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Medication use during pregnancy and birth defects in Hunan province, China, during 2016–2019

A cross-sectional study

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Abstract

Safety of drug use during pregnancy attracts attentions from clinicians, pregnant woman, and even the total society. However, the studies about medication use during pregnancy and the followed birth defects (BDs) are rare in Chinese. To study condition about medication use during pregnancy and the followed BDs in Hunan province of China, here a cross-sectional study was carried out. All women using medication during pregnancy and delivering fetuses with BDs in Hunan province, China, during 2016 to 2019 were employed in this study. The descriptive analysis was carried out with Excel 2010, and the data analyses were performed by using Chi-Squared test in SPSS 16.0. After filtering, a total of 752 cases were included. In these fetuses, the males are more than females ($P < .05$). The severe BDs, leading to death or uncorrectable lifelong deformity, were observed for 346 times, and the other (minor) BDs were observed for 593 times. The most used drugs, categorized into pregnancy C, D, or X degrees by food and drug administration (FDA) or pharmaceutical manufacturers, mainly included anti-hyperthyroidism drugs, anti-epilepsy drugs, preventing miscarriage drugs, etc. This population-based data highlight the potential high risks for BDs from the aspect of drug use during pregnancy in Hunan province of China, and drugs with more safety, less kinds, and lower doses should be the better choice for pregnant women.

Abbreviation: BDs = birth defects, FDA = food and drug administration.

Keywords: birth defect, China, drug, FDA pregnancy risk category, pregnancy

1. Introduction

Birth defects (BDs), with structural or functional changes in one or more parts of the body, bring serious harms and heavy burdens for society, family, and individual. Hence, medication use during pregnancy attracts much attention from clinicians and women in childbearing age. There are many kinds of BDs. Some may be corrected by surgeries, and some may result in death or seriously mutilation for a whole life. A report from American March of Dimes showed that the prevalence rate of BDs is around 50 per 1000 live births in the world.[1] On the other hand, the prevalence rate in China is about 56 per 1000 live births.[2] Previously, we have reported that a total of 17753 in 925413 surveilled perinatal infants suffer BDs between 2005 and 2014 in Hunan province, China.[3] Our further study showed that the heredity and advanced maternal age (>35 years) are the major factors bringing BDs, and the other factors, including drinking, radiation, smoking, etc, also lead to BDs.[2] Except those factors, medication use during pregnancy is an important and complicated factor involved in BD occurrence.[4]

To help clinicians and pregnant women improve the safety of the medical prescription in clinic, some official classification systems were established to describe the risks of medications based on clinical and/or nonclinical evidences, such as the United States Food and Drug Administration (FDA) pregnancy risk category (categories A, B, C, D, and X), the Swedish classification system (Farmaceutiska Spesialiteter i Sverige, categories A, B, C, D), and the Australian classification system (categories A, B1, B2, B3, C, D, and X).[5–7] Although

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Our research complied with the guidelines for human studies and was conducted ethically in accordance with the principles enshrined in the World Medical

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FDA adopted Pregnancy and Lactation Labeling Rule from 2015, the FDA pregnancy risk category is still widely used in both developed and developing countries to guide medication prescription for pregnant women.[8,9] Compared with the pregnancy and lactation labeling rule, the FDA pregnancy risk category is more convenient to provide a rough risk description of medication use during pregnancy based on retrospective analyses.[4] There are 5 different groups in the FDA pregnancy risk category. Category A indicates the safest medications with a proof of no risk to the fetus in pregnant women; category B indicates the relatively safe medications whose reproductive toxicity was not confirmed in controlled studies in pregnant women; category C indicates the medications that showed given only if the potential benefit justifies the potential risk to the fetus; category D indicates the medications that have positive evidence of human fetal risk, and the benefits from the use in pregnant women may be acceptable despite the risk; category X indicates the medications that are contraindicated in women who are or may become pregnant.[7]

Hunan province is a high incidence area of BDs in China.[3] It is acknowledged that medication use during pregnancy is an important factor leading to BDs, but the data about medication use during pregnancy and the followed BDs in Hunan province has not been studied. Here, a cross-sectional analysis tempting to explore the current situation is carried out, based on the BD data from Birth Defect Surveillance System of Hunan province during 2016 to 2019 years, to provide meaningful information for policy makers and drug users.

2. Methods

2.1. Surveillance data

According to the requirements of the Maternal and Child Health Monitoring Manual in China formulated by the National Health Commission of the People's Republic of China, the infants with BDs should be confirmed by clinicians, and their information should be collected into the Birth Defects Registration Card. The information in this card includes: pregnant women basic information (living city or countryside, family annual per capita income, educational level, and age), reproductive history (delivery time, whether have BDs and defect types), neonatal information (number, birth weight, gestational age, gender, BD diagnosis, and types of BDs), the pregnancy status (time of malformation diagnosis, treatment after diagnosis of BDs, whether have an induced labor, whether have a fever, whether drinking during pregnancy, whether contact ray, whether exposure to chemicals and other harmful factors, and medication use during pregnancy), and the disease status of the pregnant women. The Birth Defects Registration Cards from all medical institutions in Hunan province were submitted to the Hunan Provincial Maternal and Child Health Care Hospital through the Birth Defect Surveillance System every quarter.

2.2. Patient population

All women using medication during pregnancy and delivering fetuses with BDs in Hunan province of China during 2016 to 2019 years were employed in this study. Meanwhile, the BD cases, in which mothers stated an advanced paternal age (>35 years old), family history, drinking, contacting pesticide and other toxic chemicals, suffering radiation, inhaling harmful gas, or taking 2 or more kinds of medications during pregnancy, were excluded from this study. With anonymizing the subjects before analysis, this study was approved by the Medical Ethics Committee of the Hunan provincial Maternal and Child Health Care Hospital (2020-S013).

2.3. Diagnostic and analytical criteria

Diagnosis of BDs was based on ICD-10, including congenital malformations of the nervous system (Q00-07), congenital malformations of the eyes, ears, face and neck (Q10-18), congenital malformations of circulatory system (Q20-26), cleft lip and palate (Q35-37), other congenital malformations of the digestive system (Q38-45), congenital malformations of reproductive organs (Q50-56), congenital malformations of urinary system (Q60-64), congenital malformations and deformations of musculoskeletal system (Q65-79), and other congenital malformations and chromosomal abnormalities (Q80-89).

2.4. Statistical analysis

All data were preliminarily collected by Excel 2010 software. SPSS 16.0 statistical software (SPSS Inc. Chicago) was employed for statistical differences between groups ($P < .05$) by χ^2 test.

3. Results

3.1. Enrolled subjects

As showed in Table 1, a total of 752 cases were enrolled into this study. Notably, the male fetuses are more than female fetuses. About a half of the fetuses with BDs were diagnosed during pregnancy. Among them, 68% of the fetuses were diagnosed in the second trimester. A total of 412 infants were live birth, and a total of 348 infants receive medical therapies.

3.2. Severe and minor BDs

To simplify the evaluation of the potential BD risks of drugs used during pregnancy, here all BDs were divided into severe and minor BDs. The severe BDs could lead to death or uncorrectable

Table 1

Basic information of the enrolled cases.

	Number (%)
Pregnant women	
Age (yrs)	752
<20	17 (2.26%)
20-25	126 (16.76%)
25-30	366 (48.67%)
30-35	243 (32.31%)
Number of fetuses per pregnancy	752
Single pregnancy	731 (97.21%)
Bigeminal pregnancy	21 (2.79%)
Fetuses	
Sex gender*	764
Male	457 (59.82%)
Female	276 (36.13%)
Unknown	31 (4.06%)
The time of malformation diagnosis	764
Early pregnancy	21 (2.75%)
Second trimester	259 (33.90%)
Late pregnancy	100 (13.09%)
Post partum	384 (50.26%)
Therapeutic induced labor after malformation diagnosis	764
Yes	348 (45.55%)
No	416 (54.45%)
Gestational age	764
Premature	389 (50.92%)
Full term	374 (48.95%)
Overdue	1 (0.13%)
Outcome of the childbirth	764
Stillbirth	352 (46.07%)
Live birth	412 (53.93%)

*$P < .05$ between male and female.

lifelong deformity, and the other BDs are minor BDs. The detailed classification was presented in Tables 2 and 3. Here, the observed most severe and minor BDs are malformations of the circulatory system and malformations and deformations of the musculoskeletal system, respectively.

3.3. Medicines used in pregnancy and BDs

As the pregnancy A and B degree drugs categorized by the FDA or pharmaceutical manufacturers possessed relatively good safety, the cases involving them are not depicted and discussed in this study. There are complicated chemical compounds within each traditional Chinese medicine, and these cases are also not focused here. Table 4 shows the most used 5 pregnancy C/D/X degree drugs and other chemical drugs that are not categorized as pregnancy A/B degree drugs by the FDA and pharmaceutical manufacturers. The followed BDs are also presented. Here only 1 FDA pregnancy category X drug (chorionic gonadotropin) and 2 X degree drugs (warfarin and levonorgestrel) categorized by pharmaceutical manufacturers were respectively used once.

4. Discussion

There are many studies about the medical risks for BDs in European and North American,[10–12] but the studies on the issue in Chinese are rare. As the different race may suffer different medical risk for BDs, here we tempt to look into this risk in China. In this study, the information of BD cases occurring in Hunan province during 2016 to 2019 years was collected from the Birth Defect Surveillance System. To explore the potential risks of medicines used during pregnancy for BDs, here a cross-sectional study on these cases was carried out. It is too hard for us to collect enough cases that the mothers used some kinds of medicines during pregnancy and subsequently delivered healthy babies, and hence there is no control group in this study. To elevate the quality of evidence of this study,[13] the pregnant women with high risk factors for BD, such as advanced paternal age, family history, drinking, contacting pesticide and other toxic chemicals, suffering radiation, and inhaling harmful gas,[10] were excepted from this study. To further clarify the potential relationship between individual drug and BD, the mothers received more than 2 kinds of drugs during pregnancy were also excluded.

Due to the low risk of FDA pregnancy category A/B drugs for BDs and the large number of pregnant women using these drugs, the potential relationship between BDs and drugs may be weak in this study. Therefore, we mainly focused on the drugs that are categorized into the pregnancy C/D/X degrees and were most used in this study.

Here, there is one case using FDA pregnancy category X drug chorionic gonadotropin. Chorionic gonadotropin is a risk factor for hypospadias,[14] and it supports the case observed in this study. Using levonorgestrel, categorized into the pregnant X degree by the pharmaceutical manufacturer, usually occurs in unidentified early pregnancy. The case showed that a pregnant woman took the levonorgestrel and gave a fetus with a pulmonary artery defect, agreeing with the increased incidence of congenital heart

Table 2

The observed severe birth defects.

Kinds	Frequency (%)
Congenital malformations of the circulatory system	**140 (40.46%)**
Coronary sinus septal defect; Tetralogy of Fallot; Unspecified congenital heart malformations; Other congenital malformations of the aorta (valve); Endocardial cushion defect; Other congenital malformations of the tricuspid valve; Pulmonary artery stenosis; Left heart hypoplasia syndrome; Complete transposition of great blood vessels; Other specific types of heart disease; Ventricular double outlet; Complex congenital heart disease; Congenital mitral stenosis; Other congenital malformations of the pulmonary artery; Other congenital malformations of the mitral valve; Double entrance of ventricle; Atrioventricular connection is not coordinated; Whole heart enlargement; Common atrial stem; Congenital coronary aneurysm; Congenital mitral insufficiency; Congenital heart block	
Congenital malformations of the nervous system	**57 (16.47%)**
Spina bifida; Hydrocephalus; Anencephalus; agenesis of corpus callosum; Encephalocele; Bilateral ventricular dilation; Full forebrain; Arachnoid Cyst; Cerebellar vermis dysplasia; Exencephaly; Cerebellar malformation; Cerebellar cyst; Craniocerebral abnormalities; Abnormal development of the cerebral hemispheres; Brain tumor; Microcephaly	
Congenital malformations of the musculoskeletal system	**49 (14.16%)**
Short limbs; Gastric fissure; Congenital septal hernia; Spinal abnormalities; Abdominal wall body pedicle limb syndrome; Osteogenesis imperfecta; Achondroplasia; Thanatophoric dysplasia; Spinal stenosis; Excessive cervical dorsiflexion; Congenital polyarticular contracture; Congenital spine loss	
Other congenital malformations	**41 (11.85%)**
Cervical water cyst tumor; Micrognathia; Anasarca; Teratoma of coccyxacral region; Multiple rhabdomyomas; Fetal growth restriction; Partial scalp loss; Fetal thoracic lumps(71*52*52 mm); 6*5*1.5 cm lumps on the back of the left shoulder, Dark brown, Dark brown on the left forearm; A palpable 7*7 cm hard abdominal lump is present; 9*7*6 cm lumps can be seen on the left side of the front of the fetal neck; A round mass of about 4*4*2 cm^2 size can be seen on the right knee joint; Congenital partial loss of the skin of both lower limbs; Congenital absence of epidermis; Thymic hypoplasia; Tuberous sclerosis; Primary carnitine deficiency; Ichthyosis; Visceral valgus	
Congenital malformations of the urinary system	**28 (8.09%)**
Polycystic kidney; Bilateral hydronephrosis; Giant bladder; Bladder ectropion; Echo enhancement in both kidney parenchyma; Absence of both kidneys; Pelvic ectopic dysplasia kidney; Kidney dysplasia	
Chromosomal abnormalities	**17 (4.91%)**
Chromosome deletion/abnormality/trisomy; 18-trisomy syndrome; Turner syndrome; Fetal superfemale syndrome	
Other congenital malformations of the digestive system	**6 (1.73%)**
Cystic dilatation of the bile duct; Cloaca deformity; Hiatal hernia; Congenital intestinal necrosis; Intestinal duplication	
Congenital malformations of the respiratory system	**5 (1.45%)**
Pulmonary cystadenoma malformation; Pulmonary dysplasia; High bronchial obstruction	
Congenital malformations of face, ear, eye and neck	**2 (0.58%)**
Cracked face, Missing left wing of nose, Widened eye distance; No nose bridge, no eyes, fleshy lumps between eyebrows	
Congenital malformations of reproductive organs	**1 (0.29%)**
Absence of bilateral scrotum	
Total	**346 (100%)**

Table 3

The observed minor birth defects.

Kinds	Frequency (%)
Congenital malformations of the musculoskeletal system	**180 (30.35%)**
Polydactyly/toed; Clubfoot; Digit/toe; Acromphalus; Foot valgus; Long bone dysplasia; Missing fingers/toes; Absence of radius; Congenital vertical talus; Joint deformities; Congenital pectus excavatum; Foot dorsiflexion deformity; Limited hip abduction; Toes upturned	
Congenital malformations of the circulatory system	**122 (20.57%)**
Absent atrial/ventricular septum; Patent ductus arteriosus; Aortic stenosis; Single umbilical artery; Permanent left superior vena cava; Dextrocardia; Laevocardia; Simple right aortic arch; Congenital pulmonary valve insufficiency or congenital pulmonary valve regurgitation	
Cleft lip and palate	**95 (16.20%)**
Cleft lip and palate	
Congenital malformations of face, ear, eye and neck	**62 (10.46%)**
Deformity of external auditory canal; Small ears (including no ears); Congenital malformations of the nose; Unilateral auricle atresia; Facial deformities	
Other congenital malformations	**54 (9.11%)**
G6PD deficiency; Congenital hypothyroidism; Visceral heterogeneous syndrome; Neoplasm; Intrahepatic hemangioma; Cystic nodules/ enclosed mass; Peritoneal effusion; Erythema; Compound moles, with scattered dark brown pigment spots on the whole body; Subcutaneous liquid dark area of right cheek 75*10 mm; Enlarged tongue, liver, and spleen, enlarged kidneys	
Congenital malformations of reproductive organs	**31(5.23%)**
Hypospadias; Testicular hydrocele; Cryptorchidism; Reproductive tract effusion; Clitoral hypertrophy; Testicular dysplasia; Umbilical anal ectopic	
Congenital malformations of the urinary system	**24 (4.05%)**
Unilateral hydronephrosis; Single Kidney Absence; Ectopic kidney; Congenital double renal pelvis separation; Rongheshen; Double renal pelvis; Repeat kidney/ureter	
Other congenital malformations of the digestive system	**18 (3.04%)**
Rectal anus stenosis; Atresia or narrowing of the esophagus; Duodenal atresia; Intestinal obstruction; Congenital intestinal atresia; Duodenal cyst; Gastric pyloric obstruction; No gallbladder	
Congenital malformations of the respiratory system	**4 (0.67%)**
Isolated lungs	
Congenital malformations of the nervous system	**3 (0.51%)**
Bilateral choroid plexus cyst	
Total	**593 (100%)**

disease in fetuses whose mothers orally took contraceptive during pregnancy.[15] Warfarin is categorized into the pregnant D degree by the pharmaceutical manufacturer. Here, 2 cases reported the warfarin uses during pregnancy for cardiac valve replacement and the followed BDs, including a congenital heart defect and a cephalocele, which were also reported in a previous paper.[16,17] As some studies showed the relatively low teratogenic risk of warfarin at a dose of less than 5 mg/d,[18,19] the ESC[20] and ACC/AHA[21] think that this low dose could be used during the first trimester. Nevertheless, because the studies on the teratogenic risk of warfarin were carried out on the Western population, the safe dose for the East population may need further studies.

The most used FDA pregnancy category D drugs include propylthiouracil, carbamazepine, magnesium sulfate, azathioprine, and methimazole. BDs, such as genital organ and integumentary system defects, have been found following using methimazole during pregnancy in this study, corresponding with the previous report.[22] On the other hand, a total of 17 cases reported the potential relationship between propylthiouracil use during pregnancy and BDs, including congenital heart disease, limb shortening, hydrocele of testis, hypothyroidism, cleft lip and palate, hypospadias, polydactyly, external ear defect, etc. Among them, hydrocele of testis, congenital heart disease, and external ear defect were observed in more than 2 fetuses. These defects also have been reported as congenital anomalies associated with propylthiouracil treatment during pregnancy.[23–25] During pregnancy, untreated hyperthyroidism may bring maternal morbidity and loss of fetus, and propylthiouracil shows more safety than other medicines, such as methimazole, radioiodine, and carbimazole.[26] As a dose dependent risk of BDs with antithyroid drugs were observed,[27] how to give a low but effective dose of propylthiouracil to pregnant women may desire further studies. For antiepileptic drugs, here the BDs after using carbamazepine during pregnancy included respiratory and circulatory systems defects, which were also observed in other study.[28] Valproic acid, categorized into the pregnant D degree by the pharmaceutical manufacturer, has been reported to exert teratogenic action for cardiac ventricle defect,[29] supporting the case that a pregnant mother took valproic acid and delivered a fetus with congenital absence of ventricular septum here. Studies[30–32] on the safety of antiepileptic drugs showed that valproic acid presented a relatively high risk for BDs, carbamazepine presented a modulate risk, and the lamotrigine and levetiracetam presented a relatively low risk. Nevertheless, 3 BD cases, including congenital heart disease, cleft lip and palate, and polycystic kidney, were associated with using lamotrigine, categorized into the pregnant C degree by the pharmaceutical manufacturer, during pregnancy in this study, which were also observed in the previous studies.[33,34] BDs, including cleft lip,[30] spina bifida cystica and clubfoot,[35] were found to be associated with using oxcarbazepine, categorized into the pregnant C degree in FDA, and these BDs were also observed here. Except choosing safer antiepileptic drugs, a lower dosage and single drug could also decrease the incidence of BDs.[30] Although magnesium sulfate has been categorized as D by the FDA, its benefits warrant use of this drug in pregnant women when it is used in proper duration and time. Here, 7 cases about this drug may result from the large number of pregnant women who used this drug. Although azathioprine is the general immunosuppressive medicine in many high-risk pregnancy centers because of its safety profile and steroid-sparing property,[36] the cases that the women were administrated with azathioprine during pregnancy and delivered fetuses with renal and ear defects were observed in both this study and a previous study.[37]

The clinical teratogenic action of prednisone, FDA pregnancy category C drug, has been scarcely studied. Here, BD cases, including 2 congenital heart disease cases, 2 cleft palate cases, a renal abnormality case, and an osteogenesis abnormality case, were observed after using prednisone in gestation period, which were similar in dogs.[38] Oral clefts is a kind of BD after gravidic administration of hydroxychloroquine,[39] and the similar case was also observed in this study.

Table 4

The most used 5 pregnancy C/D/X degree drugs and other chemical drugs that are not categorized as pregnancy A/B degree drugs by the FDA and pharmaceutical manufacturers.

	Case number		
	Serious BD	Minor BD	Kinds of BDs by ICD-10 (case number)
FDA pregnancy category C drugs			
Prednisone	4	5	heart disease (2); trisomy 21 syndrome (2); cleft lip and cleft palate (2); malformation of musculoskeletal system (1); malformation of digestive system (1); malformation of respiratory system (1); malformation of urinary system (1); deformities of the face, ears, eyes, and neck (1)
Hydroxychloroquine	4	3	heart disease (3); trisomy 21 syndrome (1); cleft lip and cleft palate (2); malformation of digestive system (1); malformation of respiratory system (1)
Levofloxacin	4	2	heart disease (4); malformation of urinary system (2); other malformations (hygroma colli) (2); cleft lip and cleft palate (1); malformation of musculoskeletal system (1)
Labetalol	2	4	cleft lip and cleft palate (2); deformities of the face, ears, eyes, and neck (1); heart disease (1); other malformations (glucose-6-phosphate dehydrogenase deficiency) (1); malformation of musculoskeletal system (1)
Oxcarbazepine	3	1	malformations of the nervous system (3); cleft lip and cleft palate (1); malformation of musculoskeletal system (1)
FDA pregnancy category D drugs			
Propylthiouracil	5	12	malformations of reproductive organs (4); malformation of musculoskeletal system (4); other malformations (4); deformities of the face, ears, eyes, and neck (3); heart disease (3); malformation of urinary system (1);
Magnesium sulfate	2	5	other malformations (2); deformities of the face, ears, eyes, and neck (1); heart disease (1); malformation of digestive system (1); malformation of musculoskeletal system (1); chromosome malformation (1)
Carbamazepine	2	4	deformities of the face, ears, eyes, and neck (1); heart disease (1); malformation of respiratory system (1); cleft lip and cleft palate (1); malformation of musculoskeletal system (1); other malformations (1)
Methimazole	1	1	malformations of reproductive organs (1); malformation of musculoskeletal system (1)
Azathioprine	0	1	deformities of the face, ears, eyes, and neck (1); malformation of urinary system (1)
FDA pregnancy category X drug			
Chorionic gonadotropin	0	1	malformations of reproductive organs (1)
Other chemical drugs that are not categorized as A/B degree drugs by pharmaceutical manufacturers			
Dydrogesterone	6	10	malformation of musculoskeletal system (4); heart disease (3); other malformations (3); malformation of urinary system (2); chromosome malformation (trisomy 21 syndrome) (2); malformations of the nervous system (1); malformation of respiratory system (1); cleft lip and cleft palate (1); malformations of reproductive organs (1)
Aspirin	5	9	malformation of musculoskeletal system (4); heart disease (3); malformation of respiratory system (2); cleft lip and cleft palate (2); malformation of digestive system (2); other malformations (2); chromosome malformation (trisomy 21 syndrome) (1)
Valproic acid	4	2	heart disease (3); malformations of the nervous system (2); malformation of musculoskeletal system (2); malformation of urinary system (1)
Omeprazole	4	0	heart disease (2); malformation of respiratory system (1); cleft lip and cleft palate (1); malformation of urinary system (1); other malformations (1)
Lamotrigine	2	1	heart disease (2); cleft lip and cleft palate (1); malformation of digestive system (1); malformation of urinary system (1)

BDs = birth defects, FDA = food and drug administration.

Levofloxacin may lead to BDs of urinary system and cardiac malformations,[40] supporting the cases that the levofloxacin-exposed pregnant women delivered fetuses with urinary system and cardiac abnormality in this study. According to the guidelines from different countries,[41–43] the labetalol is one of the first choices for hypertension in pregnancy. Nevertheless, BDs including cardiovascular defects, oral clefts, and spine defects after labetalol use during pregnancy were observed in both previous[44] and this studies.

In this study, other drugs, which have not been assigned in FDA pregnancy category, are also associated with BDs, such as aspirin, amantadine, etc. Aspirin, with its relatively satisfactory safety, is recommended to be used during pregnancy by many guidelines. Here, most of the BDs associated with aspirin may be due to undefined inducing factors. However, inducing BD of necrotizing enterocolitis has been reported when it is used during pregnancy,[45] and here a small intestine obstruction defect case was also observed. Dydrogesterone is a common preventing abortion drug in China. Although a total of 16 BD cases with using dydrogesterone during pregnancy were occurred in this study, previous studies stated that dydrogesterone treatment during pregnancy did not bring additional congenital abnormalities.[46–50] BDs, including congenital heart disease (2 cases), polycystic kidney, pulmonary retardation, and facial deformity were found after the using of omeprazole in this study and previous studies,[51–53] although omeprazole is considered as a relatively safe reagent during pregnancy and is categorized as C degree by the pharmaceutical manufacturer.

Notably, here male fetuses with BDs are more than female fetuses, which may suggest a more susceptible characteristic to drugs for male fetuses, in accordance with the previous report.[54]

There are many shortcomings within this study. Firstly, as the Birth Defect Surveillance System only collects the BD positive cases, control group is not available in this study, which lowers the quality of evidence.[13] Secondly, it is difficult to discuss the safety of traditional Chinese medicines due to the complex constitutes within each prescription. Thirdly, some information is missing when the case was recorded into the Birth Defects Registration Card, such as during which trimester did the women take the medicine.

5. Conclusions

BD cases occurred in 2016 to 2019 years in Hunan province, China, were collected for surveying the potential relationships between BDs and medicine uses during pregnancy. As far as we know, here we first reported the potential relationships in mainland China. This study mainly focused on the relatively high BD risks drugs that are categorized into pregnancy C, D, or X

degrees by FDA or pharmaceutical manufacturers, and found that some kinds of patients, such as hyperthyroidism and epilepsy patients, confronted more risks. This population-based data will help clinicians and policy makers improve clinical prescription during pregnancy.

Authors' contributions

Wei Zou: Study concept and design, data analysis, and manuscript drafting. Shuting Xie: Data analysis and manuscript drafting. Changbiao Liang: Data analysis. Donghua Xie: Interpretation of data. Junqun Fang: Study design. Ouyang Bo: Supervision of analyses. Li Sun: Critical revision of the manuscript. Hua Wang: Study concept and design.

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