index on the antenatal detection of congenital anomalies. BJOG. 2012;119(12):1503-11.
42. Braz P, Machado A, Roquette R, Dias CM. A doença crónica materna e o nascimento de crianças com anomalias congénitas em Portugal. Registo Nacional de Anomalias Congénitas – Instituto Nacional de Saúde Dr Ricardo Jorge, 2014.
43. El Koumi MA, Al Banna EA, Lebda I. Pattern of congenital anomalies in newborn: a hospital-based study. Pediatr Rep. 2013;5(1):e5.
44. Sheridan E, Wright J, Small N, Corry PC, Oddie S, Whibley C, Petherick ES, Malik T, Pawson N, McKinney PA, Parslow RC. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet. 2013;382(9901):1350-9.