Variation Trend of Adverse Pregnancy Outcomes in a High Prevalence Region of Birth Defects in Northern China from 2007 to 2012

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Abstract

Background Shanxi Province in northern China has been identified as an area with the highest prevalence of neural tube defects in the world; however, the constituent and prevalence of adverse pregnancy outcomes (APOs) has changed in recent years. The aim of our study was to investigate the constituent and variation trend of the birth prevalence of APOs in rural northern China.

Methods A population-based descriptive study was conducted. Data were derived from two birth surveillance systems that recorded all pregnancy outcomes from 2007 to 2012 in Pingding and Xiyang County in Shanxi Province, China.

Results From 2007 to 2012, the birth prevalence of APOs in the two counties was 154.7 per 1,000 births. The birth prevalence of neonatal death, stillbirths, birth defects, premature birth, low birth weight (LBW), and macrosomia was 3.4 per 1,000 births, 12.3 per 1,000 births, 12.2 per 1,000 births, 21.9 per 1,000 births, 40.5 per 1,000 births, and 64.5 per 1,000 births, respectively. Birth prevalence of macrosomia increased from 59.6 per 1,000 births in 2007 to 74.4 per 1,000 births in 2012(${\chi }_{trend}^{2}=20.314, P < 0.001$). Birth prevalence of LBW and premature birth declined, from 43.8 per 1,000 births and 19.1 per 1,000 births in 2007 to 30.1 per 1,000 births and 11.8 per 1,000 births in 2012 (${\chi }_{trend}^{2}=21.748$, $P < 0.001$; ${\chi }_{trend}^{2}=14.342$, $P < 0.001$). The birth prevalence of neonatal death, stillbirth and birth defects stayed at a relatively low level. The distribution of APOs birth prevalence took an obvious “U-shape” as maternal age rose from <20 year to over 40 year except for macrosomia.

Conclusions More efforts should be made on finding causes and ways of interventions on APOs, especially prematurity, LBW and macrosomia which are currently under insufficient attention.

Background

Worldwide, adverse pregnancy outcomes (APOs), including early pregnancy loss, stillbirths, birth defects, neonatal deaths, prematurity, low birth weight (LBW), intrauterine growth retardation, small for gestational age, Large for gestational age and macrosomia, are important public health issues. Currently in China, regional incidence rate of APOs ranged from 5–20%[1–3], bringing large burden both to their families and to the society since even a small percentage means a lot for this world largest populated country. A body of researches have revealed that APOs might have short-term and long-term influence on both mothers and children[4–6], the most serious one of which is maternal or neonatal deaths. Birth defects, for example, have the highest mortality and disability rate among all the APOs, ranking top in causes of infant deaths and child disabilities and accounting for 11% of child deaths in China[7, 8].

Though risk factors behind APOs are extremely complicated, most would agree that they are the comprehensive consequences of genetic, maternal behavioral and environmental factors. Maternal weight and age, chronic diseases, birth-related complications such as neonatal sepsis and pneumonia, pregnancy exposures to smoking and unfavorable socio-economic conditions are all commonly seen influence factors[9, 10]. Patterns of some of APOs are found to vary in different ethnic groups and researchers often focus on a specific type of APOs[11], yet there are few researches depicting the epidemiology of APOs as a whole in China.

Shanxi Province in northern China has been identified as a region with the highest prevalence of birth defects nationwide and also the highest prevalence of neural tube defects in the world[12–14]. Since over 30 years ago, large amount of financial support has been devoted to the prevention and intervention strategy for birth defects. However, with the improvement of social economy and nutrition, the constituent of APOs has changed in recent years. The prevalence of major birth defects is decreasing, while the prevalence of other adverse pregnancy outcomes, especially spontaneous abortion, premature, LBW and macrosomia, is rising. The aim of our study was to investigate the constituent and variation trend of birth prevalence of APOs and to provide evidence for new strategies for APOs prevention and intervention in rural areas in northern China.

Methods

Study design and location

This is a population-based descriptive study of APOs in Pingding and Xiyang County in Shanxi province, northern China. Shanxi was a world-renowned place for its high birth defects incidence rate and has long established comprehensive and complete birth surveillance systems since 1993[15], making it an ideal site for analyzing APOs. According to local government annual reports, in 2012, Pingding County had 336,788 permanent residents with 163,134 women; Xiyang County had 228,831 permanent residents with 107,707 women. Basic health services are provided through 3-tier (county, township, and village) health-care networks. Health facilities and service capacity are similar in the two counties. The surveillance included subjects as all live births, all stillbirths of at least 20 weeks' gestational age, and pregnancy terminations following the prenatal diagnosis of a major structural external anomaly and recorded information of maternal deliveries and neonates or fetuses at any gestational age.

Data collection

Data were derived from two birth surveillance systems in northern China: Perinatal Health Care Surveillance System and the Birth Defects Surveillance System. Established in 1993, the two systems monitor women and their fetuses/infants from the onset of pregnancy to day 42 after deliveries in Pingding and Xiyang County[16]. Women included must have lived in the counties for more than one year. Information on all pregnancy outcomes (live births, stillbirths, fetal deaths, neonatal deaths, pregnancy terminations due to the diagnosis of birth defects, birth weight, gestational age, and maternal delivery records) was collected at birth or in hospital charges (if it's a hospital delivery) or during the first week after deliveries (if it's a home delivery) or at the time of termination of the pregnancy by trained obstetricians or nurses. For the structural external anomaly in particular, trained obstetricians or nurses took photos of the baby at pregnancy termination and conducted detailed reviews of the birth records and timely data verification independently, and several times of follow-up were performed until 42-days. Multiple data checking procedures were implemented to minimize data entry errors, missing information and improbable data. The population-based birth defects surveillance system has been described in detail elsewhere[16]. Therefore, the two surveillance systems can detect dynamic changes in the birth prevalence of adverse pregnancy outcomes completely and accurately.

The study protocol was reviewed and approved by the Institutional Review Board of Peking University Health Science Center, and written informed consents were obtained from all subjects before completing the questionnaires.

The definition of adverse pregnancy outcomes

Adverse pregnancy outcomes were measured using the following 6 outcomes: neonatal deaths, stillbirths, birth defects, low birth weight, microsomia and preterm births and each was defined as most commonly used international standards. Neonatal deaths were deaths among live births during the first 28 completed days of life and stillbirths were fetal loss in pregnancies beyond 20 weeks of gestation[17, 18]. Birth defects data were collected and reported by professionally and regularly trained healthcare workers and reviewed by three pediatricians who coded the defect independently[16]. Prematurity was defined as a gestational age of 20–36 weeks, and was associated with medical or obstetrical complications constituting indications for preterm delivery. Those indications include pregnancy-induced hypertension, chronic hypertension, diabetes, placenta previa, and placental abruption similar to the indications defined by Li et al[19]. Gestational age at birth was measured as the number of days of completed gestation based on the date of delivery and the first day of the last menstrual period. Low Birth Weight referred to infants born weighing at birth less than 2500 gram, regardless of gestational age and the cause.[18] Macrosomia was defined as > 4000 gram birth weight.[9]

Statistical analysis

The "birth prevalence" is regarded as an indicator of incidence, as it is not practicably possible to determine exact incidence because the population at risk at any given time changes during gestation[13, 20]. The total prevalence rate of APOs was calculated by using stillbirths, neonatal deaths, LBW, prematurity, macrosomia and birth defects as the numerators and all births as the denominators and was described as the number of APOs cases per 1,000 births. We used the $\chi 2$ test to compare prevalence rates. Significance was expressed as $P < 0.05$. R version 3.6.1 was used for the analysis.

Results

Birth prevalence of APOs in Pingding and Xiyang County from 2007 to 2012.

From 2007 to 2012, there were 31,394 births in total, including 18,749 births in Pingding and 12,645 births in Xiyang County. Among them were 4,858 APOs cases. The total birth prevalence of APOs was 154.7 per 1,000 births. The birth prevalence of neonatal deaths, stillbirths, birth defects, prematurity, LBW, and macrosomia was 3.4, 12.3, 12.2, 21.9, 40.5 and 64.5 per 1,000 births, respectively (Table 1). Birth prevalence of stillbirths, neonatal deaths and birth defects was relatively higher in Xiyang County (21, 6.4 and14.6 per 1,000 births) than that in Pingding (6.3, 1.4 and 10.6 per 1,000 births), while premature births and LBW was higher in Pingding (42.4 and 24.6 per 1,000 births) than that in Xiyang (37.7 and 17.9 per 1,000 births) (Table 1).

Table 1
Birth Prevalence of Adverse Pregnancy Outcomes in Pingding and Xiyang from 2007 to 2012

	Pregnancy	Stillbirth		Neonatal Death(≤7d)		Birth Defects		Low Birth Weight		Premature Birth		Macrosomia at birth	
	n	n	‰	n	‰	n	‰	n	‰	n	‰	n	‰
County													
Pingding	18749	118	6.3	26	1.4	198	10.6	795	42.4	462	24.6	1177	62.8
Xiyang	12645	267	21.1	81	6.4	184	14.6	477	37.7	226	17.9	847	67.0
Year													
2007*	4497	44	9.8	10	2.2	59	13.1	197	43.8	86	19.1	268	59.6
2008	6459	88	13.6	24	3.7	66	10.2	317	49.1	158	24.5	410	63.5
2009	5658	64	11.3	26	4.6	87	15.4	232	41.0	175	30.9	377	66.6
2010	5371	75	14.0	25	4.7	69	12.8	207	38.5	133	24.8	348	64.8
2011	4895	56	11.4	18	3.7	59	12.1	183	37.4	83	17.0	286	58.4
2012*	4490	56	12.5	4	0.9	42	9.4	135	30.1	53	11.8	334	74.4
Gender													
Male	16301	203	12.5	61	3.7	210	12.9	562	34.5	365	22.4	1335	81.9
Female	15048	180	12.0	44	2.9	170	11.3	683	45.4	316	21.0	689	45.8
Maternal age													
< 20	311	20	64.3	3	9.6	4	12.9	18	57.9	12	38.6	5	16.1
20-	19363	179	9.2	51	2.6	211	10.9	697	36.0	367	19.0	1082	55.9
30-	10296	135	13.1	39	3.8	125	12.1	475	46.1	264	25.6	818	79.4
40-	981	22	22.4	9	9.2	17	17.3	62	63.2	35	35.7	85	86.6
Total	**31394**	**385**	**12.3**	**107**	**3.4**	**382**	**12.2**	**1272**	**40.5**	**688**	**21.9**	**2024**	**64.5**

*2007, Xiyang's data are from Oct. to Dec.

2012, Xiyang's data are from Jan. to Sep.

Variation trend of Birth prevalence of APOs by year

Figure 1 shows the variation trend of birth prevalence of different APOs from 2007 to 2012. Birth prevalence of macrosomia increased from 59.6 per 1,000 births in 2007 to 74.4 per 1,000 births in 2012 and there was a significant statistical difference by the trend test (χ^2_{trend}=20.314,P < 0.001). Birth prevalence of LBW and premature births declined, from 43.8 and 19.1 per 1,000 births in 2007 to 30.1 and 11.8 per 1,000 births in 2012, respectively, also with significant differences (χ^2_{trend}=21.748, P < 0.001; χ^2_{trend} =14.342, P < 0.001). The birth prevalence of neonatal deaths, stillbirths and birth defects stayed at a relatively low level of 3.3, 12.1 and 12.2 per 1,000 births, respectively, with no significant differences (neonatal deaths χ^2_{trend}=0.888, P > 0.05; stillbirth χ^2_{trend}=0.323, P > 0.05; birth defects χ^2_{trend}=0.977, P > 0.05).

Constituent ratio of six APOs

Figure 2 presents the constituent ratio of six APOs in two counties. 2,024 macrosomia (accounting for 41.7% of all APOs cases), 1,272 LBW (26.2%), 688 premature births (14.2%), 385 stillbirths (7.9%), 382 birth defects (7.8%), and 107 neonatal deaths (2.2%) were identified. Weight-related issues (either too high or too low) were most severe in newborn babies, accounting for 77.2% of six adverse outcomes, with macrosomia taking up 41.7%. Prematurity was another nonnegligible problem, making up 14.2% of six APOs, nearly twice of that of birth defects.

Discrepancies of APOs among different maternal ages

Figure 3 shows birth prevalence of APOs by maternal age. The distribution of birth prevalence of five APOs (LBW, prematurity, stillbirths, birth defects and neonatal deaths) took an obvious “U-shape” as maternal age rose from < 20 years to over 40 years. The bottoms of the “U-shapes” all lied in age group 20–29 years, indicating it a comparatively “safe” time for pregnancy.

Maternal age < 20 years and ≥ 40 years presented much higher birth prevalence of LBW, with 57.9 and 63.2 per 1,000 births, respectively. Similarly, maternal age < 20 years and ≥ 40 years showed higher birth prevalence of prematurity, with 38.6 and 35.7 per 1,000 births, respectively. Maternal age group < 20 years had the highest birth prevalence of stillbirths (64.3 per 1,000 births), declined to the lowest (9.2 per 1,000 births) in maternal age 20–29 years, and then gradually rose to 13.1 per 1,000 births in maternal age 30–40 years and 22.4 per 1,000 births in maternal age ≥ 40 years. Due to the large scale of y-axis, the shape of birth defects was not so overt, yet its birth prevalence did go significant downward and then upward as age increased (12.9, 10.9, 12.1 and 17.3 per 1,000 births, respectively; going through a 15.5% decrease, a 11.0% increase and a sharp 30.6% increase). In contrast, birth prevalence of macrosomia elevated monotonically as maternal age rose from 16.1 to 86.6 per 1,000 births.

Discrepancies of birth prevalence for six APOs between offspring genders

Birth prevalence of six APOs by offspring genders is presented in Fig. 4. There were significant differences between genders in terms of birth prevalence of macrosomia (χ^2=168.34,P<0.001) and LBW (χ^2=24.429,P<0.001), as birth prevalence of LBW was higher in female offspring and macrosomia higher in male. There were no significant differences between genders in birth prevalence of stillbirths, neonatal deaths, birth defects, and premature births (P > 0.05).

Discussion

This study was a population-based surveillance for APOs in Shanxi Province in northern China. To the best of our knowledge, this study is the first report on the APOs prevalence and epidemiology in Shanxi Province of northern China. Firstly, we found that birth prevalence of premature births, LBW and macrosomia was extremely high among all APOs, with macrosomia showing an obvious upward trend from 2007 to 2012. While birth prevalence of birth defects, neonatal deaths and stillbirths stayed around at a relatively low level. For years, the whole nation has provided large sum of financial support in researches on birth defects, stillbirths and neonatal deaths and established a complete and effective 3-Level Prevention System (namely, the primary, secondary and tertiary health network). Achievements were world-recognized, as China has seen dramatic reductions in infant and child mortalities particularly in the past 15 years and in incidence rate of major birth defects from 2.74‰ (1987) to 0.15‰ (2017), a 94.5% decline[21, 22].

China has made remarkable achievements in prevention and intervention of birth defects for the past 30 years. With the social, economic and nutritional improvement, the constituent of APOs has changed in recent years. The infant mortality caused by birth defects, stillbirths and neonatal deaths declined, while the prevalence of children’s chronic diseases relevant to prematurity, LBW and macrosomia surged. Currently, population policy in China still gives large financial support for birth defects research. By contrast, the other three APOs have been relatively neglected (like macrosomia) or received insufficient attention (like prematurity and LBW). Investment in prevention and community coverage is far from enough. There exists a clear knowledge gap for prematurity in China, and research into its burden, determinants, and effects is urgently needed[23]; in some places, macrosomia is not even taken as a problem by their families. Yet their unfavorable consequences might be huge and nonnegligible and continuing for lifelong. Lots of studies have shown that preterm births are under greater risks of neurodevelopmental impairments (such as mental retardation and cerebral palsy), behavioral sequelae (such as dysfunction in cognitive areas) and other problems like hospital readmissions[24]; LBW newborns are at an increased risk of the development of coronary heart disease[25], depression and anxiety[26], poor long-term consequences on lung functions[6], diabetes, blood pressure and neurological functions in later life[27]; macrosomia infants are at elevated short-term risks like shoulder dystocia and long-term risks of metabolic syndrome, asthma and even cancer[28]. What's more, prematurity-associated complications and macrosomia are proven to be closely related to neonatal deaths and both fetal growth restriction and preterm births are strongly associated with placental dysfunction and subsequent poor fetal health, carrying increased risks of stillbirths[9, 17, 23]. In another word, China can't effectively reduce the infant mortality and incidence of chronic diseases without prevention of prematurity, LBW and macrosomia. Enough attention, investment and measures must be taken to address the three previously-neglected APOs.

The second important finding of the study was that there appeared a "U-shape" distribution of birth prevalence of five APOs (namely, prematurity, neonatal deaths, birth defects, stillbirths, LBW), as maternal age increased. For macrosomia, its prevalence rose monotonously with rising maternal ages, a phenomenon consistent in previous researches[29]. For other APOs, previous researchers have mostly agree that there exists a "nadir" maternal age where the risks of APOs are the lowest, as our study found out, but the exact age of the "nadir" hasn't come to consistent conclusion and it seems to vary in different populations, with some finding extremes of maternal childbearing age as risk factors for APOs and taking 20–29, 25–29 or 20–35 age-group as the "nadir" and some others observing a proportionally increased risks of APOs with maternal age in African-Americans and calling it "weathering effect"[11, 27, 30]. The latter views argue that the "weathering effect" is a manifestation of worsening health status and cumulative exposure to hardship as maternal age increases[31]. In fact, it's seen that adolescent mothers are mostly single, with low incomes, inadequate prenatal care and lower antenatal maternal weight,[32] all of which are commonly seen risk factors of APOs.

Similarly, for the older age group, it's important to ask whether the higher risks are the results of age itself, of age accumulation of biological disadvantages such as hypertension and diabetes[27] that lead to pregnancy complications, of accumulation of unfavorable social-economic behaviors and environmental exposures like smoking and air pollution[33, 34], or of a composite or interactions of the above[33, 35]. The answer of this question is crucial for formulating public health policies and allocating public health resources in different maternal age groups. Some investigations state that the weathering effect is modified by the mother's socio-economic situation and tends to be most pronounced in women of lower socio-economic status[33]. If it's true, then it seems that the "weathering effect" for most APOs did be "modified" in Pinding and Xiyang County, indicating the relatively fine local maternal socio-economic situation. However, as discussed before, the underlying relationship between maternal age and APOs is complex and incompletely understood, especially in China where few literatures looked specifically into it. Our study can only serve as a clue and it calls for more well-designed studies to explore the cause-effect relations.

Thirdly, gender differences existed in birth weights, with macrosomia happening more for male fetuses and LBW more for females, a conclusion in accordance with other researches[27, 29]. This difference is thought to be generated by different androgen actions and the fact that at a given birth weight boys have younger gestational age indicates that males grow more and faster[36, 37]. It's suggested that male fetuses are more vulnerable than their female counterparts and that male fetuses are at greater risks of death or damage from almost all the obstetric catastrophes that can happen before birth[38]. It is observed by some studies that neonatal deaths, congenital anomaly and stillbirths are commoner in boys[39]. In our cohort study, however, such gender differences were not detected.

There are some strengths in our study. It was a population-based surveillance study for APOs in Shanxi Province in northern China. It's one of few researches to describe the overall situation of APOs in rural Shanxi Province, China, providing clues for epidemiological distribution of APOs in rural China and future analysis of causal effect of demographic factors. Our surveillance system was based on an improved 3-tier health care system, and the case ascertainment was relatively complete. The population design and higher population covering (over 95%) minimized the selection bias. In addition, all APOs were detected, coded and reviewed carefully by well-trained investigators and professional physicians in every effort to reduce possible detection bias. However, potential limitation should also be acknowledged. The surveillance system was confined to resident women, and therefore might omit some with short-term stay. Yet considering population migration was not significant in these two counties and the population design insured over 95% population covering[40], the omission wouldn't affect the estimation of birth prevalence for the six APOs.

Conclusion

Our findings provide new evidence for prevention and intervention strategies of APOs in northern China. Future research should focus on comprehensive intervention of multiple APOs, especially prematurity, LBW and macrosomia, with emphasis on periconceptional harmful exposures.

Abbreviations

APOs
adverse pregnancy outcomes
LBW
low birth weight

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of Peking University Health Science Center (approval number: IRB00001052-08083), and written informed consents were obtained from all subjects before completing the questionnaires.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Ms. Shiqi Lin and Ms. Yuan Zhang designed the study, conducted the analysis and writing of the article and reviewed and revised it.

Dr Lijun Pei conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content.

Dr Jilei Wu designed the data collection instruments, acquired data, and reviewed the manuscript for important intellectual content.

Mr. Jiajia Li collected data, carried out the initial analyses, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

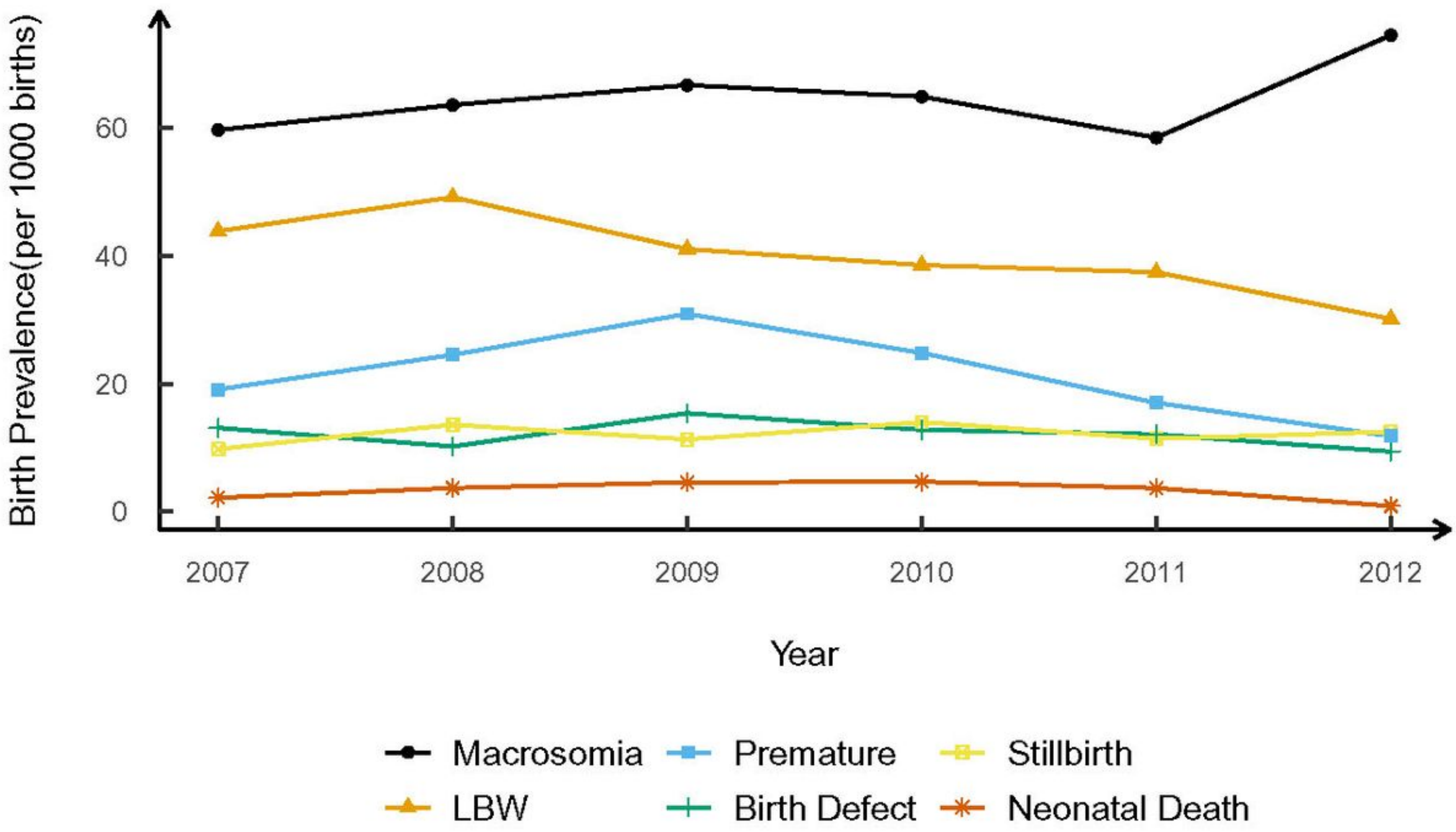

Figure 1

Birth prevalence of adverse pregnancy outcomes in two counties from 2007-2012 *Cochran-Armitage Trend Test of Stillbirth: χ^2trend =0.323P=0.570Neonatal Death: χ^2trend =0.888P=0.346Birth Defects: χ^2trend =0.977P=0.323 LBW(Low Birth Weight): χ^2trend =21.748P0.001Premature Birth: χ^2trend =14.342P0.001Macrosomia: χ^2trend =20.314P0.001.

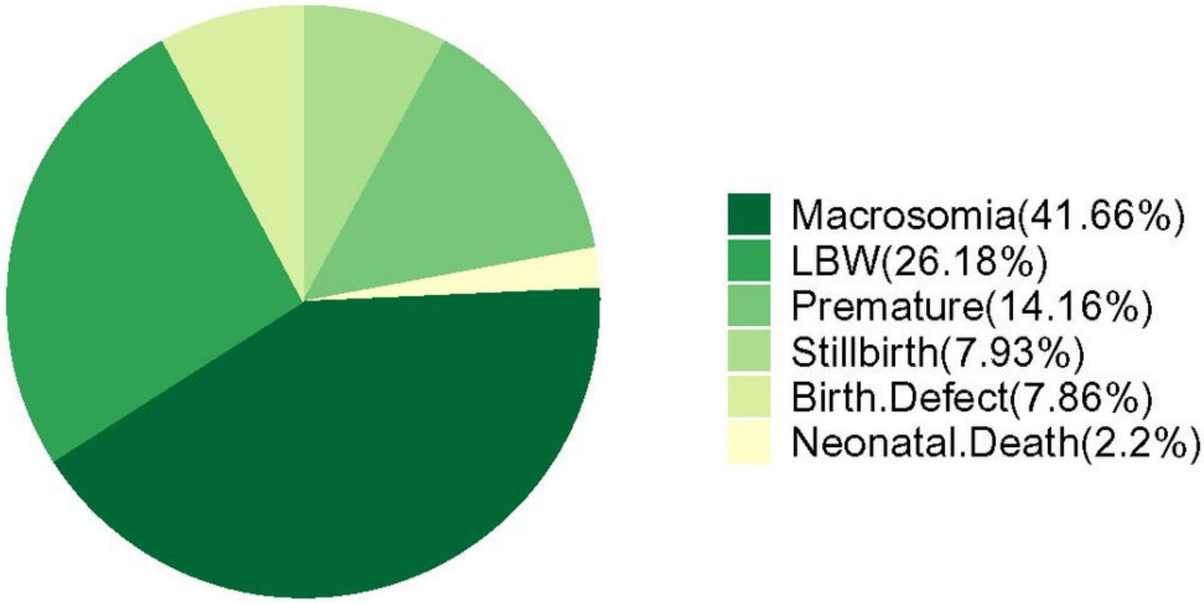

Figure 2

Constituent ratio of six adverse pregnancy outcomes between 2007 and 2012 in two counties

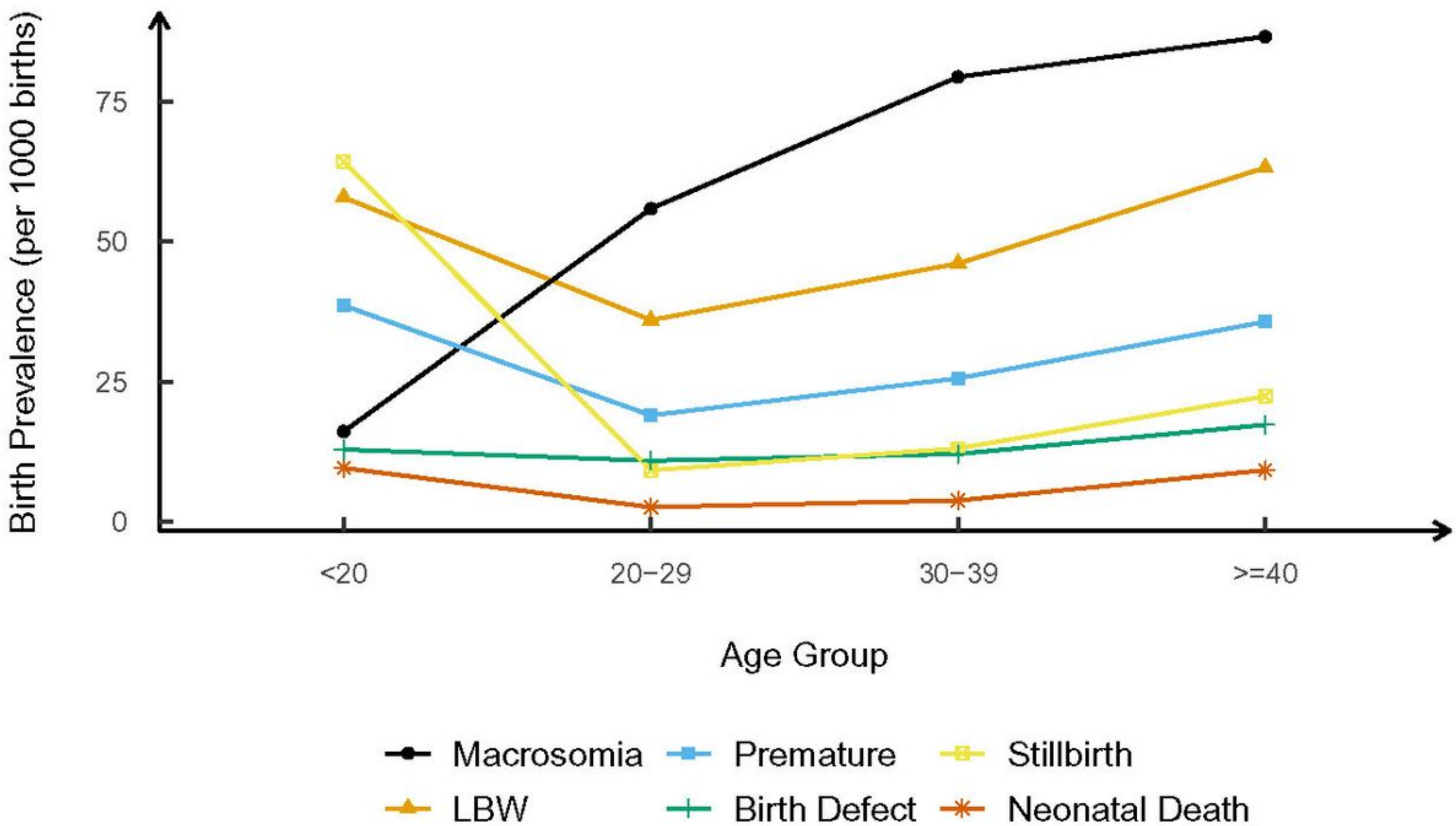

Figure 3

Birth prevalence of adverse pregnancy outcomes by maternal age

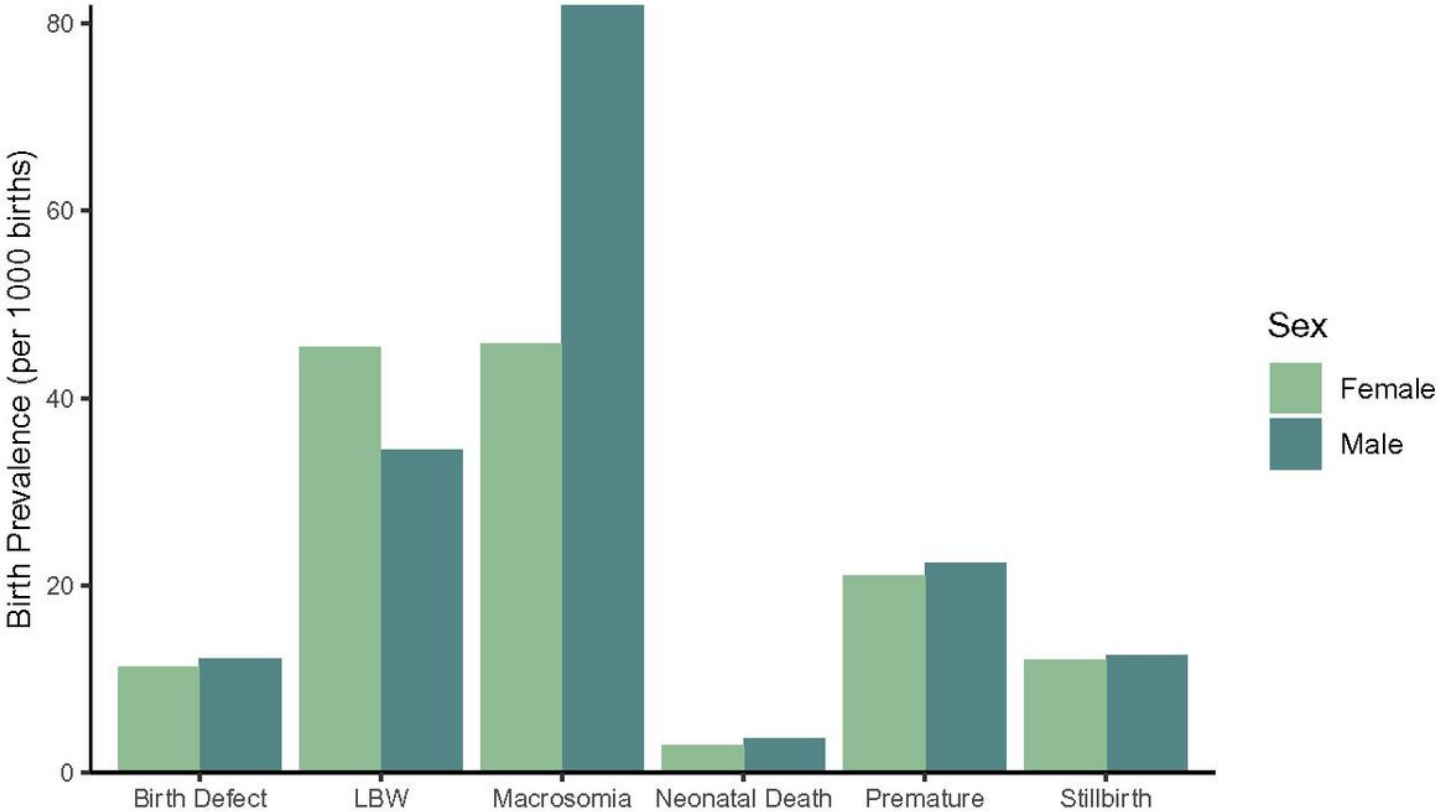

Figure 4

Birth prevalence of six adverse pregnancy outcomes by offspring genders