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Epidemiological Characteristics, Outcome Distribution and Pregnancy Risk Factors of Low Birth Weight with Birth Defects

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Abstract: This paper summarized the occurrence of low birth weight with birth defects in Xi'an, China, so as to provide a new scientific basis for further improving the birth defects surveillance system and reducing the incidence of birth defects. Data were collected from all the perinatal infants from 28-week-old fetuses to 7-day-old infants born in all the hospitals with obstetrical department in Xi'an from 2003 to 2014. 1957 cases of low birth weight with birth defects were surveyed. The gestational age distribution was 28-45w. The weight distribution was 100g-2500g. Single type birth defect rate was 77.2%. The proportion of premature infants<37W was 72.4%. The outcomes of low birth weight birth defects were 702 live births (36.8%), 1045 fetal deaths (54.7%), 86 stillbirths (4.5%) and 77 deaths within 7 days (4.0%), respectively. The five common types of birth defects were 320 cases of congenital hydrocephalus (16.3%), 267 cases of spina bifida (13.6%), 197 cases of congenital heart disease (10.1%), 164 cases of anencephaly (8.4%), 159 cases of cleft lip with cleft palate (8.1%). The difference between the outcomes of low birth weight with birth defects and those normal birth weight with birth defects ($\chi2$=647.59,P<0.01). Exposure history in early pregnancy($\chi2$=3369.61, P<0.01), sickness during pregnancy($\chi2$=4040.38,P<0.01), medication during pregnancy($\chi2$=4331.43,P<0.01) and exposure to harmful substances during pregnancy ($\chi2$=5764.97, P<0.01) were statistically significant between low birth weight with birth defects and normal weight with birth defects. Children with low birth weight birth defects are more likely to have adverse birth outcomes than those normal birth weight with birth defects. There is a

statistical correlation between low birth weight infants with birth defects and maternal exposure to risk factors during pregnancy.

1. Introduction

Birth defects refer to the congenital embryo abnormality caused by genetic or environmental reasons or the interaction of the above two, ranking first cause of infant death. As an important factor influencing the comprehensive prevention and treatment of birth defects, the surveillance and analysis of birth defects is of great significance [1-3]. From 2003 to 2012, there was a significant positive correlation between birth defects and low birth weight, and the difference was statistically significant(χ^2=22660.94, P<0.01).The risk of birth defects at low birth weight was 20.23 times higher than that at non low birth weight (95% CI: 19.14-21.37) [4]. Most birth defects were significantly associated with low birth weight[5]. This study explored the relationship between birth defects and low birth weight, provided new scientific basis for further improving the birth defect surveillance system and reducing the incidence of birth defects.

2. Materials and Methods

From 2003 to 2014, regardless of household registration, all the infants during perinatal period (28 weeks of gestation to 7 days after birth) who were born in hospitals of Xi'an City, no matter stillbirth or live birth were included in this study. Infants born with innate defects and older than 28 weeks of gestation were required to fill a case card. Born within 7 days with unconfirmed defects would not be reported until a definite diagnosis is made.

Considering the quality of surveillance and the data scientificalness, unified training was carried out before and throughout the surveillance every year. According to the data of every single register card, the summary table has to be filled.

The diagnosis of birth defects was based on the Chinese national criteria of birth defects and tiny deformities given in "maternal and child health monitoring manual in China". The diagnosis involves professionals in Obstetrics Department, Pediatrics Department, Pathology Department, Clinical Laboratory, and Physics Diagnostic Division (such as B-ultrasound room).Experts from each monitoring hospital are in charge of confirmation of birth defects and providing technical support for diagnosis. The classification is based on the International Classification of Diseases-10. The diagnosis of some internal anomalies needs to be considered in combination with laboratory testing, clinical symptoms, evaluation of case history, and clinical manifestations.

The essential contents were recorded in detail, for example, the situation of baby birth, birth defects diagnoses, the basic information of mother (such as her residence, economy, and education),

the history of her illness and drug use during pregnancy, finding out whether she had childbearing before, hereditary family history, etc. If the type of birth defect falls into one of the 23 common categories, then one needs to tick the space corresponding to the name, otherwise write in detail in the remarks column. Risk factors during pregnancy: illness, medication, exposure to pesticides and other harmful factors.

All levels of participants of surveillance must set up opinion of quality first and carry out strict quality control on every segment of operation (filling, collection, entry, and analysis).To avoid cases of under-reporting and redundant reports, Double-checking is needed and surveillance hospitals should pay attention to misdiagnosis of congenital fetal abnormalities at birth, the child entering the room, physical examination, and bathing. Maternal and Child Health Care Center of the city examines the reports and cards from all surveillance hospitals. Questionable reports or cards should be returned for correction or supplementation. Periodical quality control inspection and examination of surveillance hospitals were administered twice a year at city level and quarterly at district level. The content of quality control includes under-reporting investigation, diagnosis checking, and quality checking of monitoring tables (cards).

3. Statistical analysis

Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) was used for data input. Statistical Package for the Social Sciences (International Business Machines Corporation, NewYork, NY, USA) version 16.0 was used for statistical analysis. If the $P < 0.05$, the difference would be considered as statistically significant.

4. Results

1957 low birth weight infants with birth defects were collected. The gestational age distribution was 28-45 weeks and the average gestational age was 33.8 weeks. The birth weight distribution was 100g-2500g and the average birth weight was 1909.5g.

Defect types of low birth weight with birth defects were mainly single defect (1510, 77.2%). 446 cases (22.8%) had multiple birth defects. See Tab.1 for details. The proportion of premature infants<37W was 72.4%. The outcomes of low birth weight birth defects were 702 live births (36.8%), 1045 fetal deaths (54.7%), 86 stillbirths (4.5%) and 77 deaths within 7 days (4.0%), respectively(Table 2). The five common types of birth defects were 320 cases of congenital hydrocephalus (16.3%), 267 cases of spina bifida (13.6%), 197 cases of congenital heart disease (10.1%), 164 cases of anencephaly (8.4%), 159 cases of cleft lip with cleft palate (8.1%).

Table 1 Epidemiological distribution and birth outcomes of low birth weight infants with birth defects

		Gestational age (w)	Weight(g)
Sample distribution	Sample size	1957	1954
	Mean value	33.8	1909.5
	Standard deviation	3.9	486.0
	Minimum value	28	100
	Maximum value	45	2500
	Median	34	2000
	P25	30	1600
	P75	37	2300
		Frequency(n)	Percentage(%)
Types	Single type	1510	77.2
	Multiple types	446	22.8
Gestational age	<37 week	1417	72.4
	≥37 week	540	27.6
Weight	<1000g	127	6.5
	1000-1500g	329	16.8
	≥1500g	1498	76.7
Birth outcome	Live birth	702	36.8
	Fetal death	1045	54.7
	Stillbirth	86	4.5
	Death within 7 days	77	4.0
	Missing value	47	2.4
Seqencing	Congenital hydrocephalus	320	16.3
	Neural tube defects	267	13.6

	Congenital heart disease	197	10.1
	Anencephaly	164	8.4
	Cleft lip with cleft palate	159	8.1
	Polydactyly	135	6.9
	Encephalocele	110	5.6
	Equinovarus	86	4.4
	Cleft lip	84	4.3
	Rectoanal atresia or stricture	65	3.3
	Hypospadias	55	2.8
	Upper limb reduction defects	55	2.8
	Esophageal atresia or stenosis	50	2.6
	Lower limb reduction defects	46	2.3
	Gastroschisis	45	2.3
	Other malformations of the external ear	33	1.7
	Syndactyly	30	1.5
	Cleft palate	27	1.4
	Microtia	25	1.3
	Umbilicus bulging out	25	1.3
	Congenital diaphragmatic hernia	8	0.4
	Down's syndrome	8	0.4

	Conjoined twins	1	0.1
	Bladder exstrophy	0	0.0
	Other malformations	370	18.9

Table 2 Comparison of birth outcomes between low weight birth defects and normal weight birth defects

	Normal weight birth defects		Low weight birth defects			
	Frequency(n)	Percentage(%)	Frequency(n)	Percentage(%)	χ^2	*P*
Live birth	4789	68.6	702	36.8	647.592	<0.001
Fetal death	1801	25.8	1045	54.7		
Stillbirth	203	2.9	86	4.5		
Death within 7 days	188	2.7	77	4.0		
Total	6981	100	1910	100		

From 2003 to 2014, 1030 (11.26%) pregnant women whose baby with birth defects suffered from diseases during pregnancy, 777 (8.49%) took medication during pregnancy, and 258 (2.82%) were exposed to harmful substances such as radiation and pesticides during pregnancy (Table 3).

Table 3 Exposure to risk factors during pregnancy of mothers giving birth to defective children in Xi'an from 2003 to 20154[n (%)]

Year	Diseases during pregnancy		Medication during pregnancy	Exposure to harmful materials during pregnancy
	Virus infection	Non-virus infection		
2003	27(6.96)	52(13.40)	53(13.66)	22(5.67)
2004	10(2.40)	36(8.63)	47(11.27)	22(5.28)
2005	34(8.15)	24(5.76)	53(12.71)	23(5.52)
2006	29(6.29)	48(10.41)	66(14.32)	15(3.25)
2007	19(3.19)	48(8.05)	50(8.39)	20(3.36)

2008	27(3.92)	65(9.45)	86(12.50)	22(3.20)
2009	12(1.46)	59(7.16)	57(6.92)	25(3.03)
2010	13(1.42)	78(8.5)	83(9.05)	27(2.94)
2011	8(0.88)	95(10.44)	64(7.03)	37(4.07)
2012	7(0.76)	78(8.45)	73(7.91)	10(1.08)
2013	9(0.78)	108(9.34)	68(5.88)	14(1.21)
2014	11(0.76)	133(9.17)	77(5.31)	21(1.45)
Total	206(2.25)	824(9.01)	777(8.49)	258(2.82)

Comparison of risk factors exposure during pregnancy between normal weight birth defects and low weight birth defects was statistically significant. Exposure history in early pregnancy (χ^2=3369.61, P<0.01), sickness during pregnancy(χ^2=4040.38, P<0.01), medication during pregnancy (χ^2=4331.43, P<0.01) and exposure to harmful substances during pregnancy(χ^2=5764.97, P<0.01) were all related to low birth weight with birth defects. (Table 4)

Table 4 Comparison of risk factors exposure during pregnancy between normal weight birth defects and low weight birth defects

	Normal weight with birth defects n(%)	Low weight with birth defects n(%)	χ^2	P
Diseases during pregnancy			4040.381	<0.001
yes	817(11.7)	1681(85.9)		
no	6164(88.30)	277(14.1)		
Virus infection			1.447	0.229
yes	195(2.79)	66(3.4)		
no	6786(97.21)	1893(96.6)		
Medication during pregnancy			4331.427	<0.001
Yes	677(9.70)	1663(84.9)		
no	6304(90.30)	295(15.1)		
Exposure to harmful			5764.971	<0.001

materials during pregnancy				
yes	237(3.39)	1656(84.6)		
no	6744(96.60)	302(15.4)		

5. Discussion

About 3% to 4% of infants are diagnosed with serious birth defects in their first year of life[6]. Because many babies with birth defects have intrauterine growth retardation, premature delivery or both, the incidence of birth defects will undoubtedly vary with the birth weight of the baby[7]. However, as far as we know, the extent of this change has not been fully studied in well-defined populations. Hospital surveillance is currently recognized as the most suitable mode of birth defect surveillance in developing countries. Due to the wide variety of birth defect diseases surveyed and the low incidence of many birth defect diseases, it is less feasible to carry out a birth defect survey with large sample size, long time span, and a large amount of manpower and financial resources. Xi'an birth defect hospital surveillance covers all delivery hospitals in Xi'an. In recent years, the hospital delivery rate in Xi'an is close to 100%. Hospital surveillance can reflect the incidence of birth defects in the population, and continuous surveillance can find the potential law of birth defect occurrence and development.

From 2010 to 2013, the average incidence of adverse pregnancy outcomes in Shaanxi Province was 25.45%, in which macrosomia (31.91%), low birth weight (23.42%), spontaneous abortion (18.94%), premature delivery (16.65%), intrauterine birth defects (7.38%), and embryo death (1.70%) were ranked according to the composition ratio [8]. The overall proportion of low birth weight, premature delivery and intrauterine birth defects reached 47.45%, so it is necessary and urgent to study the relationship between birth defects and premature delivery and gestational age to reduce adverse pregnancy outcomes.

5.1. Birth defects and birth weight

The occurrence of birth defects was significantly positively correlated with low birth weight, and the difference was statistically significant(χ^2=37097.79, P<0.01), the risk of birth defects at low birth weight is 20.22 times higher than that at non-low birth weight (95% CI: 19.37-21.10).

Sorting the common birth defects types of low birth weight infants, it was found that the top five were congenital hydrocephalus, spina bifida, congenital heart disease, anencephaly, cleft lip and cleft palate, and the above birth defect types were relatively more influential to birth weight.

The outcome of birth defects of normal weight infants is mainly live birth, accounting for 68.60%, while the outcome of birth defects of low weight infants is mainly stillbirth, accounting for 54.72%. The difference between the outcome of birth defects of low weight infants and that of

normal weight infants is statistically significant(χ^2=647.59, P<0.01)。

5.2. Limitations

Many infants with birth defects are accompanied by intrauterine growth retardation, premature delivery or both. A large sample study of 317499 live births from 1978 to 1988 in the United States found that low birth weight infants had a higher risk of birth defects. The birth defect rate of newborns weighing less than 1500g at birth is 16.2%, 13.2% for infants weighing from 1500g to 1999g, 6.2% for infants weighing from 2000g to 2499g, 3.2% for infants weighing from 2500g to 3999g, and 2.8% for infants weighing 4000g or more[9]. Birth defects are significantly related to premature delivery and low birth weight. It is possible that defects may lead to intrauterine growth retardation of the fetus and lead to premature delivery of some fetuses that can not develop to normal gestational age. To sum up, the current surveillance system has the following deficiencies: ①Due to the lack of classification of the birth weight of perinatal infants in the hospital surveillance of birth defects, it is not possible to compare the birth defect rates of different weight ranges at present. ②The birth defects surveillance only surveys perinatal infants ⩾28w. The actual birth defects rate should be higher than the surveyed birth defects rate. The surveillance time can be further moved forward.

5.3. Discussion on occurrence mechanism

Birth defects are overlapping adverse perinatal outcomes that may share common pathogenic mechanisms.①Severe birth defects are risk factors for intrauterine growth retardation or premature delivery. Some studies have shown that hemodynamic factors, such as low oxygen saturation or perfusion, may contribute to the cause of fetal intrauterine growth retardation and may be related to some heart diseases. The risk increased substantially as the number of defects increased[10,11].② Some evidence shows that the growth of embryology fetus is related to the exposure of genes, environment and nutrients, fetal and placental hormones, growth factors, alcohol and other factors[12-14].

72.4% of low birth weight infants are premature infants, and 27.6% infants are lighter weight for gestational age of ≥37 weeks. Premature birth and low birth weight were concomitant in 72.4% of children. There were statistically significant differences between mothers of normal weight birth defects and low weight birth defects in terms of pregnancy sickness, medication and exposure to harmful substances. Although the high rate of premature delivery can be partly explained by the blood supply and absorption disorders of some abnormal fetuses, the susceptibility of premature delivery may be related to genetic and environmental risk factors.The study found that environmental endocrine disruptors (EEDs) can cause adverse outcomes such as low birth weight, premature delivery, reproductive damage, hypospadias and so on in the offspring by changing the

hormone level of mothers, and also have potential developmental neurotoxicity[15]. EEDs refer to chemical components or substances that exist naturally in nature or synthesized artificially.EEDs can act directly or indirectly on the fetus, change the maternal hormone balance, and affect the normal biological functions of the mother and offspring[16].EEDs including organochlorine pesticides, bisphenol A, polychlorinated biphenyls and phthalates[17]. Some studies have confirmed that maternal hypertension or alcohol consumption increase the risk of premature birth and low birth weight in offspring[18]. A paired study of infants and their mothers born in Shaanxi Province from 2010 to 2013 found that infection during pregnancy can increase the risk of birth defects and low birth weight in offspring, especially young, low-educated and poor pregnant women[19]. Malnutrition during pregnancy can lead to low birth weight and premature delivery, which can directly affect the development of fetal brain cells and cause neurological and intellectual development disorders[20-24]. Therefore, it is necessary to conduct epidemiological retrospective analysis and familial susceptibility gene analysis for premature birth defects to find out their possible environmental risk factors and genetic susceptibility factors. The suevellance of fetal birth defects at risk should be further refined, and the identification of birth defects related to premature delivery should help improve the measures to prevent premature delivery, especially for the fetus at risk.

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