ORIGINAL RESEARCH

Medication Use During Pregnancy in Mainland China: A Cross-Sectional Analysis of a National Health Insurance Database

Jingyuan Zhang [iD][1]
Carolina Oi Lam Ung[2]
Anita Katharina Wagner[3]
Xiaodong Guan[1,3,4]
Luwen Shi[1,4]

[1]Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, People's Republic of China; [2]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, People's Republic of China; [3]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA; [4]International Research Center for Medicinal Administration, Peking University, Beijing, People's Republic of China

Purpose: This study aims to illustrate the prevalence and patterns of medication use among pregnant women in mainland China.

Patients and methods: Hospital and drugstore service data for a nationally representative sample of basic medical insurance (BMI) beneficiaries in 2015 were obtained from the China Health Insurance Association (CHIRA) database. A total of 7946 women who had singleton deliveries in 2015, aged between 12 and 54, and whose records in the CHIRA database covered at least one trimester were included in this study. We conducted descriptive analyses of sample characteristics, medication use prevalence, and number and types of medications used.

Results: We found that 11.7% of women used at least one medication during the course of pregnancy (median number of medications used = 6.7). Medication use was more common among those who were older, residing in Eastern China, or employed. Most commonly used medication groups by the Anatomical Therapeutic Chemical Classification System were B (Blood and blood forming organs, 49.3%), A (Alimentary tract and metabolism, 48.1%), G (Genito urinary system and sex hormones, 38.1%) and J (Antiinfectives for systemic use, 31.6%). Intravenous solutions, vitamins and minerals, progestogens, and beta-lactam antibacterials were the most frequently used medications from each of these four ATC groups, respectively. Moreover, 7.1% used at least one medication contraindicated in pregnancy.

Conclusion: This study showed that around one in 10 women used medication during pregnancy in mainland China and found possible cases of inappropriate or unsafe medication use.

Keywords: medication use, pregnancy, China, cross-sectional, health insurance database

Introduction

Medication use during pregnancy has drawn global attention since the thalidomide disaster in 1960's.[1] Considering the potential risks of maternal medication exposure to the fetus, clinicians and women must carefully weigh the risks and benefits of medication use during pregnancy. On one hand, most medications and their metabolites can pass the placental barrier. Except for medications indicated for pregnant women, most medications should thus be avoided during pregnancy.[2] On the other hand, withholding necessary medication treatments may place the life of the mother and the fetus in danger.[3,4]

There is a scarcity of information on medication use during pregnancy. In 1987, the World Health Organization (WHO) Regional Office for Europe conducted a collaborative study on drug use in pregnancy to assess maternal medication use internationally.[5–7] Since then, as an effective approach exploring potential risks

Correspondence: Luwen Shi; Xiaodong Guan
Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, People's Republic of China
Tel/Fax +86-010-82805019;
+86-13911232199
Email shiluwen211@163.com;
Guanxiaodong@pku.edu.cn

related to medication use during pregnancy, various drug utilization studies have been conducted to assess the prevalence and patterns of medication use during pregnancy in different countries and regions.[8–10] Furthermore, researchers have identified factors associated with maternal medication use such as age under 25[11] or above 35 years,[12] lower education level,[13,14] less household income,[14] presence of smoking habits,[11] and poorer health status.[11,13]

The number of live births was 17.6 million in 2017 in China.[15] Previous studies found a wide variation in the prevalence of medication use by pregnant women across different regions ranging from 12.4% to 75.9%.[16–20] Dietary supplements (38.7–65.2%),[20] traditional Chinese medicines (TCM, 7.8–47.5%),[17,18] antibiotics (1.7–34.3%),[16–18] and hormones (3.7–7.2%)[17,18] were reportedly the most commonly used medications during pregnancy in the country. In these studies, patient-reported data were collected through survey studies at local hospitals that involved small sample sizes. Due to the size, location and design of the studies, the findings could easily be subject to selection and recall biases which might contribute to variations in the prevalence estimation. So far, no national data about the prevalence of medication use during pregnancy in China is available. To fill this important knowledge gap and to better inform clinical practice, we aimed to estimate the prevalence of medication use among pregnant women across China based on a national health insurance database. We further assessed the prevalence and patterns of medication use stratified by the stage of pregnancy, and identified the most commonly used medications in each trimester.

Materials and Methods
Data Source
By the end of 2015, over 1.33 billion people in China (97% of the population) were enrolled in one of the three public health insurance schemes: (1) the Urban Employee Basic Medical Insurance (UEBMI) which was mandatory for urban employees; (2) the Urban Resident Basic Medical Insurance (URBMI) which covered mainly the unemployed, children, students, and the disabled in urban areas; and (3) the New Rural Cooperative Medical Scheme (NRCMS) for rural residents.[21] Medical service utilization information of every UEBMI and URBMI (hereafter jointly referred to as BMI) beneficiary in hospitals and BMI designated drugstores is routinely collected in BMI databases at city level and includes: (1) BMI beneficiaries' demographic information, eg, unique personal identifiers,

birth date, and gender; (2) inpatient and outpatient medical encounter information, eg, principal diagnosis for each encounter coded with International Classification of Diseases 10th Revision (ICD-10) codes, admission and discharge dates, and healthcare facility information; and (3) all medical service utilization data at each encounter, eg the name, date, price, and quantity of medications dispensed and procedures performed whether they are covered by the BMI or not.

The China Health Insurance Association (CHIRA) employs a two-stage systematic sampling design to obtain a national representative sample of BMI beneficiaries and extracts cross-sectional medical service utilization data annually from the city-level BMI databases. The extract forms the unique national health insurance database known as the CHIRA database. Using sampling proportional to size, the percentage of sampled BMI beneficiaries is 2% in the centrally administered municipalities and provincial capitals, 5% in the prefecture-level cities, and 10% in the counties.[22]

The data in our study were obtained from the CHIRA database in 2015, which at the time contained inpatient and outpatient diagnosis and medical service utilization data of 37.3 million BMI beneficiaries sampled from 82 cities nationwide, representing about 2% of the total population in Mainland China. Since the CHIRA data was de-identified, this study was exempt from Institutional Review Board review by the Ethics Committee of Peking University Health Science Center, Beijing, China (No. IRB00001052-17022).

Study Population
Women aged 12–54 with a singleton delivery between January 1, 2015 and December 31, 2015 were identified in the CHIRA database from one of the two beneficiary groups predefined according to ICD-10: (1) codes O80-O84 and (2) codes O60-O75. As direct measures of gestational age such as the last menstrual period (LMP) were lacking in the database, we used a delivery date-based algorithm validated by Li et al (2013) to assign pregnancy trimesters. We assumed a gestational duration of 270 days (245 days for preterm delivery), with three 90-day trimesters during pregnancy (65 days of the third trimester for preterm delivery) based on admission date for delivery.[23] Only women who had a singleton delivery in 2015, were between 12 and 54 years old at delivery, and whose records in the CHIRA database covered at least one trimester were included in this study.

Medication Information

In the CHIRA database, medications were categorized as Western medicines or TCM according to the registration status as shown distinctively in the registration approval number given by the National Medicinal Product Administration (NMPA). Western medicines were further classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. Consistent with previous studies, we classified vitamins (A11A-A11J), minerals (A12A-A12C), iron preparations (B03A), and folic acids (B03B) as medications indicated in pregnancy.[9,24,25] We also identified the US Food and Drug Administration (FDA) Pregnancy Risk Category X (contraindicated during pregnancy) medications as listed in the MicroMedex and the Monthly Index of Medical Specialties (MIMS) databases.[26–28] Medication dispensing records with missing information (name of medication, dispensing date) were excluded from the analysis.

Outcome Measures and Statistical Analysis

To measure the extent to which medications were used in each trimester and throughout the entire pregnancy, we estimated the prevalence of overall medication use as the proportion of women with any medication dispensed. The prevalence of specific medication use was defined as the percentage of women with a specific medication dispensed of all women with at least one medication dispensed in the time frame of interest. Among women with at least one medication dispensed in each trimester and during the entire pregnancy, we calculated the median number of different medications dispensed based on their generic names.

We conducted descriptive analyses of sample characteristics, medication use prevalence, number and types of medications used. Numerical variables were summarized with medians and categorical variables with proportions. To test differences between groups, we used Chi-square tests for categorical variables and Wilcoxon rank-sum tests for numerical variables.

Results

A total of 11,373 women aged 12–54 with a singleton delivery in 2015 were identified in the national database, of which 7946 women had records in the CHIRA database that covered at least one trimester. According to our estimates of each gestational period, among these 7946 women, there were 2896, 5377, and 7946 women included in the analysis of medication use during the first trimester/ entire pregnancy, second, and third trimester, respectively (Figure 1, Supplementary material 1).

Demographic Information of the Study Sample and the Users

The majority of the pregnant women included in this study were between 25 and 29 years old, lived in Eastern China, were covered by URBMI and underwent spontaneous delivery. We found that 11.7% of 2896 women (from the entire pregnancy group) used at least one medication during the entire course of pregnancy. The prevalence of medication use during the entire pregnancy and in each trimester was further stratified based on the demographic characteristics of the women included in their corresponding groups as shown in Table 1. Medication use during pregnancy was more common among older women with the prevalence among women aged 35 or above three times higher than that among women under 25 years old. Women in Eastern areas or those with a job (enrolled in the UEBMI) had a considerably higher prevalence of medication use, ranging from five to ten times higher than their counterparts in Middle and Western regions and those enrolled in the URBMI. The same associations were also observed in each of the three-trimester groups.

The Types and Number of Medications Used During Pregnancy and in Each Trimester

As shown in Table 2, the prevalence of medication use including and excluding vitamins and minerals during pregnancy were similar (11.7% and 11.5%). Overall, only 2.0% of pregnant women used iron preparations or folic acid during pregnancy with an increasing prevalence from the first to the third trimester (0.4–1.7%). The proportion of women using Western medicines during pregnancy (11.1%) was more than twice that of women using TCM (5.2%). The median number of medications used during pregnancy per women was 6.7. Women who used four or more medications accounted for more than half (52.5%) of women who used at least one medication during pregnancy.

As shown in Supplementary material 2, among the women who used at least one medication during the course of pregnancy, 65.5% used medications in only one trimester and 12.4% used medications throughout all three
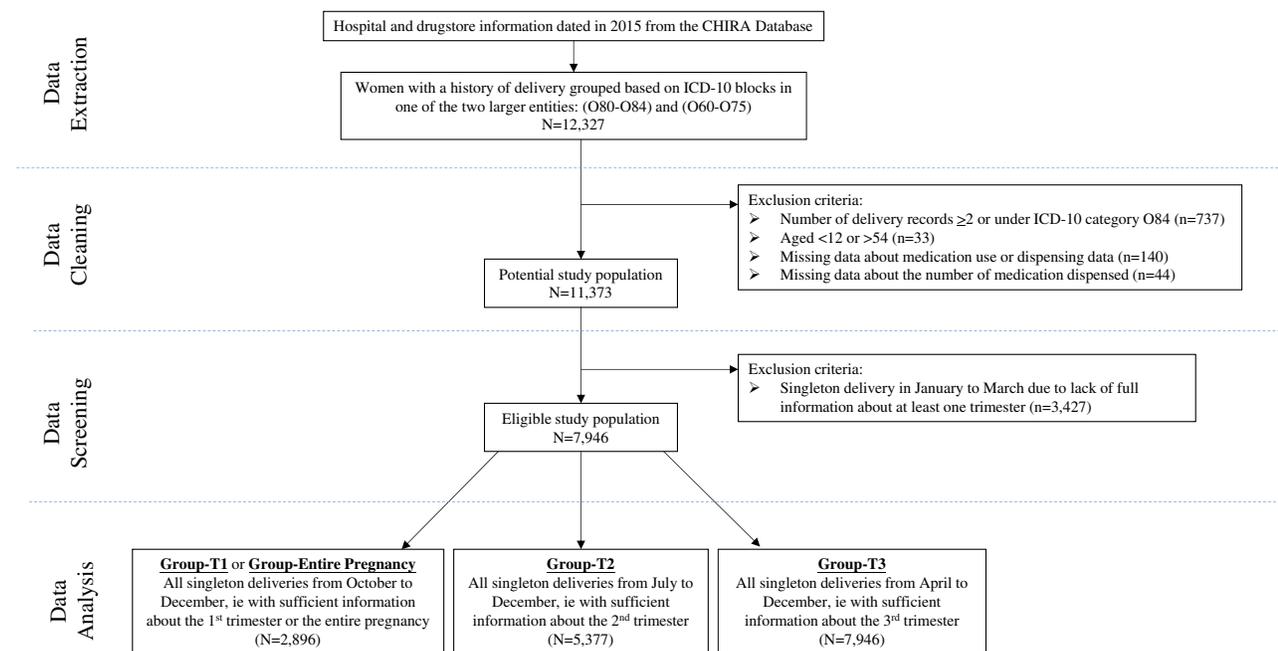
Figure 1 Diagram of sample extraction process from the CHIRA database.
Abbreviations: CHIRA, the China Health Insurance Association; ICD-10, the International Classification of Diseases 10th Revision.

trimesters. One in two women (50.1%) used medication during the first trimester.

Most Commonly Used Western Medicines During Pregnancy

Table 3 shows the prevalence of Western medicine use by ATC Class (first code level) with the highest prevalence for class B (blood and blood forming organs, 49.3%), followed by class A (alimentary tract and metabolism, 48.1%), class G (genito urinary system and sex hormones, 38.1%) and class J (antiinfectives for systemic use, 31.6%). Further information about the most commonly used Western medicines by ATC third-level codes and by generic names is provided in Supplementary material 3 and Supplementary material 4. The most commonly used ATC code B medicines included solutions for injection or infusion (B05X, B05B) such as glucose (28.9%) and sodium chloride (23.9%), iron preparations (B03A) and vitamin B12 and folic acid (B03B). In ATC group A, multivitamins (A11A), vitamin C (A11G), other vitamin preparations (A11H), such as potassium chloride (8.3%) and magnesium sulfate (6.2%) as well as omeprazole (3.0%) were the most frequently used medicines. The use of progestogens (G03D) was significantly more prevalent during the first trimester (53.5% in the group T1) than in the other two trimesters (10.0% in group T2, 3.0% in group T3). The prevalence of

antiinfective medicine use (ATC code J) remained relatively stable throughout the three trimesters (21.2% in group T1, 23.3% in group T2, 21.9% in group T3) and amoxicillin (beta-lactam antibacterial agent, J01C) was the most commonly used antibiotic.

As shown in Table 4, 7.1% of women (from the entire pregnancy group) were exposed to potentially harmful medicines (FDA Category X) during pregnancy. The prevalence of use in group T1, group T2 and group T3 were 5.3%, 1.9% and 5.9%, respectively. The most frequently used Category X medicines were hormonal preparations such as oxytocin (3.0%) and misoprostol (0.9%). The use of the category X antiviral drug ribavirin during pregnancy (1.5%) was also prominent.

Discussion

In this study, we found that 11.7% of women in mainland China used at least one medication during the course of pregnancy. The prevalence of overall medication use was much lower than those reported in other countries: 46.2–57.6% in Nordic countries,[9,14,29,30] 63.5–68.8% in the North America and Japan,[28,31,32] and over 90% in Germany and France.[33,34] However, the median number of 6.7 medications among medication users found in this study was higher than the average of 1–4 medications per user reported in most developed countries.[24] Given diverse

Table 1 Demographic Information of the Study Sample and Medication Users

	Prevalence of Medication Use in Women Observed During the Entire Pregnancy n/N (%, 95% CI)	Prevalence of Medication Use in Each Trimester Group n/N (%, 95% CI)			
		T1	T2	T3	p Value[a]
Total	339/2896 (11.7, 10.6–12.9)	170/2896 (5.9, 5.0–6.8)	270/5377 (5.0, 4.5–5.6)	506/7946 (6.4, 5.8–6.9)	0.005**
Age, n (%) <25 25-29 30-34 ≥35 p value[b]	42/646 (6.5, 4.7–8.7) 148/1282 (11.5, 9.8–13.4) 102/688 (14.8, 12.3–17.7) 47/280 (16.8, 12.6–21.7) 0***	14/646 (2.2, 1.2–3.6) 78/1282 (6.1, 4.8–7.5) 55/688 (8.0, 6.1–10.3) 23/280 (8.2, 5.3–12.1) 0***	37/1128 (3.3, 2.3–4.5) 110/2393 (4.6, 3.8–5.5) 92/1316 (7, 5.7–8.5) 31/540 (5.7, 3.9–8.0) 0***	51/1607 (3.2, 2.4–4.2) 217/3601 (6.0, 5.3–6.9) 158/1935 (8.2, 7.0–9.5) 80/803 (10.0, 8.0–12.2) 0***	0.369 0.041* 0.452 0.022*
Area, n (%) Eastern Middle-western p value[b]	294/1621 (18.1, 16.3–20.1) 45/1275 (3.5, 2.6–4.7) 0***	153/1621 (9.4, 8.1–11.0) 17/1275 (1.3, 0.8–2.1) 0***	231/3235 (7.1, 6.3–8.1) 39/2142 (1.8, 1.3–2.5) 0***	451/4833 (9.3, 8.5–10.2) 55/3113 (1.8, 1.3–2.3) 0***	0.001** 0.523
Insurance type, n (%) URBMI UEBMI p value[b]	107/2170 (4.9, 4.1–5.9) 232/726 (31.0, 28.6–35.5) 0***	29/2170 (1.3, 0.9–1.9) 141/726 (19.4, 16.6–22.5) 0***	69/3947 (1.8, 1.4–2.2) 201/1430 (14.1, 12.3–16.0) 0***	140/5833 (2.4, 2.0–2.8) 366/2113 (17.3, 15.7–19.0) 0***	0.004** 0.003**
Deliver type, n (%) Spontaneous delivery Other p value[b]	236/1795 (13.2, 11.6–14.8) 103/1101 (9.4, 7.7–11.2) 0.002**	116/1795 (6.5, 5.4–7.7) 54/1101 (4.9, 3.7–6.4) 0.099	182/3362 (5.4, 4.7–6.2) 88/2015 (4.4, 3.5–5.4) 0.102	341/4981 (6.8, 6.2–7.6) 165/2965 (5.6, 4.8–6.5) 0.027*	0.029* 0.161

Notes: [a]The p value of Chi-square tests across the three trimesters. [b]The p value of Chi-square tests across subgroups within the same time frame of interest. *p<0.05; **p<0.01; ***p<0.001.
Abbreviations: URBMI, Urban Resident Basic Medical Insurance; UEBMI, Urban Employee Basic Medical Insurance.

study methods (including differences in recruitment strategies, data sources, criteria for medications included, and analysis methods) and health system contexts (health insurance system and drug policies), interpretation of differences in medication use in pregnancy across studies is limited. However, the relatively low prevalence of

Table 2 The Types and Number of Medications Used During the Course of Pregnancy and in Each Trimester

	Women Observed During the Entire Pregnancy	Women in Each Trimester Group			
		T1	T2	T3	p Value[a]
All women					
Population, n	2896	2896	5377	7946	
Used ≥ 1 medications, %	11.7	5.9	5.0	6.4	0.005**
Used ≥ 1 medications (excl. vitamins and minerals), %	11.5	5.7	4.6	6.1	0.001**
Use of vitamins and minerals, %	4.5	1.4	2.1	2.4	0.006**
Use of iron preparations or folates, %	2.0	0.4	0.7	1.7	0.000***
Use of Western medicines, %	11.1	5.4	4.5	6.0	0.001**
Use of TCM, %	5.2	2.6	1.7	2.3	0.006**
Women who used ≥ 1 medication					
Number of different medications used, median	6.7	5.5	4.2	4.3	0.218
Women who only used 1 medication, %	21.5	35.3	38.2	32.4	0.271
Women who used 2–3 medications, %	26.0	27.1	30.7	30.8	0.629
Women who used ≥ 4 medications, %	52.5	37.6	31.1	36.8	0.228

Notes: [a]The p value of comparison tests across three trimesters. **p<0.01; ***p<0.001.
Abbreviations: TCM, Traditional Chinese Medicine.

Table 3 The Prevalence of Use of Western Medicines by ATC 1st Level Code Among Medication Users in Each Group (%)

ATC 1st Level Code	Women Observed During the Entire Pregnancy	Women in Each Trimester Group		
		T1	T2	T3
Number of medication users, n	339	170	270	506
B: Blood and blood forming organs	49.3	22.4	41.1	58.5
A: Alimentary tract and metabolism	48.1	29.4	49.6	48.0
G: Genito urinary system and sex hormones	38.1	55.3	15.6	10.9
J: Antiinfectives for systemic use	31.6	21.2	23.3	21.9
H: Systemic hormonal preparations, excluding sex hormones and insulins	15.6	7.1	7.8	17.6
V: Various	13.9	5.9	8.5	14.0
N: Nervous system	10.6	7.1	4.8	6.9
R: Respiratory system	7.7	4.7	5.6	6.7
C: Cardiovascular system	6.2	2.4	6.3	6.7
D: Dermatologicals	6.2	4.7	5.6	5.5
S: Sensory organs	4.4	2.4	3.7	2.4
M: Musculo-skeletal system	3.0	1.8	2.2	1.6
L: Antineoplastic and immunomodulating agents	1.8	1.8	0.7	0.8
P: Antiparasitic products, insecticides and repellents	0.3	/	0.4	1.4

Abbreviation: ATC, the WHO Anatomical Therapeutic Chemical drug classification system.

medication use among pregnant women and the higher number of medication used per user observed in this study suggest that international variations do exist.

In this study, the prevalence of overall medication use varied by trimester and sample characteristics. More intense medication use during the first trimester (50.1%) is consistent with previous studies,[28] which may be due to a potentially higher demand for medication treatment in early pregnancy, or a result of unidentified or unplanned pregnancy.[35,36] Similar to previous researchers,[37–39] we found that older women, those enrolled in the UEBMI, or those living in Eastern areas had significantly higher medication use compared to their respective counterparts. Women enrolled in UEBMI or living in Eastern areas tended to have higher income levels and better access to medical services which might lead to more intense medication use.

A few medications accounted for a large proportion of total antenatal medication use. Exposure to intravenous solutions, vitamins and minerals, progesterone, and antibiotics like amoxicillin, were prevalent during pregnancy, which is in accordance with findings by others.[33,40,41] However, the use of iron preparations or folates was uncommon (2.0%). That may be because our study did not capture information about free distribution of folates and iron supplements in communities. These products are recommended for pregnant women by WHO (2016) to prevent neural tube defects,[42] a preventable cause of morbidity. In China, a nationwide program was launched in 2009 by the National Health Commission that aimed to prevent neural tube defects. All women of child-bearing age who planned to become pregnant were given access to folates and iron supplements free of charge from their community health service centers.[43]

The common use of intravenous solutions accompanied with other injections during pregnancy found in this study may be mainly due to the typical prescribing pattern involving potential overuse of intravenous medications in mainland China.[44] Given that the oral route should be used whenever possible and intravenous fluids can usually be avoided in patients who are capable of eating and drinking,[45] the appropriateness and safety of the prevalent use of intravenous infusion among pregnant women in China remain questionable. It is also noteworthy that 53.5% of women with medication exposure during the first trimester used progestogens (G03D), possibly in an attempt to prevent early pregnancy loss. However, the American College of Obstetrician and Gynecologists (ACOG) Guideline has stated that conclusive evidence supporting progestogen use to avoid early pregnancy loss is lacking.[46,47] Physicians should balance benefits with risks based on the patient's condition and prescribe with caution only when clearly indicated.

The use of contraindicated medications during pregnancy warrants special attention. The prevalence of

Table 4 The Prevalence of FDA Category X Medicines Among Medication Users in Each Group (%)

Generic Name	Women Observed During the Entire Pregnancy	Women in Each Trimester Group		
		T1	T2	T3
Number of medication users, n	339	170	270	506
Any Category X medicines	7.1	5.3	1.9	5.9
Oxytocin	3.0	1.2	0.4	4.0
Ribavirin	1.5	/	1.1	1.0
Misoprostol	0.9	0.6	/	0.8
Chorionic gonadotrophin	0.6	1.2	/	/
Mifepristone	0.6	0.6	/	0.2
Goserelin	0.3	0.6	/	/
Clomifene	0.3	0.6	/	/
Medroxyprogesterone	0.3	0.6	/	/
Isotretinoin	0.3	0.6	/	/
Estradiol Valerate	0.3	/	0.4	0.4

Abbreviation: FDA, US Food and Drug Administration.

potentially harmful (FDA Category X) medicine use (7.1%) was higher than those reported in the United States (2.9%),[27] Canada (2.5–3.9),[28,48] the United Kingdom (1.0%),[49] France (1.6%),[34] Serbia (0%),[50] and North Ethiopia (0%).[51] The most commonly used Category X medicines was oxytocin (2.95%), especially in the third trimester which may be used in the treatment of delay in labour.[52] The use of ribavirin was also prominent (1.5%) despite the availability of more effective and safer alternatives (eg, Category B medicines such as sofosbuvir or Category C medicines such as oseltamivir) for pregnant women in China.[53,54] Efforts are needed to understand the reasons for use of Category X products and, where appropriate, to facilitate interventions to avoid unnecessary medication exposure during pregnancy.

To our best knowledge, this is the first study illustrating the prevalence and patterns of medication use during pregnancy in mainland China based on a unique and representative national health insurance database. Compared to traditional health insurance data which only cover reimbursable items, the CHIRA database can be considered an "extensive health insurance database" that contains information on all medications dispensed to BMI beneficiaries, both prescription medicines and over-the-counter products (OTC), whether or not they are covered by the local BMI schemes. The CHIRA database enabled a more accurate and reliable assessment of medication use than other data sources and may be considered an important database to advance Chinese population-based research for integration of real-world evidence into clinical practice and local policymaking.

However, our results may be subject to several limitations. First, because the CHIRA database mainly contains information on BMI beneficiaries and rural residents mostly enroll in the NRCMS, our findings may not be generalizable to pregnant women in rural areas. Second, we employed an algorithm to estimate gestational stages, which may lead to misclassification of medication exposure periods. However, given that the validated algorithm has been proved to perform well in classifying prenatal medication exposure status,[23] its impact on the results should be limited. Third, we only included pregnancies resulting in a singleton live birth. These women may have had better health status than those who had miscarriages, terminations of pregnancy, and stillbirths. This may result in some bias to our estimates of prevalence of medication use during pregnancy. Fourth, we examined high-risk (category X) medication use according to the FDA pregnancy risk category, which has been replaced by a narrative labelling system in 2015 because of its oversimplification and incompetence to guide clinical practice. Our reference to the former FDA pregnancy risk category can only provide a rough description of medication use risk during pregnancy on a population basis. The appropriateness and safety of medication use require further evaluation on a case-by-case basis. Finally, our analysis was based on medication dispensing records from pharmacies and did not take into account other potential pathways of medication supply; we also had no data on the treatment adherence of pregnant women, which may lead to some overestimation of medication exposure in pregnancy. In addition, since there were only a limited number of variables captured in the CHIRA database, we were unable to fully explore all the possible factors associated with medication use during pregnancy, such as parity, complication of chronic diseases and so on.

Conclusion

This study showed that in 2015 around one in 10 women used at least one medication during pregnancy in mainland China; there may be cases of inappropriate or unsafe medication use. More efforts should be made to understand the reasons for possible over- and underuse of medications in

pregnancy and to design, implement, and test interventions to optimize safe and appropriate use of medications during pregnancy.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. XDG and JYZ conceived the study idea and contributed to the study design. JYZ implemented literature review, cleaned and checked the data, wrote the code, did the analysis for the study. JYZ and COLU wrote the initial draft, and amended the final manuscript. XDG, AKW supervised and checked the analysis, gave suggestions to the initial draft, and reviewed the final manuscript. LWS contributed to data access, supervised the study design and data interpretation, and reviewed the final manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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