Epidemiology and major subtypes of congenital heart defects in Hunan Province, China

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Abstract
Congenital heart defects (CHDs) are the most common birth defects (BDs) and account for nearly one-third of all BDs. The aim of this article was to investigate the epidemiology and major subtypes of CHDs in Hunan Province, China in the last 5 years.

CHD surveillance data from 2012 to 2016 were collected from 52 registered hospitals in Hunan. The prevalence rates of CHDs, incidence rates of CHDs combined with other BDs, and rates of termination of pregnancy (TOP) for CHDs among different regions, infant sexes, and maternal ages were calculated for both early fetuses (<28 weeks of gestation) and perinatal infants (PIs) (between 28 weeks of gestation and 7 days after birth). Both the constituent ratio and prevalence rates were computed among subtypes.

CHDs were found in 6289 out of 673,060 births. The overall prevalence was 93.44 per 10,000 PIs, with 19.27 and 74.17 per 10,000 in early fetuses and PIs, respectively. The risks of CHDs were higher in infants from urban areas than those from rural areas during the whole gestation and were higher in male infants than in female infants during the perinatal period. The total prevalence of CHDs increased significantly with maternal age (χ\(^2\) trend = 141.84, P < .05). Among fetuses in early gestation, there were 288 cases (22.21%) of CHDs combined with other BDs and 1292 cases (99.61%) of TOP for CHD. The 3 major subtypes of CHDs were ventricular septal defect (VSD) (22.06%), Tetralogy of Fallot (TOF) (9.43%), and atrioventricular septal defect (AVSD) (6.69%). Among PIs, there were 1541 cases (30.87%) of CHD diagnosed before delivery and 1184 cases (76.83%) were TOP. The 3 major subtypes were atrial septal defect (ASD) (42.81%), patent ductus arteriosus (PDA) (16.07%), and VSDs (15.21%).

The total prevalence of CHD in Hunan Province and the rate of TOP for CHD was high, especially for early-gestation fetuses. Pregnancies in urban women, male PIs, and maternal age were the risk factors for CHDs. Among early-gestation fetuses, the most common types were VSD, TOF, and ASD, and among PIs, the most common types were ASD, PDA, and VSD.

Abbreviations: ASD = atrial septal defect, AVSD = atrioventricular septal defect, BDs = birth defects, CHDs = congenital heart defects, CI = confidence intervals, DBD = diagnosed before delivery, DORV = double outlet right ventricle, OCMCCC = other congenital malformations of cardiac chambers and connections, OCMTV = other congenital malformations of the tricuspid valve, OR = odds ratio, OSCMH = other specified congenital malformations of the heart, PDA = patent ductus arteriosus, PFO = isolated patent foramen ovale, PIs = perinatal infants, TOF = Tetralogy of Fallot, TOP = termination of pregnancy, VSD = ventricular septal defect.

Keywords: congenital heart defects, epidemiology, subtypes, surveillance

1. Introduction
Congenital heart defects (CHDs) are the most common type of birth defect (BDs) and the leading cause of infant mortality. The incidence rates of CHDs reported in different studies vary from approximately 4 to 50 per 1000 live births.\textsuperscript{[1]} Some subtypes of CHDs are mild diseases with relatively little need for medical care, but other subtypes are complicated diseases requiring great expertise in this field. Thus, understanding the epidemiology and major subtypes of CHDs is important for recommending valuable changes in health policies.\textsuperscript{[2]}

The estimates of early CHD prevalence in China based on postnatal case assessment alone range from 2.7 to 6.6 per 1000 live births, lower than those reported in some developed countries.\textsuperscript{[1]} Recently, hospital-based studies of prenatal CHD detection have been conducted in China.\textsuperscript{[4]} The Ministry of Health of China initiated a national hospital-based Birth Defect Surveillance System in 1986 in order to track perinatal infants (Pis), including live births up to 7 days, fetal deaths, stillbirths or terminations of pregnancy due to fetal anomaly. CHDs were recorded in detail in this surveillance system. In Hunan, the surveillance system that involved 52 hospitals began in 1991 (selected by urban, rural and were uniformly distributed in 14 cities of Hunan province), and recorded information such as...
incidence, distribution, and determinants of BDs, including CHDs.[9]

Hunan has been confronted with tremendous challenges in BDs prevention in recent years. The prevalence rates of BDs were ranked third in China in 2011, fourth in 2012, and fifth in 2013.[6] In particular, almost one-third of BDs were CHDs.[7] Moreover, the patterns and incidence rates of CHDs differ geographically due to racial and ethnic factors.[8] However, studies of CHDs usually focus only on the late gestational period (>20 or 28 weeks) or live births.[8,9] The total prevalence of CHDs among all fetuses may be higher than that reported among live births alone or among fetuses later in gestation alone, since complex CHDs are common throughout the gestational period[10] and may result in spontaneous abortion or stillbirth, especially early in gestation. This study aimed at investigating the epidemiology and major subtypes of CHDs among all infants, including both early in gestation and during the perinatal period by using results from the surveillance system in Hunan for the last 5 years.

2. Methods

2.1. Study population and ethics statement

This study was cross-sectional study, involving all infants (including stillbirths, dead fetuses, or live births) during the perinatal period and CHD cases at <28 weeks of gestation born in the 52 registered hospitals of Hunan between 2012 and 2016. The CHD records were reported both on paper and online, and anonymized and de-identified prior to analysis. The records of CHD included the maternal and fetal characteristics, such as maternal census data, maternal age, fetus gestation, fetus sex, the subtype of CHD, outcome, and so on. This study was approved by the Medical Ethics Committee of Hunan Maternal and Child Health Hospital. Written informed consent was obtained from all participants’ guardians.

2.2. Criteria for CHD diagnosis

The diagnosis of CHDs was based on the Chinese National Criteria of Birth Defects and Tiny Deformities and confirmed within 7 days of birth (postural defects were excluded from the monitoring system). The main diagnostic tool for CHDs is echocardiography. The clinical diagnosis of CHD was finished within 7 days after delivery. Isolated patent foramen ovale (PFO) and PDA that failed to close during the supervised period were included. Experts from each registered hospital provided diagnostic technical support and were responsible for confirming the diagnoses. Complex CHDs were diagnosed in a higher-level hospital or with expert consultation. CHDs were coded according to the International Classification of Diseases Clinical Modification Codes, tenth edition (ICD-10).

2.3. Quality control

According to the require of Health and Family Planning Commission of China, the maternal and children’s hospitals and health administrative departments audited the CHD cases and perinatal data. The monitoring hospitals were inspected and examined at quarterly intervals by county-level administrators and at half-yearly intervals by city-level or province-level administrators to ensure quality control and reduce the probability of misreporting or failure of reporting or missing data of reports. After quality control, we deleted some cases missing important information which we could not completed before analysis.

2.4. Statistical analysis

The prevalence rates of CHDs, incidence rates of CHDs combined with other BDs, and rates of TOP for CHD with 95% confidence intervals (CI) among the different regions, infant sexes, and maternal ages were calculated separately. Gestation was divided into early gestation (<28 weeks of gestation) and the perinatal period (between 28 weeks of gestation and 7 days after birth). The relationship of each maternal characteristic with CHDs was explored using the Chi-squared test and the crude odds ratio (OR). The proportion and prevalence rates of the major CHD subtypes were also presented and ranked. Prevalence estimates were reported as “per 10,000 PIs” (perinatal infants). The data were analyzed using SPSS 21.0 (SPSS, Chicago, IL) with the significance level at $P<.05$.

3. Results

3.1. Prevalence of CHDs in Hunan

A total of 673,060 PIs (approximately 16.71% of the total births in Hunan Province, 673,060/4,027,317) were reported to the Birth Defect Surveillance System of Hunan, and of these, 1297 cases (20.62%) during early gestation and 4992 cases (79.38%) during the perinatal period were diagnosed as CHDs. The total prevalence rate of CHDs was 93.44 (95% CI: 91.38–95.50) per 10,000 PIs, while the average prevalence rates in early gestation and in the perinatal period were 19.27 (95% CI: 18.18–20.36) and 74.17 (95% CI: 72.07–76.27) per 10,000 PIs, respectively. Among the fetuses early in gestation, the average prevalence rate of CHDs was significantly higher in urban areas versus rural areas (20.87 vs 17.92 per 10,000 PIs) (OR = 1.18, 95% CI: 1.05–1.30, $P=.006$). No significant difference was found between male and female infants (OR = 1.06, 95% CI: 0.94–1.18, $P=3.36$). The prevalence rate of CHDs was lowest in the maternal age group of 30 to 34 and highest in the age group ≥35 (17.09 vs 23.47 per 10,000 PIs) (OR = 1.18, 95% CI: 1.05–1.30, $P=.005$) (Table 1).

Among PIs, the average prevalence rate of CHDs was significantly higher in urban versus rural areas (20.87 vs 17.92 per 10,000 PIs) (OR = 1.37, 95% CI: 1.10–1.72, $P=.005$) (Table 1).

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Combining the data for fetuses in early gestation with PIs, the total prevalence rate of CHDs significantly increased with maternal age ($\chi^2\text{ trend}=141.84, P<.001$). Age group <20 as a reference, the ORs were 1.18 (group 20–24, 95% CI: 0.94–1.50), 1.59 (group 25–29, 1.27–2.01), 1.74 (group 30–34, 1.38–2.19), and 1.77 (group ≥35, 1.39–2.26).

3.2. Incidence rate of CHDs combined with other BDs and the rate of TOP for CHDs

Among the fetuses early in gestation, there were 288 cases (22.21%) of CHDs combined with other BDs and 1292 cases (99.61%) of TOP. Five cases (0.39%) were premature infants who were diagnosed with CHDs after delivery.

Among the PIs, there were 1541 cases (30.87%) of CHD diagnosed before delivery (DBD) and 1184 cases (76.83% of
Table 1
Prevalence for CHDs and rate of TOP less than 28 weeks of gestation with maternal characteristics.

| Region    | PI (n) | CHD (n) | Prevalence of CHD (per 10,000 PIs) | OR (95%CI) | Combing with other BDs | TOP |
|-----------|--------|---------|----------------------------------|------------|------------------------|-----|
|           |        |         |                                  |            | Case (n) | Rate (%) | Case (n) | Rate (%) |
| Region    |        |         |                                  |            |          |          |          |          |
| Urban     | 308034 | 643     | 20.87 (18.73–23.01)              | 1.16 (1.05–1.30) | 154      | 23.95    | 639      | 99.38    |
| Rural     | 365026 | 654     | 17.92 (16.80–19.04)              | reference  | 134      | 20.49    | 653      | 99.85    |
| Infant gender        |        |         |                                  |            |          |          |          |          |
| Male       | 356007 | 635     | 17.81 (16.68–18.94)              | reference  | 154      | 24.25    | 632      | 99.53    |
| Female     | 316324 | 595     | 18.81 (17.67–20.95)              | 1.06 (0.94–1.18) | 113      | 18.99    | 593      | 99.66    |
| Maternal age        |        |         |                                  |            |          |          |          |          |
| <20        | 12077  | 23      | 19.04 (12.35–28.75)              | 1.12 (0.73–1.71) | 5        | 21.74    | 23       | 100.00   |
| 20–24      | 188786 | 344     | 18.22 (16.05–20.39)              | 1.07 (0.90–1.27) | 72       | 20.93    | 342      | 99.42    |
| 25–29      | 294136 | 592     | 20.13 (18.99–22.28)              | 1.18 (1.01–1.38) | 136      | 22.97    | 589      | 99.49    |
| 30–34      | 125233 | 214     | 17.09 (14.88–19.30)              | Reference  | 46       | 21.50    | 214      | 100.00   |
| 35–        | 52828  | 124     | 23.47 (19.11–26.83)              | 1.37 (1.10–1.72) | 29       | 23.39    | 124      | 100.00   |
| Total      | 673060 | 1297    | 19.27 (18.18–20.36)              |           | 288      | 22.21    | 1292     | 99.61    |

BDs = birth defects, CHD = congenital heart defects, CI = confidence intervals, OR = odds ratio, PIs = perinatal infants, TOP = termination of pregnancy.

DBD cases, 23.72% of total CHD cases were TOP for CHD. Among the CHD cases, 442 cases (8.85%) were combined with other BDs.

3.3. Major subtypes of CHDs in Hunan
Among the fetuses early in gestation, the five major subtypes of CHDs were VSD (22.06%), TOF (9.43%), AVSD (6.69%), other BDs.

Table 2
Prevalence of CHD and rate of TOP between 28 weeks of gestation and 7 days after birth according to different characteristics.

| Region    | PI (n) | CHD (n) | Prevalence of CHD (per 10,000 PIs) | OR (95%CI) | Diagnosed before delivery (DBD) | TOP |
|-----------|--------|---------|----------------------------------|------------|---------------------------------|-----|
|           |        |         |                                  |            | Case (n) | Rate (%) | Case (n) | Rate (%) |
| Region    |        |         |                                  |            |          |          |          |          |
| Urban     | 308,034 | 3211    | 104.24 (100.12–108.28)           | 2.15 (2.03–2.28) | 693     | 69.12    | 14.92    | 226      | 7.04    |
| Rural     | 365,026 | 1781    | 48.79 (47.63–50.95)              | reference  | 848     | 83.14    | 39.58    | 216      | 12.13   |
| Infant gender        |        |         |                                  |            |          |          |          |          |
| Male       | 356,007 | 2729    | 76.53 (74.39–80.67)              | 1.07 (1.02–1.14) | 821     | 77.22    | 23.23    | 244      | 8.94    |
| Female     | 316324  | 2256    | 71.32 (68.16–74.48)              | reference  | 714     | 76.19    | 24.11    | 194      | 8.60    |
| Maternal age        |        |         |                                  |            |          |          |          |          |
| <20        | 12077  | 52      | 43.06 (33.18–56.95)              | reference  | 34      | 88.24    | 57.69    | 8        | 15.38   |
| 20–24      | 188786 | 1047    | 55.46 (52.24–58.68)              | 1.29 (0.98–1.70) | 433     | 82.22    | 34.00    | 106      | 10.12   |
| 25–29      | 294136 | 2308    | 78.47 (75.32–81.62)              | 1.82 (1.39–2.41) | 628     | 75.32    | 20.49    | 177      | 7.67    |
| 30–34      | 125233 | 1130    | 90.23 (85.60–95.39)              | 2.07 (1.57–2.73) | 307     | 73.29    | 19.91    | 106      | 9.38    |
| 35–        | 52828  | 455     | 86.13 (78.83–94.42)              |            | 139     | 71.94    | 21.98    | 45       | 9.89    |
| Total      | 673,060| 4992    | 74.17 (72.07–76.27)              |           | 1541    | 118.83   | 23.72    | 442      | 8.85    |

BDs = birth defects, CHD = congenital heart defects, CI = confidence intervals, OR = odds ratio, PIs = perinatal infants, TOP = termination of pregnancy.

Among PIs, the 5 major subtypes of CHDs were ASD (42.81%), PDA (16.07%), VSD (15.21%), other congenital malformations of cardiac chambers and connections (OCMCCC) (3.94%), and other congenital malformations of the tricuspid valve (OCMTV) (2.66%) (Table 4).

4. Discussion
The total prevalence rate of CHDs (93.44 per 10,000 PIs, 95% CI: 91.38–95.50) observed in this study is higher than in most other studies.[11,13] For example, the overall prevalence of CHDs was 62.10 per 10,000 PIs in China in 2016[13] and 6.5 per 1000
Table 3

The major 10 subtypes of CHDs among fetuses less than 28 weeks of gestation.

| Subtypes                                      | Case (n) | Proportion (%) | Prevalence (95%CI) |
|-----------------------------------------------|----------|----------------|--------------------|
| Ventricular septal defect (VSD)               | 419      | 22.06          | 6.23 (5.21–7.24)   |
| Tetralogy of Fallot (TOF)                     | 179      | 9.43           | 2.66 (2.62–2.84)   |
| Atrioventricular septal defect (ASD)          | 127      | 6.69           | 1.89 (1.86–1.92)   |
| Other specified congenital malformations of heart (OSCMH) | 80      | 4.21           | 1.19 (1.16–1.22)   |
| Double outlet right ventricle (DORV)          | 78       | 4.11           | 1.16 (1.13–1.19)   |
| Congenital malformation of heart, unspecified (CMHU) | 70      | 3.69           | 1.04 (1.02–1.06)   |
| Stenosis of pulmonary artery (PS)             | 68       | 3.58           | 1.01 (0.99–1.03)   |
| Other congenital malformations of aorta (OCMA) | 63      | 3.32           | 0.94 (0.92–0.96)   |
| Other congenital malformations of other great arteries (OCMGA) | 60      | 3.16           | 0.89 (0.87–0.91)   |
| Other congenital malformations of tricuspid valve (OCMTV) | 56      | 2.95           | 0.83 (0.81–0.85)   |

CHD = congenital heart defects, CI = confidence intervals.

Table 4

The major 10 subtypes of CHDs among PIs.

| Subtypes                                      | Case (n) | Proportion (%) | Prevalence (95%CI) |
|-----------------------------------------------|----------|----------------|--------------------|
| Atrial septal defect (ASD)                     | 2752     | 42.81          | 40.89 (40.77–43.01) |
| Patent ductus arteriosus (PDA)                | 1033     | 16.07          | 15.35 (14.26–16.44) |
| Ventricular septal defect (VSD)               | 978      | 15.21          | 14.53 (13.45–15.61) |
| Other congenital malformations of cardiac chambers and connections (OCMCCC) | 253     | 3.94           | 3.76 (3.71–3.81)   |
| Other congenital malformations of tricuspid valve (OCMTV) | 171     | 2.66           | 2.54 (2.50–2.58)   |
| Tetralogy of Fallot (TOF)                     | 144      | 2.24           | 2.14 (2.11–2.17)   |
| Congenital malformation of heart, unspecified (CMHU) | 133     | 2.07           | 1.98 (1.95–2.01)   |
| Other specified congenital malformations of heart (OSCMH) | 128     | 1.99           | 1.90 (1.87–1.93)   |
| Atrioventricular septal defect (ASD)          | 81       | 1.26           | 1.20 (1.17–1.23)   |
| Other congenital malformations of great arteries (OCMGA) | 58      | 0.90           | 0.86 (0.84–0.88)   |

CHD = congenital heart defects, CI = confidence intervals. PI = perinatal infants.
medical management for those affected. CHDs have led to the development of prenatal diagnosis policies. It is the parents’ option to choose whether to have an infant with CHD. In our study, the rate of TOP with CHD was 99.61% before 28 weeks of gestation, while it was 76.83% among DBD cases. In agreement with our data, a previous study reported 4366 cases that were diagnosed with the 11 most severe malformations (2 types were CHD). Of these, 64% (2806/4366) were diagnosed prenatally and 66% (1863/2806) resulted in TOP. In some countries, such as South Africa and Malta, the proportion of TOP due to CHDs is small and TOP is even prohibited. These countries are completely opposed to TOP due to personal experiences or moral, ethical, or religious convictions. In these countries, TOP is regarded as controversial and remains a taboo topic, even though this procedure is becoming more acceptable and demanded. In addition, a high prenatal detection rate and early prenatal diagnosis will increase the proportion of TOP.

This study comprehensively illustrates the epidemiological characteristics of CHDs in Hunan, the most populated province in China, and includes all cases of CHDs in the last 5 years throughout early gestation and the perinatal period. Thus, the prevalence of CHD observed in this study is closer to the reality. However, there are some limitations. First, this surveillance system does not include the TOP cases without BDs before 28 weeks of gestation, so the denominator in the prevalence of CHDs for early gestation is “Pics” rather than “all fetuses.” Second, for cultural reasons, autopsies are seldom conducted in China, and chromosome tests were rarely used in our study, so some infants with CHDs combined with other BDs were failed to be identified. Thus, the observed rate of CHDs combined with other BDs may be underestimated.

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