Effect of Pathoanatomic Diagnosis on the Quality of Birth Defects Surveillance in China[1]

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Objective To provide evidence for more accurate diagnosis of birth defects based on the pathoanatomy of congenital malformations. **Methods** Data used in this study were obtained from Luliang City Hospital and three county hospitals of Shanxi province between February 2004 and March 2006. Autopsy and pathological examination of 160 dead fetuses and stillbirths were performed. Photos of dead fetuses and stillbirths were taken, tissues were cut into sections for pathological examination under microscope, all pathological information was recorded, and percentage of birth defects was calculated. **Results** The proportion of dead fetuses and stillbirths with or without congenital malformations was 84.4% (135/160) and 15.6% (25/160), respectively. There were 16 categories of major external and internal birth defects in 135 cases of such defects. Congenital heart defects, anencephaly and spina bifida had a higher prevalence rate in the study period. The prevalence rate of non-malformation death and birth defects < 28 gestational weeks and internal anomalies ⩾ 28 gestational weeks was 14.61% (61/4175) and 17.25% (72/4175), respectively. A total of 413 *in situ* anomalies were found in 135 cases of autopsy. Spina bifida, anencephaly, congenital heart defects, aplasia or accessory lobe of lung, renal agenesis and dysplasis and congenital hydrocephaly were more closely associated with severe malformations than with mitis malformations. The cases of dead fetuses and stillbirths with multiple malformations (⩾ 2 *in situ* anomalies) had a higher proportion (74.1%), whereas those with isolated malformations had a lower proportion (25.93%). **Conclusion** The occurrence of congenital malformations in different embryonic developmental stages affects multiple organs. Postmortem examination of internal and multiple malformations of fetal deaths and stillbirths can provide more accurate diagnostic information for birth defects.

Key Words: Birth defects; Pathoanatomy; Congenital internal anomaly; Congenital external anomaly; ICD-10 codes

INTRODUCTION

Although the infant mortality rate has decreased over the last few decades, the proportion of deaths due to congenital anomalies is increasing, demonstrating that birth defects prevention and access to appropriate care in public health strategies play an important role in the reduction of infant and early childhood mortality[1]. Birth defects is the leading cause of death in infants and children in China. The prevalence of birth defect and neural tube defects (NTDs) in four counties of Shanxi province was 232.4 and 138.7 per 10 000 births, respectively, in 2002-2004[2-3]. The prevalence of NTDs was 199.38 per 10 000 births in Luliang Prefecture of Shanxi Province in 2002-2004[4]. The birth prevalence of NTDs was more than 19 times that of the national average in 1993-2000 (10.63/10 000)[5]. Compared with previous surveillance data, the NTDs prevalence rate did not significantly decline in high risk areas[2]. The situation in Shanxi Province is extremely serious and worthy of intensive investigation.

The impact of birth defects on mortality is usually evaluated using death certificate data. At present, birth defects registers are suitable for birth defects monitoring among birth cohorts and collection of more meaningful data on infants with birth defects[1]. Assessment of the impact of birth defects on infant mortality depends on

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death record statistics and is limited to external structural congenital anomalies[1].

Congenital anomalies are underreported, while the most serious or apparent anomalies can be observed and documented prior to birth defects surveillance report. Early recognition and reporting of congenital anomalies are limited because many anomalies are not recognizable at birth. However, data from pathoanatomic examination can be used in birth defects surveillance and support an etiologic association between environmental risk exposure and birth defects[5] .

The proportion of all deaths to infants diagnosed with birth defects is not well documented. The study was to estimate the proportion of all deaths of fetuses and infants at 9- gestational weeks or 7 days after birth and how and why this proportion differed from the proportion of previous birth defects surveillance using the pathoanatomic data on perinatal deaths in the high prevalence areas of birth defects in China. The cause of all deaths of infants or fetuses with birth defects was examined by autopsy, and their etiology was studied.

MATERIAL AND METHODS

Study Subjects

The data used in this study were obtained from Luliang City Hospital and three county hospitals (Liulin, Zhongyang, Jiaokou counties) of Shanxi province between February 2004 and March 2006[7]. A total of 295 samples of dead fetuses and stillbirths were collected. Postmortem of intrauterine fetal death，fetal death with major birth defects such as NTDs, and fetal death from maternal unwanted pregnancy and termination of pregnancy was performed. Finally, 135 cases were excluded from the study, and 160 cases were included in the final analysis.

Study Areas

The 4 hospitals are located in Luliang mountainous area. Pathoanatomic laboratories have been established in these hospitals since 2004. Dead fetuses and infants were dissected periodically by pathoanatomic experts from the Capital Institute of Pediatrics, Beijing. *In situ* malformation photography of all birth defects was taken followed by autopsy and pathological examination. Tissue samples of all organs were collected and sent to the Capital Institute of Pediatrics, Beijing. Tissue was cut into sections for pathological diagnosis. All pathologic information was recorded. All cases of birth defects were classified using ICD-10 codes. The study protocol was approved by the Institutional Review Board of the Capital Institute of Pediatrics and the Shanxi Medical University. Written informed consents were obtained from all subjects.

Data Collection

A field work group consisting of pediatrician, pathologists and trained healthcare workers from the Capital Institute of Pediatrics and the Shanxi Medical University was established to collect data on birth defects and stillbirths. Since most of the cases did not survive, as pregnancies were either terminated by therapeutic abortion or delivered stillbirths, women were interviewed by trained healthcare workers to fill in the epidemiological questionnaire.

Statistical Analysis

Detection rates of dead fetuses and stillbirths with congenital defects were calculated, including isolated and associated birth defects (multiple defects with two anomalies at least), as well as internal and external anomalies. Isolated defects were assigned by ICD-10 codes Q00 through Q99[6] Joaqu´ın Salvador *et al*, 2005). Percentages of birth defects by ICD-10 codes after pathological diagnosis were calculated, which other than percentage of birth defect itself included the number of anomalies, proportion of multiple malformations, percentage of external and internal anomalies, lethal malformation, non-lethal and affected function, and non-lethal and non-affected function. Distribution of fetuses and infants with birth defects was calculated. Data analyses were performed using a two-tailed test with the aid of the SPSS software package version 11.0 for Windows. $P<0.05$ was considered statistically significant.

RESULTS

Of the 160 cases of birth defects and still births, 135 had major external and internal malformations. The average gestational time was 25.39 ± 7.53 weeks. The proportion of the autopsy cases at their age <20, 20-28 and ⩾28 gestational weeks was 8.7% (14/160), 29.4% (47/160) and 61.9% (99/160), respectively. Nearly 90% of the cases were found at their age ⩾20 week. Fetal deaths in cases of birth defects at their age <28 or ⩾28 gestational weeks accounted for 38.1% and 61.9%, respectively. The proportion of males and females was 54.4% (87/160) and 45.0% (72/160), respectively. One case of hermaphroditismus was associated with eight *in situ* anomalies. There was no significant difference in non-malformation cases and birth defects cases as

well as in external and internal anomaly cases between males and females (P>0.05).

Of the 160 cases of stillbirths and fetal deaths, 135 had congenital malformations and 25 were without congenital malformations, accounting for 84.4% and 15.6%, respectively. The prevalence rate of birth defects in pregnancies was 32.34‰ (135/4175) between February 2004 and March 2006. The percentage and prevalence rate of birth defects (ICD-10 codes) identified by autopsy are shown in Table 1 and Fig. 1. The prevalence rate of congenital heart defects, anencephaly, spina bifida in pregnancies was 6.95‰, 6.71‰, and 6.23‰, respectively. The top five categories of congenital malformations accounted for 66.3% of all autopsy cases. The prevalence rate of neural tube defects (including anencephaly, spina bifida and encephalocele) in pregnancies was 13.89‰ (58/4175).

TABLE 1

Percentage and Prevalence of Birth Defects (ICD-10 Codes) by Autopsy

Malformations	ICD10-code	Proportion *n* (%)	Prevalence** (1/1 000 Briths)
Congenital Heart Defects	Q21.0-Q21.2	29 (18.13)	6.95
Anencephaly	Q00.0	28 (17.50)	6.71
Spina Bifida	Q05.0 - Q05.8	26 (16.25)	6.23
Aplasia or Accessory Lobe of Lung	Q33.2- Q33.9	13 (8.13)	3.11
Congenital Hydrocephaly	Q03.9	10 (6.25)	2.40
Spleen Anomalies/Splenunculus	P89.0/ Q89.0	5 (3.13)	1.20
Renal Dysplasis or Absence	Q60.0- Q63.9	5 (3.13)	1.20
Encephalocele	Q01.0-Q01.9	4 (2.50)	0.96
Single Umbilical Artery	Q27.0	3 (1.88)	0.72
Cleft lip with/without Cleft Palate	Q37.8- Q37.9	3 (1.88)	0.72
Anomalies of Liver	Q44.7	3 (1.88)	0.72
Atresia and Stenosis of Large Intestine	Q41.2/Q42.9/ Q43.8	2 (1.25)	0.48
Funnel Chest	Q67.6	1 (0.63)	0.24
Varus Talipes	Q66.0	1(0.63)	0.24
Diaphragmatocele	Q79.0	1(0.63)	0.24
Umbilical Hernia	Q79.2	1(0.63)	0.24
Non-malformation's Death*		25(15.63)	5.99
Total		160 (100.00)	38.32

Note. *25 cases died of other diseases and non-congenital malformation, **represents the prevalence rate per 1 000 births. The denominator is 4 175 births in February 2004 - March 2006.

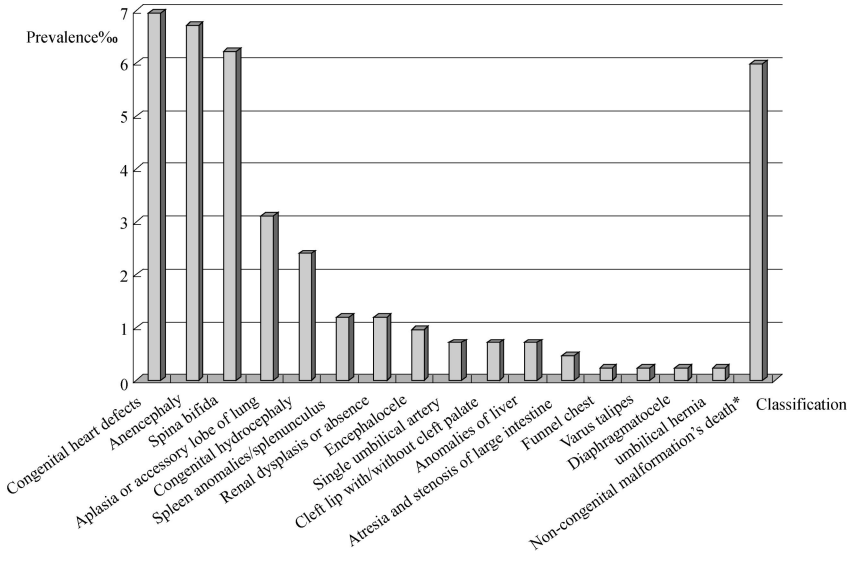

FIG. 1. Prevalence rate of birth defects (ICD-10 codes) finding by autopsy.

The prevalence rates of external and internal anomalies, and isolated and multiple anomalies by ICD-10 codes classification at different gestational weeks are shown in Table 2. The prevalence rate of external plus internal anomalies, multiple internal anomalies, multiple external anomalies, isolated internal anomaly, and isolated external anomaly in autopsy cases of pregnancies was 9.34‰, 7.19‰, 6.71‰, 5.27‰, and 3.83‰, respectively. The prevalence rate of autopsy cases at their age <20, 20-28, and ⩾28 gestational weeks was 3.35‰, 11.26‰, and 23.71‰, respectively. The prevalence rate of non-malformation deaths and birth defects in cases of pregnancies at their age <28 gestational weeks was 14.61‰ (61/4 175). The prevalence rate of internal anomalies in cases of pregnancies at their age ⩾28 gestational weeks was 17.25‰ (72/4 175). The prevalence rates of external anomalies at their age ⩾28 gestational weeks have been registered in the Birth Defects Surveillance System of China. Therefore, only nearly 32‰ (133/4 175) of dead cases and birth defects are included in this system, indicating that the prevalence rate of birth defects is definitely underestimated.

TABLE 2

Prevalence Rates of Internal Plus External Anomalies, Isolated and Multiple Anomalies by ICD-10 Codes Classification at Different Gestational Weeks (1/1 000 Births)

In situ Anomaly	<20 Gestation		⩾20-28 Gestation		⩾28 Gestation		Total	
	n	Rate*	*n*	Rate	*n*	Rate	*n*	Rate
Non-malformation Death	4	0.96	4	0.96	17	4.07	25	5.99
External + Internal Anomalies	1	0.24	13	3.11	25	5.99	39	9.34
Multiple Internal Anomalies	1	0.24	3	0.72	26	6.23	30	7.19
Multiple External Anomalies	5	1.20	18	4.31	5	1.20	28	6.71
Isolated Internal Anomaly	1	0.24	0	0.00	21	5.03	22	5.27
Isolated External Anomaly	2	0.48	9	2.16	5	1.20	16	3.83
Total	14	3.35	47	11.26	99	23.71	160	38.32

Note. *The denominator is 4 175 births in February 2004 - March 2006.

The *in situ* number of other associated malformations (multiple anomalies) by ICD-10 codes is shown in Table 3. There were 413 *in situ* anomalies in 135 cases. Spina bifida, anencephaly, congenital heart defect, aplasia or accessory lobe of lung, renal agenesisand dysplasis, congenital hydrocephaly, and severe phynotype anomalies were found to be more closely associated with severe malformations than with mitis malformations. The total proportion of *in situ* anomalies in spina bifida, anencephaly, congenital heart defect was up to 72.6% (300/413). Anencephaly in 1 case was associated with 12 other anomalies (including spina bifida, encephalocele, adhesions of cheek and shoulder, aplasia of lung lobe, dissymmetry of bilateral thoracic skeleton, Varus talipes, eventration of bilateral diaphragm, atrachelia, absence of right kidney, absence of right adrenal gland, right ureter, bilateral undescended testis.

TABLE 3

In situ Number of Other Associated Malformations by ICD-10 Codes

Malformation (ICD10 Code)	No. of Cases	Number of Other Associated Malformations					
		1	2	3	4	⩾5	Total *n* (%)
Spina Bifida	26	0	6	4	7	9	115 (27.85)
Anencephaly	28	5	9	1	1	12	108 (26.15)
Congenital Heart Defects	29	7	8	7	5	2	77 (18.64)
Aplasia or Accessory Lobe of Lung	13	4	7	2	0	0	24 (5.81)
Renal Dysplasis or Absence	13	5	1	1	0	2	24 (5.81)
Congenital Hydrocephaly	10	6	2	2	0	0	16 (3.87)
Cleft Lip with/without Cleft Palate	3	0	1	0	0	2	12 (2.91)
Encephalocele	4	1	1	1	1	0	10 (2.42)
Anomalies of Liver	3	2	0	0	1	0	6 (1.45)
Spleen Anomalies/splenunculus	5	5	0	0	0	0	5 (1.21)
Single Umbilical Artery	3	1	2	0	0	0	5 (1.21)
Atresia and Stenosis of Large	2	1	0	0	1	0	5 (1.21)
Diaphragmatocele	1	0	1	0	0	0	2 (0.48)
Umbilical Hernia	1	0	1	0	0	0	2 (0.48)
Funnel Chest	1	1	0	0	0	0	1 (0.24)
Varus Talipes	1	1	0	0	0	0	1 (0.24)
Total	135	35	78	51	68	181	413 (100.00)

TABLE 4

Composition of Number of Other Associated Anomalies in Autopsy Cases

Other Associated Birth Defects (*n*)	Percentage of Congenital Anomaly Cases	
	n	%
Isolated Anomaly	35	25.93
Two Anomalies	39	28.89
Three Anomalies	17	12.59
Four Anomalies	17	12.59
Five Anomalies	10	7.41
Six Anomalies	7	5.19
Seven Anomalies	3	2.22
Eight Anomalies	3	2.22
Nine Anomalies	1	0.74
Ten Anomalies	1	0.74
Twelve Anomalies	1	0.74
Thirteen anomalies	1	0.74
Total	135	100.00

The proportion of multiple anomaly cases (the number of in situ anomalies was $\geqslant$2) was higher (74.07%), while the proportion of isolated anomaly cases was 25.93%, and the percentage of cases was gradually reduced with the increasing number of *in situ* anomalies (Table 4), suggesting that congenital malformations affected multiple organs.

The distributions of lethal malformations (which may directly cause intrauterine death or neonatal death), non-lethal and affected function, non-lethal and unaffected function by ICD-10 codes are shown in Table 5. The total proportion of anencephaly, spina bifida, congenital hydrocephaly, congenital heart defect, encephalocele was up to 88.24% (75/85). Nearly all perinatal fetuses with lethal malformations died before delivery or immediately after birth. Most congenital heart defects were due to non-lethal and affected function (67.74%) followed by aplasia or accessory lobe of lung (9.68%). The percentage of aplasia or accessory lobe of the lung, spleen anomalies or splenunculus and anomalies of the liver was 36.84% (7/19), 26.32% (5/19), and 10.53% (2/19), respectively. The total proportion of these three anomalies was nearly 73.68% (14/19).

TABLE 5

Distributions of Lethal malformation, Non-lethal and Affected Function, Non-lethal and Non-affected Function by ICD-10 Codes Classification

ICD-10 Codes	Lethal Malformation		Non-lethal and Affected Function		Non-lethal and Unaffected Function		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Anencephaly	28	32.94	0	0.00	0	0.00	28	20.74
Spina Bifida	25	29.41	1	3.23	0	0.00	26	19.26
Congenital Hydrocephaly	10	11.76	0	0.00	0	0.00	10	7.41
Congenital Heart Defects	8	9.41	21	67.74	0	0.00	29	21.48
Encephalocele	4	4.71	0	0.00	0	0.00	4	2.96
Aplasia or Accessory Lobe of Lung	3	3.53	3	9.68	7	36.84	13	9.63
Renal Dysplasis or Absence	3	3.53	1	3.23	1	5.26	5	3.70
Cleft Lip with /without Cleft Palate	1	1.18	2	6.45	0	0.00	3	2.22
Atresia and Stenosis of Large Intestine, Rectum, and Colon	1	1.18	1	3.23	0	0.00	2	1.48
Diaphragmatocele	1	1.18	0	0.00	0	0.00	1	0.74
Anomalies of Liver	1	1.18	0	0.00	2	10.53	3	2.22
Spleen Anomalies/splenunculus	0	0.00	0	0.00	5	26.32	5	3.70
Single Umbilical Artery	0	0.00	2	6.45	1	5.26	3	2.22
Varus Talipes	0	0.00	0	0.00	1	5.26	1	0.74
Funnel Chest	0	0.00	0	0.00	1	5.26	1	0.74
Umbilical Hernia	0	0.00	0	0.00	1	5.26	1	0.74
Total	85	100.00	31	100.00	19	100.00	135	100.00

TABLE 6

Distributions of Dead Causes of Non-lethal Malformations

Causes of Death	Non-lethal and Affected Function		Non-lethal and Unaffected Function		Total	
	n	(%)	*n*	(%)	*n*	(%)
Diffuse Pneumonorrhagia	7	22.58	10	52.63	17	34.00
Meconium Aspiration Syndrome	9	29.03	4	21.05	13	26.00
Respiratory Distress Syndrome	7	22.58	1	5.26	8	16.00
Intracranial Hemorrhage	2	6.45	0	0.00	2	4.00
Other Non-birth Defects	3	9.68	2	10.53	5	10.00
Therapeutic Abortion of Birth Defects	1	3.23	0	0.00	1	2.00
Other Therapeutic Abortion	1	3.23	2	10.53	3	6.00
Missing	1	3.23	0	0.00	1	2.00
Total	31	100.00	19	100.00	50	100.00

The distributions of dead causes of non-lethal malformations are shown in Table 6. Diffuse pneumonorrhagia, meconium aspiration syndrome and respiratory distress syndrome were the leading causes of fetal and infant death. The total percentage of such causes of death was 76% for birth defects cases with no lethal malformations.

DISCUSSION

The data presented in this study were obtained from the first epidemiological pathoananotmic investigation of the prevalence rate of autopsy anomaly cases in high prevalence regions of birth defects in China to evaluate the quality of birth defects surveillance and diagnostic accuracy of birth defects based on the pathoanatomy of congenital malformation in Luliang Prefecture of Shanxi Province. In this study, the prevalence rate of deaths in cases of non-malformation and birth defects at their age <28 gestational weeks and that of internal anomalies at their age ⩾28 gestational weeks was 14.61‰ (61/4175) and 17.25‰ (72/4175), respectively. At present, only cases of external anomaly at their age ⩾28 gestational weeks have been registered in the Birth Defects Surveillance System of China. Therefore, nearly 32‰ (133/4175) of dead cases and birth defects are included in this system, indicating that the prevalence rate of birth defects is definitely underestimated.

Internal malformations are hardly detectable if pathoananotmic examination is not performed. This means that 32‰ cases of pregnancies with birth defects and major internal anomalies at the age <28 gestational weeks are not detectable, and the actual prevalence rate of birth defects and NTDs is much higher in Shanxi Province[2-4], suggesting that NTDs remains one of the most common birth defects in this province. Programs on surveillance and prenatal diagnosis of birth defects have greatly improved the rate of major external birth defects. Routine monitoring may detect approximately one third of structural birth defects with current technique. The monitoring has covered the cases at the age of 28 gestational weeks-7 days after birth, and about two thirds of birth defects could not detected, and internal anomalies can be terminated in cases at the age <28 gestational weeks[8]. Therefore, to improve the birth defects surveillance system it will be essential to upgrade the current diagnostic techniques for internal malformations.

The findings in this study have shown the role of pathoanatomic diagnosis in the high prevalence areas of birth defects in China. First, the percentage of detected birth defects accounted for 84.4% in all autopsy cases. Second, the prevalence rate of NTDs was 13.89‰ (58/4175) in cases of pregnancies, the proportion of detected NTDs was 50.4% (68/135). Third, 74.5% of cases had multiple malformations, whereas 25.9% of isolated cases had malformations. The *in situ* number of multiple malformations increased gradually with the severity of affected anomalies, suggesting that the occurrence of congenital malformation in different embryonic developmental stages affects a large number of organs and the severity of affected malformations is associated with other anomalies.

Although the timing of initiating prenatal care is associated with risks of congenital malformation, it has not been extensively studied[9]. The data used in this study were obtained from the Shanxi Medical University in 2006[7]. Various types of external anomalies were detected. The most important thing was to interpret the internal anomalies which could not be detected by routine monitoring. Another

manifestation of anomalies was that most severe and lethal birth defects were complicated by other impairments, such as diffuse pneumonorrhagia, meconium aspiration syndrome, respiratory distress syndrome, Intracranial hemorrhage, which may be the leading causes of death. The pattern of NTDs in Northern China shows increased NTDs that is rare in low-prevalence areas such as metropolitan Atlanta[10]. Increased awareness of varying patterns of NTDs in different populations may have important implications for identifying etiologic and pathogenic mechanisms of NTDs. Therefore, future birth defects surveillance should be carried out on the basis of accurate pathoanatomy that is much more reliable. The findings from autopsy and pathologic examination suggest that major congenital malformation may be associated with other anomalies. Occurrence of congenital malformation may affect more organs in early embryonic development when pregnant women are exposed to hazard environmental factors.

The methods for surveillance and prenatal diagnosis have impacts on the prevalence rate of birth defects. It is impossible to detect most internal anomalies before delivery because the limited technique of prenatal diagnosis cannot detect more than 60% of birth defects[8]. Therefore, internal anomalies were neglected in previous population-based birth defects surveillance. In this study, 38.1% of (61/160) birth defects were not detected in autopsy cases at the age <28 gestational weeks, while 61.9% (99/160) birth defects were not detected in autopsy cases at the age of 7 days, which is consistent with the reported findings in Shanxi Province[2], indicating 38.1% of internal or external anomalies or non-malformation deaths are underestimated in high risk areas of this province. The prevalence rate of NTDs had no obvious trend to decline in high risk areas[2] .

The efficient ways to register birth defects must be found. Some types of birth defects can be prenatally diagnosed, population-based surveillance systems have proven to be a valuable tool for both research and surveillance of birth defects. The birth defects surveillance system in China can monitor stillbirths or fetuses at the age of more than 28 gestational weeks and live births delivered in hospitals[5]. The average delivery rate in rural hospitals is 65.1%[11], which is thus inaccurate to predict the prevalence of birth defects. Villages are scattered in mountainous areas far from local hospitals and not all pregnant women deliver their babies in hospitals. In order to systemically monitor all birth defects cases, we should collect samples of fetal deaths delivered at home. This approach may enable us to accurately assess the prevalence of birth defects in these regions. However, more internal anomalies should be detected and the diagnostic accuracy of birth defects should be improved. Therefore, it is necessary to perform pathoanatomic examination of prenatal deaths. The data on birth defects in China were mainly obtained from population-based or hospital-based birth defects surveillance. The hospital delivery rate of pregnant women in some rural areas is relatively low. It is necessary to perform postmortem examination of dead fetuses and stillbirths to collect data from population-based or hospital-based birth defects.

Birth defects surveillance can collect more data about the impact of birth defects on early fetus and infant mortality. Data collected based on patoanatomic diagnosis of early birth defects can become a reference point for the evaluation of birth defects surveillance system and development of intervention targets. If mortality data are collected through the birth defects surveillance, the death risk of children with birth defects can be decreased. Postmortem examination of specific internal and multiple malformations can provide useful information for population-based birth defects surveillance[8]. The program of preventing and reducing birth defects in China requires accurate data concerning health problems affecting the quality of population of child bearing age. The key to the success of program is to collect information regarding the changing tendency in birth defects for policy decisions[12] .

Congenital heart defects (CHD), a most common type of birth defects, is the leading cause of infant death. In this study, the prevalence rate of CHD in pregnancies was 6.95‰. Various estimates of CHD in pregnancies are available[13-14]. However, the prevalence of moderate to severe lesions in live births is approximately 6‰[15-16]. These estimates can be used to evaluate prevalence trend and assess the impact of CHD on public health. Furthermore, CHD is associated with several risk factors and can be used as a basis to develop preventive interventions[11-20]. However, it will be difficult to compare prevalence estimates and evaluation of the consistent risk factors between various studies because of their methodological differences.

Combination of population-based birth defects surveillance with pathoanatomy of fetal deaths and stillbirths can improve prenatal diagnosis and estimate the prevalence of birth defects in a more accurate way.

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