Real world based on FAERS database:To explore the mining and analysis of adverse pregnancy events related to drug exposure

Fu Xu

875934291@qq.com

Guizhou University of Traditional Chinese Medicine

WU Ai-lin

Hubei University of Traditional Chinese Medicine

Ye Dingxun

Guizhou University of Traditional Chinese Medicine

FAN Ke-lin

Guizhou University of Traditional Chinese Medicine

Meng Xia

Guizhou University of Traditional Chinese Medicine

Di Wei

The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine

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Real world based on FAERS database:To explore the mining and analysis of adverse pregnancy events related to drug exposure

Fu Xu[1], WU Ai-lin[2],Ye Ding-xun[1], FAN Ke-lin[1], MengXia[1]，Di Wei[3] *

1. Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China

2. College of Traditional Chinese Medicine, Hubei University of Traditional Chinese Medicine, Wuhan 430000, China

3. The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 550001, China

Abstract: Objective To explore and analyze the Adverse Pregnancy Events associated with drug exposure through FAERS database, summarize the risk drugs, and provide reference for clinical safe medication in pregnant patients. Methods The APE reports related to drug exposure from the FAERS database from the first quarter of 2004 to the first quarter of 2025 were extracted, and the signal drugs were identified by proportion imbalance (ROR), proportional reporting odds ratio (PRR) and Bayesian trusted propagation neural network (BCPNN). To explore the association between drug exposure and adverse pregnancy events, so as to analyze demographic information, occurrence time and pregnancy outcome. Results A total of 257443 APE related drugs were found. The World Health Organisation Drug Dictionary (Mar 2025) was used to manually standardize drug names (drugnames) in adverse event reports to generic drug names. A total of 1266 reports were screened. After excluding combination drugs and repeated data, a total of 112 drugs met the signal detection of this study, including dermatological drugs, digestive and metabolic system drugs, blood and hematopoietic organs drugs, anti-tumor and immunomodulatory drugs, etc. The median time of APE was about 146d by Weierb distribution analysis. By analyzing this data, it was found that the proportion of death, hospitalization, disability and fetal congenital malformation in the outcomes of APE related to drug exposure was as high as 30.78%. Conclusions APE associated with drug exposure involves more drugs and has poor pregnancy outcomes. This study shows that adverse pregnancy events associated with drug exposure may be related to the accumulation of drug therapy over a long period of time. Therefore, careful use of drugs during pregnancy is the key to avoid APE. Prevention of drug-related adverse pregnancy events.

Key words: Drug exposure; Adverse pregnancy events; Pharmacovigilance; Pregnancy outcome;

First Author: Fu Xu, female, master, E-mail: 875934291@qq.com;

Wu Ailin, female, Ph.D., E-mail:1466022913@qq.com.

Second author: Ye Dingxun, male, Master, E-mail:799694509@qq.com

Fan Kelin, female, master, E-mail:1483411415@qq.com;

Third author：Meng Xia, female, PhD in Botany, Physiological Research of Medicinal Plants, E-mail: lwmengxia421@163.com

Corresponding author: * Di Wei, male, PhD, master supervisor, Research interest in dermatology and venereology of traditional Chinese Medicine, E-mail:diwei203@163.com.

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In recent years, studies have shown that improper use of drugs during pregnancy may expose pregnant women to more and greater potential risks, and even lead to drug exposure related adverse reactions in some pregnant women and fetuses. The prevalence of pregnant women has increased to 70.4% year by year [1]. However, due to the fact that most pregnant women do not take drugs regularly during pregnancy, and most clinical drug instructions advise caution or contraindications during pregnancy, the data on pregnant women's attitudes and drug use are seriously underreported. Therefore, this paper mainly studies the real data of FAERS database to mine and analyze the adverse events of pregnancy caused by drug exposure, so as to provide reference for future clinical medication of pregnant patients.

1. Materials and Methods

1.1 Data source and collation

The data were extracted from FAERS database and coded by the International Council of Medical Scientific Organizations (MedDRA) version 28.0. The terms describing adverse events were mapped and translated using the SOC and PT levels of the MedDRA adverse Drug Reaction terminology set. We extracted reports that set the preferred term "pregnancy" as the adverse reaction field, retrieved the PT field of "pregnancy" in the DEMO-DRUG and REAC tables in the FAERS database, and restricted the role-cod field to "primary suspect". The extracted Drug names (DRUGNAME field) were standardized using the World Health Organisation Drug Dictionary (Mar 2025) to standardize drug names in the database. The mapping relationship between the DRUGNAME fields and the generic name of drugs related to adverse pregnancy events was found out, and the data were imported into SAS9.4 software for data cleaning and statistical analysis.

1.2 Data analysis

This paper mainly uses the reporting odds ratio (ROR) and proportional reportingratio methods in the analysis of proportion imbalance. PRR) and Bayesian confidence propagation neural network (Bayesian confidence propagation neural network, PRR). BCPNN) were all positive methods (that is, the number of adverse event reports ≥3, the lower limit of 95% CI of ROR value > 1, PRR≥2 and $\chi 2 \geq 4$ were used as the judgment conditions to determine the effective signal of adverse events.) The correlation between APE and drug exposure was explored, and the statistical analysis was performed using Microsoft Excel software, in which the larger the value of the signal, the stronger the signal, that is, the stronger the association between the target drug and the adverse event [2]. The specific calculation methods and thresholds are shown in Table 1 and Table 2.

Table 1 Two-by-two contingency table for disproportionality analysis

Item	Target adverse events reported	Other adverse events reported	Total
Target drugs	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

Table 2The principles of disproportionate measurement and the criteria for signal detection

Method	Calculation formula	Criteri
ROR	$ROR=\frac{a/c}{b/d}$ $SE(lnROR)=\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%CI=e^{\ln(ROR)\pm1.96se}$	a ≥ 3 95%CI (lower limit) > 1
PRR	$PRR=\frac{a/(a+b)}{c/(c+d)}$ $SE(lnPRR)=\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$ $95\%CI=e^{\ln(PRR)\pm1.96se}$	a ≥ 3 95%CI (lower limit) > 1
BCPNN	$\chi2=\frac{(ad-bc)^2(a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$ $IC=log_2\frac{p(x,y)}{p(x)p(y)}=log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$ $E(IC)=log_2\frac{(a+\gamma11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha1)(a+c+\beta1)}$ $V(IC)=\frac{1}{(ln2)^2}\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma11}{(a+\gamma11)(1+a+b+c+d+\gamma)}\right]+\left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha1}{(a+b+\alpha1)(1+a+b+c+d+\alpha)}\right]+\left[\frac{(a+b+c+d)-(a+c)+\beta-\beta1}{(a+c+\beta1)(1+a+b+c+d+\beta)}\right]\}$ $\gamma=\gamma11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha1)(a+c+\beta1)}$ $IC\text{-}2SD=E(IC)-2\sqrt{V(IC)}$ $\alpha1=\beta1=1$；$\alpha=\beta=2$；$\gamma11=1$	a ≥ 3 PRR ≥ 2 χ2≥4 IC-2SD>0

Note: Using one method to calculate the signal value may cause the probability of false positive to increase, but using multiple methods at the same time may reduce the s ensitivity and thus lose the positive signal. Considering comprehensively, the author chooses ROR combined with PRR and BCPNN as the signal calculation method in this paper.

1.3 Data screening

Data reported by 22775812 patients were extracted from the FAERS database and ded uplicated according to the FDA rules (for reports with the same CASEID, the report with the largest FDA_DT value was retained, and for those with the same CASEID and FDA _DT, the report with the largest PRIMARYID value was retained. Secondly, since the first quarter of 2019, there is a list of deleted reports in the data package of each quarter. Af ter the data is deduplicated, the reports are removed according to the CASEID in the list of deleted reports. A total of 3837944 duplicate reporting data of the same patient were e xcluded, and 9 937868 patients were left after removing duplicate reporting, involving 563 21150 adverse event reports (a patient may report several different adverse events at the s ame time in one data). The data were further filtered, and a total of 21495699 reports fro m 6249840 patients were included in the analysis. The target ades were screened in the p referred language of the MedDRA dictionary (related terms are shown in the table below), and were classified by system organ class, System organ class, and System organ class i n the latest version of the MedDra dictionary. SOC) and preferred terms (PT) were used f or subsequent analysis. A total of 33843 patients with target ADES were obtained, and 45 197 reports involving target ades were obtained (see Table 3 for details).Table 3 List of ta rgeted ADE screening PT terms

Table 3 List of target ADE PT terms

Preferred language coding	Preferred Language English
10063130	Pregnancy with contraceptive device
10067082	Pregnancy with contraceptive patch
10067667	Pregnancy on contraceptive
10074497	Ectopic pregnancy with contraceptive device
10053394	Pregnancy with injectable contraceptive
10072271	Chronic villitis of unknown etiology
10072811	Pregnancy of unknown location
10000217	Abortion incomplete
10069150	Discordant twin
10061050	Labour complication
10003118	Arrested labour
10036872	Prolonged labour
10000153	Abnormal labour

Preferred language coding	Preferred Language English
10000154	Abnormal labour affecting foetus
10029767	Normal labour
10036417	Postpartum haemorrhage
10061469	Postpartum disorder
10049589	Afterbirth pain
10048738	Postpartum state
10036423	Postpartum uterine subinvolution
10034248	Pelvic haematoma obstetric
10056311	Caput succedaneum
10004954	Birth trauma
10086944	Bone injury due to birth trauma
10086941	Scalp injury due to birth trauma
10022343	Injury to spinal cord secondary to birth trauma
10011308	Cranial nerve injury secondary to birth trauma
10016056	Facial nerve injury due to birth trauma
10059204	Labour pain
10027975	Morning sickness
10083523	Postnatal growth restriction
10067508	Low birth weight baby
10078661	Birth weight normal
10044520	Traumatic delivery
10069615	Pregnancy with young maternal age
10043449	Third stage postpartum haemorrhage
10084825	Superimposed pre-eclampsia
10028243	Multiple pregnancy
10052848	Brow presentation
10085701	Lochiostasis
10046267	Unwanted pregnancy
10067647	Delivery
10061781	Complication of delivery
10067703	Intrapartum haemorrhage
10036595	Premature delivery
10090664	Succenturiate placenta
10000218	Abortion incomplete complicated
10061615	Abortion complicated
10000212	Abortion complete complicated
10000239	Abortion spontaneous incomplete complicated
10014349	Elderly primigravida
10036582	Pregnancy with advanced maternal age
10020065	High foetal head
10088619	High risk infant
10052744	High risk pregnancy
10029934	Obstructed labour
10008267	Cervical incompetence
10054939	Cervix dystocia
10064228	Heterotopic pregnancy
10080022	Uterine tachysystole
10083336	Pelvic girdle pain
10023789	Large for dates baby
10036877	Prolonged pregnancy
10036392	Postmature baby
10044456	Transverse presentation
10079272	Short interpregnancy interval
10034528	Perineal repair breakdown
10049550	Live birth
10000230	Abortion missed
10073727	Ectopic pregnancy under hormonal contraception
10036519	Precipitate labour
10016194	False labour
10040613	Shoulder dystocia
10051459	Imminent abortion
10068875	Mirror syndrome
10053700	Foetal macrosomia
10036567	Pregnancy on oral contraceptive
10000210	Abortion
10036244	Post abortion complication
10036246	Post abortion haemorrhage
10016035	Face presentation
10036656	Previous caesarean section
10065942	Molar abortion
10076714	Umbilical cord occlusion
10064534	Umbilical cord haemorrhage
10045453	Umbilical cord short
10079122	Umbilical cord cyst
10064270	Omphalorrhexis
10045447	Umbilical cord around neck
10045451	Umbilical cord compression
10045452	Umbilical cord prolapse
10045454	Umbilical cord vascular disorder
10071652	Umbilical cord thrombosis
10048596	Umbilical cord abnormality
10084854	Abnormal cord insertion
10067731	Umbilical granuloma
10035119	Placenta praevia
10035121	Placenta praevia haemorrhage
10047036	Vasa praevia
10062936	Placenta accreta
10036556	Pregnancy
10061452	Complication of pregnancy
10070538	Gestational hypertension
10020614	Hyperemesis gravidarum
10067010	Anaphylactoid syndrome of pregnancy

Preferred language coding	Preferred Language English
10089358	Gestational rhinitis
10018981	Haemorrhage in pregnancy
10049975	Uterine contractions during pregnancy
10090561	Gestational hyperthyroidism
10078085	Somatic symptom disorder of pregnancy
10063412	Gestational oedema
10018209	Gestational diabetes
10052397	Third trimester pregnancy
10052395	First trimester pregnancy
10052396	Second trimester pregnancy
10049469	Gestational trophoblastic detachment
10049058	HELLP syndrome
10072596	Subchorionic haematoma
10080381	Chorioamniotic separation
10071010	Subchorionic haemorrhage
10063639	Biochemical pregnancy
10082976	Lithopedion
10063671	Pregnancy after post coital contraception
10016142	Failed trial of labour
10038773	Retained products of conception
10067553	Tubal rupture
10071398	Vanishing twin syndrome
10024787	Locked twins
10045188	Twin pregnancy
10082173	Placenta duplex
10042062	Stillbirth
10086915	Increased foetal movements
10016871	Foetal-maternal haemorrhage
10016846	Foetal arm prolapse
10061191	Haemorrhage foetal
10061157	Foetal disorder
10016855	Foetal distress syndrome
10083545	Foetal dystocia
10077628	Foetal compartment fluid collection
10070531	Foetal growth restriction
10077582	Foetal growth abnormality
10020529	Hydrops foetalis
10055690	Foetal death
10050347	Foetal acidosis
10016852	Foetal damage
10052088	Foetal cardiac disorder
10085689	Foetal vascular malperfusion
10016862	Foetal malnutrition
10068461	Foetal hypokinesia
10051132	Meconium abnormal
10027059	Meconium increased
10036603	Premature rupture of membranes
10054810	Placental dysplasia
10068326	Placental hypertrophy
10082008	Placental calcification
10064620	Placental infarction
10035138	Placental insufficiency
10054798	Retroplacental haematoma
10081737	Placental lake
10035139	Placental necrosis
10038758	Retained placenta or membranes
10091393	Uteroplacental acute atherosis
10035132	Placental disorder
10083196	Placental cyst
10088054	Placental oedema
10035142	Placental polyp
10036608	Premature separation of placenta
10046255	Unstable foetal lie
10016863	Foetal malposition
10058013	Foetal malpresentation
10008020	Cephalo-pelvic disproportion
10082614	Asynclitic presentation
10068735	Decidual cast
10006346	Breech delivery
10006356	Breech presentation
10061614	Abortion complete
10052847	Abortion late
10056392	Perinatal brain damage
10049430	Peripartum cardiomyopathy
10072693	Peripartum haemorrhage
10078342	Risk of future pregnancy miscarriage
10079814	Anembryonic gestation
10062935	Habitual abortion
10036562	Pregnancy in habitual aborter
10043508	Threatened labour
10000242	Abortion threatened
10036485	Pre-eclampsia
10072038	Small size placenta
10041092	Small for dates baby
10052849	Oblique presentation
10050504	Leukopenia neonatal
10023138	Jaundice neonatal
10028934	Neonatal disorder
10028976	Neonatal thyrotoxicosis
10072588	Pseudomenstruation neonatal
10052851	Anaesthetic complication neonatal
10086943	Hypoxic ischaemic encephalopathy neonatal

Preferred language coding	Preferred Language English
10006241	Breast engorgement in newborn
10001391	Adrenocortical insufficiency neonatal
10050080	Hypothermia neonatal
10050086	Poor weight gain neonatal
10047894	Weight decrease neonatal
10008014	Cephalhaematoma
10012186	Delayed delivery
10073027	Prolonged rupture of membranes
10051641	Amniorrhexis
10060936	Amniotic cavity disorder
10051133	Meconium in amniotic fluid
10036079	Polyhydramnios
10030289	Oligohydramnios
10066470	Amniorrhoea
10045542	Unintended pregnancy
10060927	Abnormal product of conception
10014166	Ectopic pregnancy
10066266	Abortion of ectopic pregnancy
10048407	Ruptured ectopic pregnancy
10021718	Induced labour
10016123	Failed induction of labour
10091364	Cryptic pregnancy
10087497	Subaponeurotic cerebrospinal fluid collection of infancy
10057673	Maternal condition affecting foetus
10056391	Maternal distress during labour
10088758	Maternal disease complicating pregnancy
10086743	Maternal death
10026912	Maternal death affecting foetus
10087010	Excessive maternal gestational weight gain
10087013	Maternal pre-pregnancy obesity
10087011	Maternal pre-pregnancy underweight
10036600	Premature labour
10036590	Premature baby
10073024	Preterm premature rupture of membranes
10052846	Abortion early
10082625	Lactation normal
10049081	Normal foetus
10029769	Normal newborn
10063122	Pregnancy with implant contraceptive
10059107	Missed labour
10066288	Uterine hyperstimulation
10079273	Cervical dilatation
10046796	Uterine inversion
10061400	Uterine contractions abnormal
10079224	Uterine irritability
10021648	Incoordinate uterine action
10082029	Uterine hypokinesia
10046790	Uterine hypertonus
10046792	Uterine hypotonus
10046763	Uterine atony
10014129	Eclampsia
10000238	Abortion spontaneous complicated
10000236	Abortion spontaneous complete complicated
10000234	Abortion spontaneous
10061616	Abortion spontaneous complete
10087390	Spontaneous rupture of membranes
10061617	Abortion spontaneous incomplete
10080681	Term baby
10072953	Term birth

1.4 Statistical analysis

All statistical analyses and data mining were performed using SAS9.4 software and Microsoft Excel 2019. Chi-square test was used to compare drug-related pregnancy adverse effects between severe and non-severe groups.

2. Mining results of adverse pregnancy events

2.1 Analysis of clinical characteristics of drug-related adverse pregnancy events

From the first quarter of 2004 to the first quarter of 2025, a total of 22775812 patient reported data were extracted from the FAERS database, and 33843 patients with ADE were analyzed, including 33502 (98.99%) female patients and 127 (0.38%) male patients. Although the proportion of male factors in this report is small, the risk of adverse events caused by male factors cannot be ignored. The median age of the reported target ADE patients was 30.00 years. A total of 18258 patients (53.95%) reported data from the United States, followed by 1580 patients (4.67%) from Germany, 1398 patients (4.13%) from the

United Kingdom, and 394 patients (1.16%) from China. Among the outcomes, there were 29998 severe outcomes, accounting for 88.64%. Serious outcomes included 755 cases (2.23%) of life-threatening patients, 6715 cases (19.84%) of hospitalization, 278 cases (0.82%) of disability, 306 cases (0.9%) of death, and 381 cases (0.98%) of congenital malformations (see Table 4).

Table 4 Characteristics of AEs reports

Index	Cases (%)
Sex	
Female	33502(98.99)
Male	127(0.38)
Not Specified	214(0.63)
Age	
<18	0(0.00)
18-44	33394(98.67)
45-64	449(1.33)
⩾65	0(0.00)
NotSpecified	0(0.00)
Year of Report	
2004	667(1.97)
2005	667(1.97)
2006	766(2.26)
2007	776(2.29)
2008	912(2.69)
2009	1021(3.02)
2010	1408(4.16)
2011	1522(4.50)
2012	1775(5.24)
2013	1697(5.01)
2014	1623(4.80)
2015	1893(5.59)
2016	1663(4.91)
2017	1906(5.63)
2018	2279(6.73)
2019	2783(8.22)
2020	2534(7.49)
2021	2326(6.87)
2022	1890(5.58)
2023	1736(5.13)
2024	1562(4.62)
2025	437(1.29)
Reporter	
Consumer	11782(34.81)
Lawyer	288(0.85)
Not Specified	3176(9.38)
Other health-professional	4813(14.22)
Pharmacist	3366(9.95)
Physician	10418(30.78)
Reporting countries	
United States of America(%)	18258(53.95)
Not Specified(%)	1794(5.30)
Germany(%)	1580(4.67)
United Kiongdom(%)	1398(4.13)
France(%)	1390(4.11)
Canada(%)	993(2.93)
Brazil(%)	909(2.69)
Japan(%)	807(2.38)
China(%)	394(1.16)
Netherlands(%)	377(1.11)
Serious	29998(88.64)
Non-Serious	3845(11.36)
outcome	
Life-Threatening	755(2.23)
Hospitalization - Initial or Prolonged	6715(19.84)
Disability	278(0.82)
Death	306(0.90)
Congenital Anomaly	331(0.98)
Required Intervention to Prevent Permanent Impairment/Damage	257(0.76)
Other	26884(79.44)
Adverse events were categorized by time-to-event (in days).	
0-30d	3477(10.27)
31-60d	996(2.94)
61-90d	870(2.57)
91-120d	838(2.48)
121-150d	613(1.81)

2.2The identification of pregnancy signals and the timing of specific adverse reactions associated with each drug were analyzed using the Weibull distribution.

After data extraction and screening, a total of 1266 "primary suspected drugs" involved in the target ADE were reported, and 112 drugs met the signal detection of this study. It included drugs for skin diseases, drugs for digestive and metabolic system, drugs for blood and hematopoietic

organs, anti-tumor and immunomodulatory drugs, etc. After signal calculation according to ROR, PRR, and BCPNN, the following conclusions were drawn: the drugs included levonorgestrel, hydroxyprogesterone, etonogestrel, retinoic acid, mifepristone, pesilizumab, levetiracetam, and ethinyl estradiol. Etonogestrel, aripiprazole, nifedipine; The median time of adverse pregnancy events caused by each drug exposure was different. For example, there were 3088 cases of adverse pregnancy events caused by levonorgestrel, and the median time of occurrence was 249.5 days during pregnancy. There were 1440 cases of adverse pregnancy events caused by mifepristone, with a median of 70 days during pregnancy (see Table 5 for details).

TABLE 5 Time-to-onset analysis using the Weibull distribution test.

			Weibull distribution			
	Cases	TTO (days)	Scale parameter		Shape parameter	
DrugName	n	Median(IQR)	α	95% CI	β	95% CI
Levonorgestrel	3088	249.50(20.00,657.00)	474.01	452.47 - 496.57	0.87	0.84 - 0.89
Hydroxyprogesterone	1440	70.00(26.00,106.00)	85.42	82.74 - 88.20	1.80	1.72 - 1.89
Isotretinoin	965	97.00(40.00,167.00)	140.68	130.11 - 152.10	0.86	0.83 - 0.90
Etonogestrel	768	205.50(16.50,599.50)	407.69	370.81 - 448.24	0.86	0.81 - 0.92
Emtricitabine;tenofovir Disoproxil	228	83.50(26.00,166.50)	138.78	118.92 - 161.96	0.92	0.83 - 1.02
Certolizumab Pegol	200	18.00(0.00,278.00)	395.66	306.71 - 510.41	0.77	0.66 - 0.89
Medroxyprogesterone	200	131.50(44.00,581.00)	453.11	360.81 - 569.01	0.70	0.62 - 0.78
Ethinylestradiol;etonogestrel	177	219.00(63.00,486.00)	407.57	332.64 - 499.39	0.78	0.70 - 0.87
Misoprostol	163	0.00(0.00,0.00)	9.20	4.66 - 18.14	0.50	0.40 - 0.62
Drospirenone;ethinylestradiol	137	243.00(69.00,705.00)	564.17	449.72 - 707.75	0.83	0.72 - 0.95
Dinoprostone	74	0.00(0.00,0.00)	2.93	1.12 - 7.69	0.60	0.43 - 0.85
Ethinylestradiol;norelgestromin	63	135.00(60.00,365.00)	276.05	210.75 - 361.59	1.02	0.83 - 1.26
Aripiprazole	62	367.50(122.00,669.00)	587.10	452.50 - 761.74	1.06	0.87 - 1.30
Ondansetron	59	178.00(121.00,207.00)	191.29	167.25 - 218.79	2.05	1.65 - 2.55
Ethinylestradiol;norgestimate	56	257.50(89.00,738.50)	480.84	348.91 - 662.66	0.88	0.71 - 1.08
Oxytocin	49	0.00(0.00,0.00)	1.00	1.00 - 1.00	3998.69	3998.69 - 3998.69
Ulipristal	46	26.00(12.00,36.00)	44.95	34.53 - 58.52	1.30	1.06 - 1.60
Enoxaparin	44	19.50(0.00,45.50)	84.20	50.69 - 139.85	0.76	0.57 - 1.01
Ethinylestradiol;levonorgestrel	44	280.50(62.00,1036.00)	713.21	441.02 - 1153.39	0.68	0.53 - 0.87
Imiglucerase	31	2585.00(228.00,4265.00)	2670.39	1705.90 - 4180.17	0.82	0.61 - 1.11
Follitropin Alfa	31	58.00(46.00,92.00)	97.80	63.40 - 150.87	0.89	0.71 - 1.13
Cladribine	30	416.00(230.00,801.00)	547.58	407.09 - 736.55	1.26	0.93 - 1.71
Progesterone	27	6.00(0.00,31.00)	50.74	22.87 - 112.57	0.62	0.44 - 0.87
Levetiracetam	27	245.00(0.00,930.00)	792.71	434.77 - 1445.34	0.77	0.55 - 1.07
Anti-D Immunoglobulin	26	3.00(0.00,42.00)	37.63	21.55 - 65.71	0.92	0.60 - 1.40
Oseltamivir	25	11.00(2.00,46.00)	46.15	23.61 - 90.23	0.69	0.50 - 0.97
Acitretin	24	348.50(182.50,698.50)	712.10	441.70 - 1148.05	0.91	0.67 - 1.23
Ethinylestradiol;iron;norethisterone	22	86.50(17.00,214.00)	216.97	110.11 - 427.54	0.72	0.51 - 1.02
Ethinylestradiol;norgestrel	20	482.50(131.00,1108.00)	789.10	484.71 - 1284.64	0.98	0.69 - 1.38
Follitropin Beta	19	38.00(24.00,62.00)	56.41	41.17 - 77.29	1.51	1.08 - 2.12
Bictegravir;emtricitabine;tenofovir Alafenamide	17	191.00(127.00,469.00)	401.01	222.63 - 722.34	0.85	0.60 - 1.23
Velaglucerase Alfa	16	1761.00(455.00,3989.50)	2325.14	1223.67 - 4418.08	0.80	0.54 - 1.19
Sapropterin	16	853.00(86.00,1271.00)	1234.96	660.72 - 2308.28	0.88	0.58 - 1.34
Tenofovir Disoproxil	15	174.00(0.00,532.00)	432.50	266.62 - 701.60	1.29	0.81 - 2.05
Cabergoline	15	567.00(242.00,1607.00)	815.25	504.71 - 1316.86	1.15	0.75 - 1.76
Entecavir	14	448.50(324.00,1005.00)	748.51	491.39 - 1140.16	1.37	0.90 - 2.07
Ethinylestradiol	13	152.00(31.00,241.00)	319.66	141.07 - 724.33	0.76	0.49 - 1.18
Clomifene	13	33.00(25.00,182.00)	99.98	49.26 - 202.92	0.81	0.53 - 1.24
Dienogest;estradiol	12	145.50(75.50,218.50)	250.50	138.50 - 453.08	1.06	0.68 - 1.64
Phentermine;topiramate	11	39.00(18.00,82.00)	56.03	34.42 - 91.21	1.28	0.82 - 2.01
Telbivudine	11	124.00(20.00,154.00)	140.29	103.67 - 189.83	2.24	1.26 - 3.98
Dolutegravir;lamivudine;tenofovir Disoproxil	11	529.00(249.00,641.00)	817.19	421.61 - 1583.90	0.95	0.62 - 1.45
Cobicistat;elvitegravir;emtricitabine;tenofovir	11	236.00(54.00,452.00)	316.56	210.69 - 475.63	1.69	0.99 - 2.88
Clotrimazole	10	0.50(0.00,9.00)	10.69	4.00 - 28.62	0.94	0.47 - 1.89
Emtricitabine;rilpivirine;tenofovir Alafenamide	9	396.00(249.00,1039.00)	719.70	456.91 - 1133.64	1.60	0.89 - 2.87
Emtricitabine;rilpivirine;tenofovir Disoproxil	9	200.00(163.00,370.00)	396.18	185.14 - 847.80	0.96	0.57 - 1.62
Tinzaparin	9	0.00(0.00,44.00)	529.01	74.88 - 3737.17	0.61	0.26 - 1.47
Citric Acid;lactic Acid;potassium Bitartrate	9	82.00(30.00,200.00)	116.44	61.37 - 220.93	1.08	0.65 - 1.81
Mifepristone	9	14.00(2.00,22.00)	19.45	10.82 - 34.97	1.24	0.69 - 2.22
Bromocriptine	9	127.00(41.00,283.00)	431.08	181.29 - 1025.02	0.91	0.51 - 1.60
Sibutramine	8	40.50(23.50,67.00)	78.82	36.31 - 171.10	0.95	0.59 - 1.54
Norethisterone	8	260.00(10.50,506.00)	406.28	219.01 - 753.70	1.34	0.66 - 2.73
Leflunomide	7	609.00(238.00,1059.00)	698.69	450.49 - 1083.62	1.78	0.98 - 3.24
Dalteparin	7	54.00(0.00,68.00)	82.91	57.95 - 118.63	2.91	1.41 - 6.02
Methylergometrine	7	0.00(0.00,4.00)	7.33	4.47 - 12.02	2.96	0.93 - 9.39
Norgestrel	7	89.00(54.00,362.00)	329.55	101.54 - 1069.60	0.67	0.39 - 1.14
Zanamivir	6	48.00(8.00,78.00)	72.79	36.58 - 144.84	1.34	0.66 - 2.71
Ethinylestradiol;norethisterone	6	310.00(30.00,1400.00)	670.40	235.73 - 1906.61	0.88	0.42 - 1.84
Ganirelix	6	54.50(49.00,59.00)	84.94	38.74 - 186.25	1.08	0.60 - 1.95
Mebendazole	5	0.00(0.00,0.00)	1.00	1.00 - 1.00	3998.69	3998.69 - 3998.69
Methyldopa	5	27.00(0.00,55.00)	82.24	39.87 - 169.63	1.66	0.68 - 4.04
Nicardipine	5	3.00(2.00,7.00)	5.67	3.49 - 9.24	2.12	0.94 - 4.80
Acetylsalicylic Acid	5	25.00(0.00,41.00)	64.96	32.85 - 128.45	1.76	0.73 - 4.25
Atazanavir	4	82.50(51.00,152.00)	113.38	57.85 - 222.24	1.54	0.72 - 3.30
Abacavir;lamivudine;zidovudine	4	47.50(26.00,66.00)	51.95	32.28 - 83.59	2.16	0.94 - 4.95
Albendazole	4	20.50(0.00,136.00)	149.24	52.00 - 428.37	1.39	0.44 - 4.41
Hydralazine	4	15.50(0.00,65.50)	74.38	36.41 - 151.95	2.05	0.65 - 6.50
Tazarotene	4	55.50(50.50,1636.00)	392.75	50.44 - 3058.10	0.51	0.25 - 1.04
Desogestrel;ethinylestradiol	4	605.00(161.00,3220.50)	1256.50	265.16 - 5954.13	0.67	0.31 - 1.42
Drospirenone	4	141.00(77.00,270.00)	190.07	89.33 - 404.42	1.37	0.63 - 2.98
Ritonavir	3	75.00(29.00,78.00)	68.06	47.51 - 97.50	3.28	1.17 - 9.19
Efavirenz;lamivudine;tenofovir	3	203.00(139.00,465.00)	306.12	171.45 - 546.56	2.07	0.86 - 4.99
Hydroxycarbamide	3	17.00(0.00,1385.00)	455.60	31.12 - 6669.27	0.55	0.17 - 1.73
Chorionic Gonadotrophin	3	7.00(7.00,11.00)	9.11	7.05 - 11.78	4.68	1.97 - 11.15
Nifedipine	3	0.00(0.00,39.00)	39.00	38.98 - 39.02	3998.69	3998.69 - 3998.69
Ampicillin	3	0.00(0.00,1.00)	1.00	1.00 - 1.00	3998.69	3998.69 - 3998.69
Insulin Bovine;insulin Porcine	2	3302.00(1095.00,5509.00)	3662.53	1367.26 - 9810.97	1.49	0.47 - 4.71
Zidovudine	2	46.00(0.00,92.00)	92.00	91.95 - 92.05	3998.69	3998.69 - 3998.69
Nevirapine	2	443.00(27.00,859.00)	358.36	43.44 - 2956.29	0.69	0.22 - 2.20
Contraceptives	2	1015.50(619.00,1412.00)	1146.41	693.29 - 1895.69	2.91	0.92 - 9.24
Estradiol;nomegestrol	2	15.50(0.00,31.00)	31.00	30.98 - 31.02	3998.69	3998.69 - 3998.69
Doxylamine;pyridoxine	2	2.50(0.00,5.00)	5.00	5.00 - 5.00	3998.69	3998.69 - 3998.69
Terbutaline	2	3629.50(99.00,7160.00)	2427.28	178.31 - 33041.9	0.56	0.18 - 1.78
Carteolol	2	1461.00(0.00,2922.00)	2922.00	2920.57 - 2923.43	3998.69	3998.69 - 3998.69
Betamethasone	2	1.50(1.00,2.00)	1.68	1.10 - 2.56	3.46	1.09 - 10.99
Ursodeoxycholic Acid	1	1558.00(1558.00,1558.00)	1558.00	1557.24 - 1558.76	3998.69	3998.69 - 3998.69
Isoniazid;pyrazinamide;rifampicin	1	152.00(152.00,152.00)	152.00	151.93 - 152.07	3998.69	3998.69 - 3998.69
Efavirenz	1	0.00(0.00,0.00)	.	. - .	.	. - .
Artemether;lumefantrine	1	23.00(23.00,23.00)	23.00	22.99 - 23.01	3998.69	3998.69 - 3998.69
Vonicog Alfa	1	0.00(0.00,0.00)	.	. - .	.	. - .
Nonoxinol	1	2.00(2.00,2.00)	2.00	2.00 - 2.00	3998.69	3998.69 - 3998.69
Ritodrine	1	0.00(0.00,0.00)	.	. - .	.	. - .
Desogestrel	1	233.00(233.00,233.00)	233.00	232.89 - 233.11	3998.69	3998.69 - 3998.69

	Cases	TTO (days)	Weibull distribution			
			Scale parameter		Shape parameter	
DrugName	n	Median(IQR)	α	95% CI	β	95% CI
Human Menopausal Gonadotrophin	1	23.00(23.00,23.00)	23.00	22.99 - 23.01	3998.69	3998.69 - 3998.69
Indometacin	1	0.00(0.00,0.00)	.	. - .	.	. - .

2.3 ATC Classification of Drug-Related Adverse Pregnancy Events

The selected medications were categorized into the following therapeutic classes according to theAnatomical Therapeutic Chemical (ATC) classification system: antineoplastic and immunomodulating agents, dermatologicals, nervous system agents, systemic anti-infectives, genitourinary system and sex hormones, and musculoskeletal system drugs (refer to Table 6 for detailed classifications).

TABLE 6 ATC system classification and drugs involved in PT

药物分类英文名称	药物名称（英文）	PT
BLOOD AND BLOOD FORMING ORGANS	ENOXAPARIN	Abortion spontaneous
	ICATIBANT	Pregnancy
	WARFARIN	Pregnancy
	ALTEPLASE	Pregnancy
	LANADELUMAB	Pregnancy
	HEPARIN	Foetal death
	TINZAPARIN	Premature labour
	EPOPROSTENOL	Pregnancy
	DALTEPARIN	Abortion
	FOLIC ACID	Premature delivery
	RIVAROXABAN	Postpartum haemorrhage
	EPTACOG ALFA (ACTIVATED)	Postpartum haemorrhage
	ELTROMBOPAG	Normal newborn
	COMPLEMENT C1 ESTERASE INHIBITOR	Delivery
CARDIOVASCULAR SYSTEM	BOSENTAN	Pregnancy
	METHYLDOPA	Live birth
	VALSARTAN	Oligohydramnios
	METOPROLOL	Premature delivery
	NIFEDIPINE	Premature delivery
	HYDRALAZINE	Premature delivery
	LISINOPRIL	Oligohydramnios
	CANDESARTAN	Oligohydramnios
	NICARDIPINE	Premature labour
	DIGOXIN	Premature delivery
	OLMESARTAN	Oligohydramnios
	LOSARTAN	Oligohydramnios
	IRBESARTAN	Pregnancy
	IVABRADINE	First trimester pregnancy
	FUROSEMIDE	Premature delivery
	NADOLOL	Oligohydramnios
	SOTALOL	Pre-eclampsia
	RAMIPRIL	Placental insufficiency
ALIMENTARY TRACT AND METABOLISM	ATORVASTATIN	Morning sickness
	ONDANSETRON	Premature delivery
	IMIGLUCERASE	Abortion spontaneous
	METFORMIN	Live birth
	VELAGLUCERASE ALFA	Pregnancy
	SAPROPTERIN	Abortion spontaneous
	INSULIN HUMAN	Premature labour
	INSULIN DETEMIR	Abortion spontaneous
	SIBUTRAMINE	Abortion spontaneous
	INSULIN LISPRO	Premature labour
	ALGLUCOSIDASE ALFA	Abortion spontaneous
	MESALAZINE	Pregnancy
	INSULIN ASPART	Stillbirth
	URSODEOXYCHOLIC ACID	Gestational diabetes
	TEGASEROD	Normal newborn
	RABEPRAZOLE	Pregnancy
	CALCITRIOL	Premature delivery
	ROSIGLITAZONE	Peripartum cardiomyopathy
	LARONIDASE	Pregnancy
GENITO URINARY SYSTEM AND SEX HORMONES	LEVONORGESTREL	Pregnancy with contraceptive device
	HYDROXYPROGESTERONE	Premature delivery
	ETONOGESTREL	Unintended pregnancy
	MEDROXYPROGESTERONE	Unintended pregnancy
	ULIPRISTAL	Unintended pregnancy
	MISOPROSTOL	Uterine tachysystole
	ESTRADIOL	Pregnancy on oral contraceptive
	PROGESTERONE	Abortion spontaneous
	FOLLITROPIN ALFA	Abortion spontaneous
	NORETHISTERONE	Pregnancy on oral contraceptive
	DINOPROSTONE	Premature separation of placenta
	CLOMIFENE	Ectopic pregnancy
	FOLLITROPIN BETA	Abortion
	DROSPIRENONE	Pregnancy on oral contraceptive
	ETHINYLESTRADIOL	Pregnancy on oral contraceptive
	NORGESTREL	Unintended pregnancy
	MIFEPRISTONE	Abortion incomplete
	FINASTERIDE	Hyperemesis gravidarum
	DESOGESTREL	Abortion spontaneous
	CHORIONIC GONADOTROPHIN	Abortion spontaneous
	METHYLERGOMETRINE	Abortion
	CONTRACEPTIVES	Pregnancy with contraceptive device
	HUMAN MENOPAUSAL ONADOTROPHIN	Abortion spontaneous
	DOXAZOSIN	Abortion spontaneous
	TADALAFIL	Twin pregnancy
ADRENOCORTICAL HORMONE DRUGS	DEXAMETHASONE	Premature delivery
	BETAMETHASONE	Premature delivery
	PREDNISONE	Premature delivery
	PREDNISOLONE	Live birth
	HYDROCORTISONE	Normal newborn
NERVOUS SYSTEM	CABERGOLINE	Abortion spontaneous
	METHADONE	Premature delivery
	LEVETIRACETAM	Pregnancy
	LAMOTRIGINE	Abortion spontaneous
	ARIPIPRAZOLE	Abortion spontaneous
	ESCITALOPRAM	Pregnancy
	BUPRENORPHINE	Abortion spontaneous
	NALTREXONE	Pregnancy
	QUETIAPINE	Gestational diabetes
	VALPROIC ACID	Abortion spontaneous
	CARBAMAZEPINE	Abortion spontaneous
	TOPIRAMATE	Abortion spontaneous

药物分类英文名称	药物名称（英文）	PT
	PAROXETINE	Pregnancy
	OLANZAPINE	Gestational diabetes
	OXYBATE SODIUM	Pregnancy
	VENLAFAXINE	Foetal death
	CITALOPRAM	Pregnancy
	LACOSAMIDE	Pregnancy
	RISPERIDONE	Somatic symptom disorder of pregnancy
	SERTRALINE	Pre-eclampsia
	FLUOXETINE	Premature labour
	VORTIOXETINE	Pregnancy
	EPTINEZUMAB	Pregnancy
	CLOMIPRAMINE	Premature baby
	BUTORPHANOL	Pregnancy
	CLONAZEPAM	Pregnancy
	ZONISAMIDE	Abortion spontaneous
	LURASIDONE	Pregnancy
	OXCARBAZEPINE	Normal newborn
	SUMATRIPTAN	Pre-eclampsia
	ZOLPIDEM	Eclampsia
	RIZATRIPTAN	Abortion spontaneous
	ZOLMITRIPTAN	Abortion spontaneous
	MODAFINIL	Abortion spontaneous
	ZIPRASIDONE	Abortion
	MIRTAZAPINE	Biochemical pregnancy
	VARENICLINE	Placental disorder
	TRAMADOL	Stillbirth
	CLOBAZAM	Pregnancy
	PERAMPANEL	Abortion spontaneous
	BUSPIRONE	Pregnancy
	METHYLPHENIDATE	Abortion
	OSELTAMIVIR	Pregnancy
	TENOFOVIR DISOPROXIL	Abortion spontaneous
	LAMIVUDINE	Abortion spontaneous
	TELBIVUDINE	Normal newborn
	ANTI-D IMMUNOGLOBULIN	Abortion spontaneous
	ENTECAVIR	Abortion spontaneous
	DOXYCYCLINE	Premature rupture of membranes
	EFAVIRENZ	Pregnancy
	AMPICILLIN	Premature delivery
	ADEFOVIR	Abortion spontaneous
	NEVIRAPINE	Premature delivery
ANTIINFECTIVES FOR SYSTEMIC USE	ZANAMIVIR	Live birth
	AZITHROMYCIN	Normal newborn
	MEROPENEM	Abnormal labour
	ATAZANAVIR	Pregnancy
	RIBAVIRIN	Anembryonic gestation
	AMOXICILLIN	Live birth
	DOLUTEGRAVIR	Abortion spontaneous
	RALTEGRAVIR	Pregnancy
	CLINDAMYCIN	Premature labour
	CLARITHROMYCIN	Premature baby
	CEFTRIAXONE	Premature separation of placenta
	VALACICLOVIR	Live birth
	IMMUNOGLOBULIN HUMAN NORMAL	Placental disorder
	OCTREOTIDE	Normal newborn
	THIAMAZOLE	Premature delivery
	BROMOCRIPTINE	Normal newborn
	THYROTROPIN ALFA	Abortion spontaneous
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	DESMOPRESSIN	Live birth
	LEVOTHYROXINE	Live birth
	OXYTOCIN	Postpartum haemorrhage
	ELAGOLIX	Live birth
	GANIRELIX	Abortion
	FUMARIC ACID	Abortion spontaneous
	DEFERASIROX	Pregnancy
VARIOUS	IODINE (131 I)	Abortion spontaneous
	METYRAPONE	Premature baby
	DEFEROXAMINE	Premature baby
	ISOTRETINOIN	Unintended pregnancy
	BOTULINUM TOXIN TYPE A	Pregnancy
	TACROLIMUS	Premature delivery
	ACITRETIN	Pregnancy
	FLUCONAZOLE	Abortion spontaneous
	DIPHENHYDRAMINE	Foetal death
	ACICLOVIR	Abortion spontaneous
	TAZAROTENE	Pregnancy
DERMATOLOGICALS	CLOTRIMAZOLE	Abortion spontaneous
	KETOCONAZOLE	Abortion spontaneous
	ITRACONAZOLE	Abortion spontaneous
	MICONAZOLE	Pregnancy
	INTERFERON ALFA-2B	Pregnancy
	LEVOCETIRIZINE	Pregnancy
	TIOCONAZOLE	Pregnancy
	DESLORATADINE	Abortion spontaneous
	NATALIZUMAB	Abortion spontaneous
	INTERFERON BETA-1A	Abortion spontaneous
	VEDOLIZUMAB	Pregnancy
	ADALIMUMAB	Live birth
	CERTOLIZUMAB PEGOL	Abortion spontaneous
	FINGOLIMOD	Normal newborn
	RISANKIZUMAB	Abortion spontaneous
	PEGINTERFERON BETA-1A	Abortion spontaneous
	GLATIRAMER	Normal newborn
	SECUKINUMAB	Normal newborn
	INFLIXIMAB	Premature labour
	MYCOPHENOLIC ACID	Abortion spontaneous
	IMATINIB	Normal newborn
	NILOTINIB	Normal newborn
	RITUXIMAB	Pregnancy
	ECULIZUMAB	Pregnancy
	CLADRIBINE	Abortion spontaneous
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	TRASTUZUMAB	Pregnancy
	ETANERCEPT	Induced labour
	LETROZOLE	Abortion spontaneous
	BELIMUMAB	Live birth
	LEFLUNOMIDE	Abortion spontaneous
	HYDROXYCHLOROQUINE	Stillbirth
	OFATUMUMAB	Normal newborn
	PEGINTERFERON ALFA-2A	Abortion spontaneous
	METHOTREXATE	Ruptured ectopic pregnancy
	INTERFERON BETA-1B	Premature labour
	DOXORUBICIN	Peripartum cardiomyopathy
	LEUPRORELIN	Foetal death
	HYDROXYCARBAMIDE	Abortion spontaneous
	CICLOSPORIN	Normal newborn
	PONATINIB	Pregnancy
	DASATINIB	Normal newborn
	CANAKINUMAB	Normal newborn
	THALIDOMIDE	Normal newborn
	SARILUMAB	Live birth

药物分类英文名称	药物名称（英文）	PT
	EPIRUBICIN	Placental disorder
	GOSERELIN	Abortion spontaneous
	TRIPTORELIN	Unintended pregnancy
	FILGRASTIM	Gestational diabetes
	OZANIMOD	Live birth
	AZATHIOPRINE	Foetal death
	CELECOXIB	Preterm premature rupture of membranes
	ERLOTINIB	Oligohydramnios
	USTEKINUMAB	Delivery
	PACLITAXEL	Oligohydramnios
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	ALBENDAZOLE	Abortion spontaneous
	MEBENDAZOLE	Abortion spontaneous
	ACETYLSALICYLIC ACID	Premature delivery
ANTIPYRETIC, ANALGESIC AND ANTI-INFLAMMATORY AGENTS	IBUPROFEN	Oligohydramnios
	DICLOFENAC	Oligohydramnios
	PARACETAMOL	Premature labour
	INDOMETACIN	Premature delivery
	DORNASE ALFA	Pregnancy
RESPIRATORY SYSTEM;BLOOD AND BLOOD FORMING ORGANS	SALBUTAMOL	Live birth
	PSEUDOEPHEDRINE	Premature labour
SENSORY ORGANS	LATANOPROST	Pregnancy

2.4 Different outcomes and occurrence time of drug-related adverse pregnancy events

The study found that the 112 signal drugs of drug expose-related APE were analyzed by Weber distribution, and the median time of adverse pregnancy events was 146d[IQR28.00-578.00], as shown in Figure 1. About 34.16% of the APE occurred > 360 days after drug use and 25.86% of the APE occurred 0-30 days after drug use (see Figure 2). According to Figure 3, the median occurrence time of adverse pregnancy events with death adverse outcome was 32.00 days [IQR1.00-299.00], and the median occurrence time of adverse pregnancy events with non-death adverse outcome was 147.00 days [IQR29.00-579.00] (see Figure 3 for details). The main outcomes were severe outcomes (29998 cases, 88.64%). Among them, 755 cases (2.23%), 6715 cases (19.84%) were hospitalized, 278 cases (0.82%) were disabled, 306 cases (0.9%) died, and 381 cases (0.98%) were congenital malformations (see Figure 4).

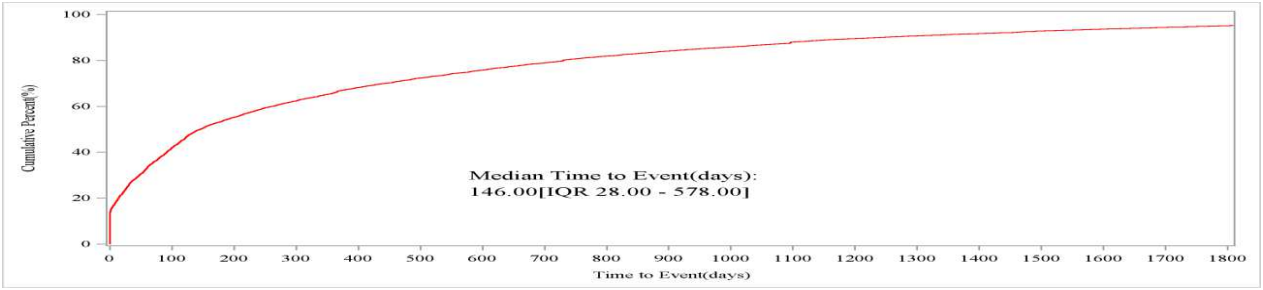

Figure 1 Timing of drug-related adverse pregnancy events

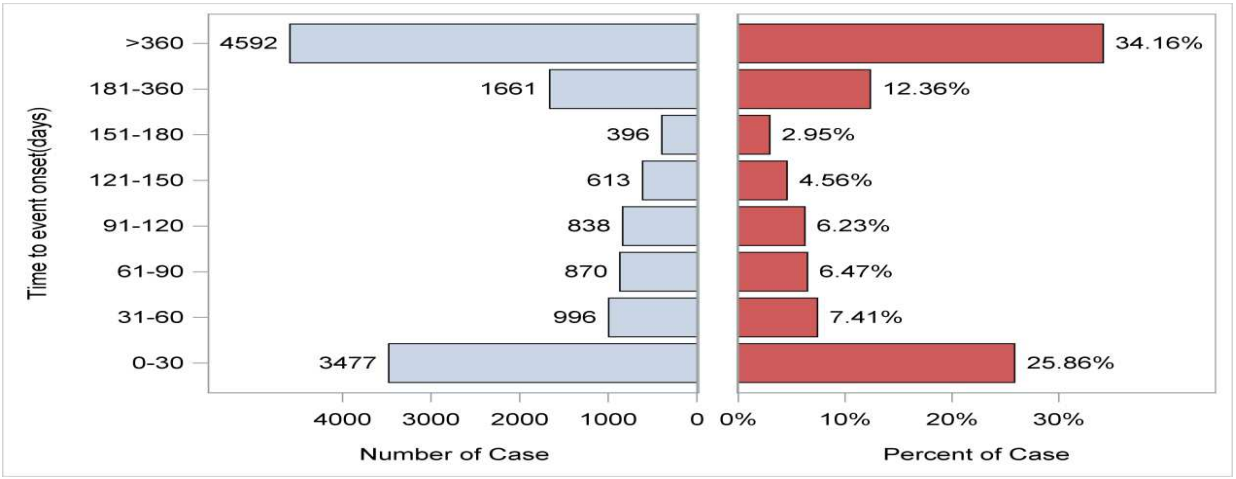

Figure 2 Proportion plot of time to occurrence of drug-related adverse pregnancy events

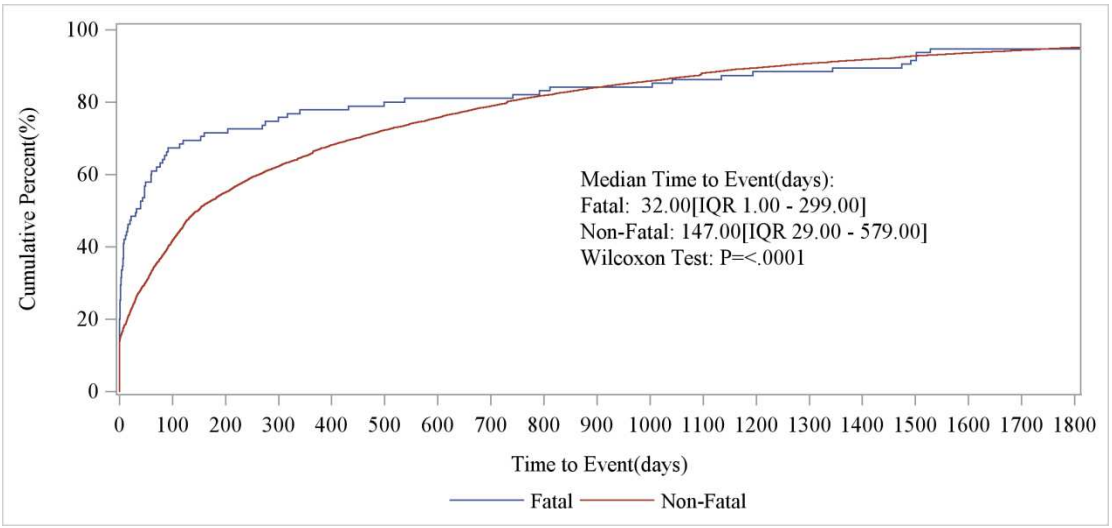

Figure 3 Timing of death and nondeath outcomes for adverse pregnancy events

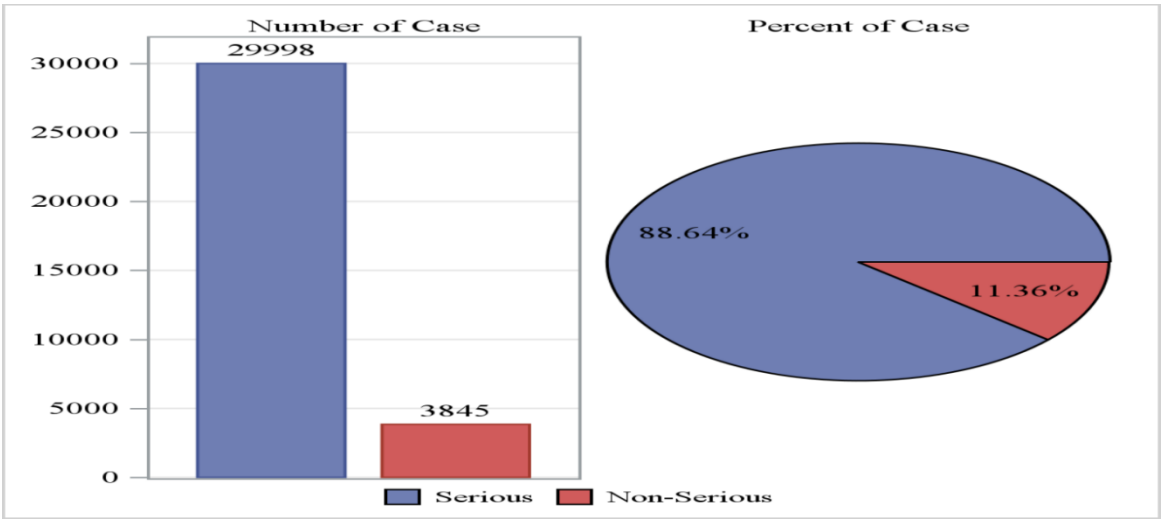

Figure 4A

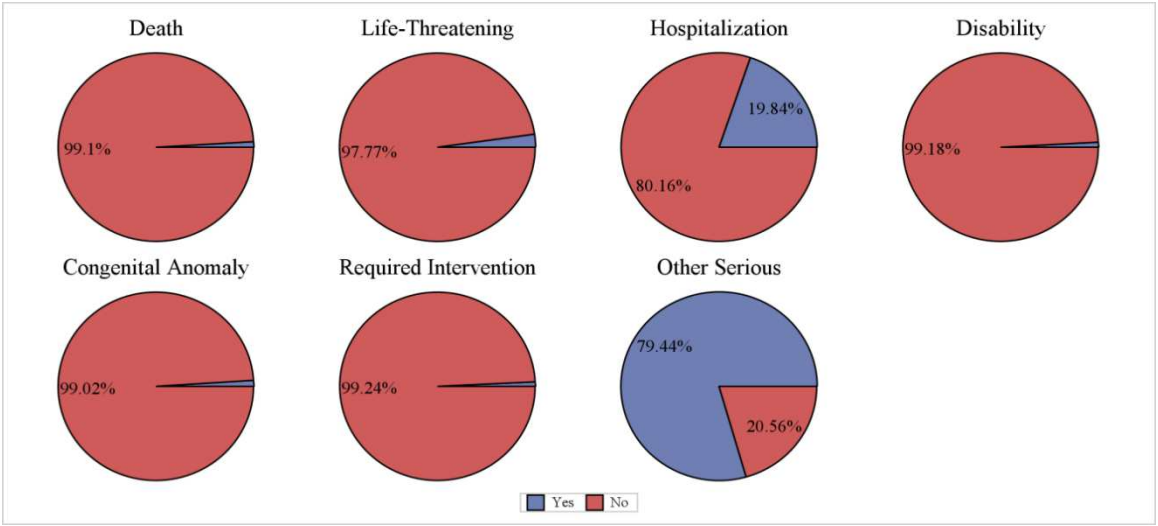

Figure 4B

Figure 4A、Figure 4B Distribution of pregnancy outcomes

3 Discuss

After reading the relevant literature, it is found that there are few research reports on adverse pregnancy events related to drug exposure. This study mainly analyzes the drug signals related to adverse pregnancy events, the time of occurrence and the clinical outcome of patients by mining faers database, and summarizes the clinical characteristics of adverse pregnancy events related to drug exposure [2]. The data show an increasing prevalence of medication use during pregnancy, with about 97% of pregnant women using at least one or more medicines during pregnancy and about 30% using at least five or more medicines18[3]. In addition, the prevalence of polydrug use during pregnancy increased from 2.8% to 10.0%. Therefore, a comprehensive assessment of drug exposure is critical for both maternal and fetal safety. This work is helpful for professionals to better avoid the occurrence of adverse events during pregnancy caused by various drugs and improve clinical safety.

3.1 Basic information of adverse pregnancy events

In the context of adverse pregnancy outcomes, women constitute the overwhelming majority；however，men still account for a small proportion—0.31%. Although this percentage is low, male factors exert a non-negligible influence on reproductive health. For instance, commonly used medications such as cimetidine, colchicine, cyclophosphamide, and methotrexate have been shown to affect male fertility. Cimetidine may lead to reversible impotence, while cyclophosphamide can result in azoospermia, oligospermia, and impaired spermatogenesis. Therefore, appropriate clinical attention should be directed toward medication use among men of reproductive age. In both daily life and clinical practice, emphasis is often placed on the safety of pregnant women and fetal development, whereas paternal health prior to conception tends to be overlooked. Evidence indicates that male fertility is closely associated with lifestyle habits and psychological well-being. According to the American Society for Reproductive Medicine, paternal obesity and metabolic disorders negatively impact semen quality and fertility outcomes. With rising obesity rates, research has increasingly suggested a potential causal relationship between paternal body mass index, metabolic health, and an elevated risk of male infertility [4]. While reproductive risks have received growing attention, fewer studies have focused specifically on the impact of male-related factors on time-to-pregnancy. Existing evidence demonstrates that many drugs can impair the male reproductive system through multiple mechanisms. Among these, traditional chemotherapeutic agents exhibit the most pronounced adverse effects. Approximately 15% to 30% of male cancer survivors experience fertility-related complications [5-6].

3.2 Occurrence time and outcome of drug-related adverse pregnancy events

In the outcome analysis, it was found that in addition to some unspecified serious adverse reports, the proportion of adverse outcomes such as fetal malformation, death, and hospitalization was as high as 30.78%. Studies have shown that drug exposure during pregnancy is associated with preterm birth, cesarean section, low birth weight, and fetal malformations. Drug use significantly increases the risk of pregnancy and alters the outcome of pregnancy. According to this study, the median occurrence time of adverse events of drug exposure during pregnancy was 121 days, and the majority of drug-related adverse events occurred more than 360 days after drug use, accounting for about 31.27%, which may be caused by the long-term use of drugs before pregnancy or the gradual increase of cumu

lative dosage after drug use in pregnant patients with chronic diseases, such as antiviral drugs, antineoplastic drugs, etc. The median time of adverse outcome of death was about 60 days after treatment, which may be related to the fact that the patient did not confirm pregnancy in early pregnancy and the fetus had not yet fully developed. According to relevant literature, drug treatment during pregnancy has gradually become common, such as levonorgestrel, hydroxyprogesterone, etonogestrel and other tocolic drugs in this study. The frequency of skin diseases such as isotretinoin, diphenhydramine, pregabalin and gabapentin is increasing year by year[6]. Moreover, drug use has been shown to be more frequent in the first trimester than in the second or third trimesters. According to this study, the adverse events of each drug during pregnancy are different. For example, the median time of levonorgestrel is about 235 days of pregnancy, most of mifepristone occurs on the 14th day of pregnancy, and the adverse reactions of isotretinic acid occur in the early pregnancy, about 98 days. Therefore, it is necessary to pay special attention to the time and cumulative dose of drug use in pregnant women and girls of appropriate age.

3.3 Drugs of each system involved abnormal PT signals

By analyzing the extracted data, PT signals associated with different drug exposures can be identified. Normal pregnancies were not considered for inclusion because of the lack of study significance. Abnormal PT signals include spontaneous abortion, labor arrest, premature delivery, fetal malformation and fetal death. High-signal drugs associated with fetal death include diphenhydramine, magnesium sulfate, heparin, tranexamic acid, and tetracycline, among others. The PT signal involved in cromolyn was arrest of labor. Ranizumab used in the sensory organ system, budesonide, montelukast, phenylephrine, epinephrine, enoxaparin and dipyridamole used in the respiratory system are all related to this PT signal. Duloxetine, ivermectin, albendazole and quinine for nervous system drugs; hydroxyurea, leuprorelin, tretinoin, mepolizumab and natalizumab for antineoplastic and immunomodulatory drugs; minoxidil, antifungal drugs, cetirizine and omalizumab for skin diseases; All showed high signal intensity with spontaneous abortion. The abnormal PT signals extracted from the drugs used in the musculoskeletal system, such as piroxicam, ketoprofen, ibuprofen and diclofenac, were oligohynios. Paclitaxel was implicated in oligohydramnios. Sirolimus, tacrolimus, prednisone, methylprednisolone, dexamethasone, ampicillin and hydroxychloroquine can lead to early delivery. Isotretinoin can cause fetal malformations. Doxycycline and ofloxacin in systemic anti-infective drugs can lead to missed abortion.

3.4 APE involved in each system

According to various ATC system classifications, this study explored the association between drug exposure and adverse pregnancy outcomes, providing an important basis for rational drug use during pregnancy. However, due to the limitations of existing studies, this article mainly focuses on the following drug categories: anti-tumor drugs and immunomodulators, dermatological drugs, nervous system drugs, systemic anti-infective drugs, genitourinary system and sex hormone drugs, and musculoskeletal system drugs. The details are described below.

3.4.1 This paragraph focuses on the analysis of the effects of antineoplastic drugs and immunomodulators on pregnancy. Adverse pregnancy events related to exposure to antineoplastic drugs and immunosuppressive drugs For pregnant patients with abnormal immune function, it is recommended that whether to maintain or discontinue immunosuppressive dr

ugs during pregnancy should be decided according to specific circumstances, mainly depen ding on the patient's disease activity [7]. For example, rituximab may be associated with f etal exposure during pregnancy. However, Wu Jie et al. used rituximab injection to treat a case of critically ill patients with primary Sjogren's syndrome and neuromyelitis optica sp ectrum disorders during pregnancy, and the patient recovered well after rituximab infusion [8]. Furthermore, in a systematic review of anti-CD20 therapy with 19 monoclonal antibod ies, rituximab had lower drug concentrations in breast milk. In the systematic review of m onoclonal antibodies, 368 breastfed infants did not develop developmental delay during a f ollow-up period of at least 6 months [9]. The level of hydroxychloroquine dosage is assoc iated with preterm birth and lower gestational age in patients with systemic lupus erythem atosus (SLE) [10]. Thalidomide is associated with fetal congenital malformations when use d to treat anxiety and insomnia and as an antiemetic [11].

3.4.2 Dermatological drugs related to adverse reactions in pregnancy mainly include is otretinoin, diphenhydramine, pregabalin, itraconazole, adapalene, acitretin, tacrolimus, etc. Is otretinoin has been shown to pose A teratogenic risk and may cause spontaneous abortion [8]. Combined with the relevant studies in recent years and the instructions, it can be pro ved that retinoids have teratogenic risk. Diphenhydramine is mainly related to maternal ex posure during pregnancy, and its use may increase the incidence of cleft lip and palate, in guinal hernia and genitourinary malformations in infants. Pregabalin inhibits abnormal nerv e impulses and is commonly used to treat herpetic neuralgia, but it may cause anhedonia and erectile dysfunction. At present, data on the risk of gabapentin or pregabalin use duri ng pregnancy are unclear. Studies in animals have shown that gabapentin may increase the risks of congenital malformations and fetal death, whereas pregabalin may increase the ri sks of congenital malformations and developmental toxic manifestations[12]. However, anot her study noted no evidence that pregabalin significantly increased the risk of congenital malformations[13]. Therefore, women of reproductive age need to be fully and carefully in formed about these risks.

3.4.3 Medication of nervous system: it includes antiepileptic drugs and antidepressant drugs, and antiepileptic drugs include carbamazepine, levetiracetam, lamotrigine, valproic ac id and topiramate, etc. Antidepressants are mainly benzodiazepines. Carbamazepine, levetira cetam, lamotrigine, and topiramate are thought to be associated with neurodevelopmental c onditions, with a substantially increased risk of autism and intellectual disability in the chi ldren of mothers who received antiepileptic treatment during pregnancy[14].A Nordic study reported a twofold increase in the incidence of neurodevelopmental disorders in children of mothers with epilepsy who took topiramate during pregnancy, as compared with those who did not[15]. In 1983, the French Registry of Birth Defects conducted the first case-co ntrol study in the area of medication safety to explore the potential association between v alproic acid and spina bifida. Subsequent studies in 2019 finally confirmed the teratogenici ty of valproic acid and other antiepileptic drugs [7]. With regard to benzodiazepines, first-t rimester exposure was associated with a modest increased risk for overall malformations a nd cardiac defects, particularly at higher daily doses. However, both absolute risk and pop ulation attributable fraction were low. Despite the potential risks, the therapeutic value of benzodiazepines for their primary indications needs to be weighed. If it must be used, the lowest effective dose should be prescribed to minimize risk [16].

3.4.4 APE related to systemic anti-infective drugs: this kind of drugs mainly includes macrolides and β-lactams. Antibiotic exposure increases risk for preterm birth in a population-based cohort study. Use of clindamycin, quinolones, or macrolides during pregnancy may cause fetal malformations. In addition, animal studies have shown that prenatal antibiotic exposure is associated with multiple complications, including adverse outcomes such as miscarriage and low birth weight [17]. Studies have shown that tetracycline exposure during the first trimester is not associated with an increased risk of major congenital malformations (MCMs) [19]. The study also showed that TMP-SMX-exposed infants had a higher risk of any malformations compared with β-lactam exposed infants; However, the risk of malformations in infants exposed to nitrofurantoin was similar to that in infants exposed to β-lactam [18].

3.4.5 Genitourinary system and sex hormone drugs are mainly divided into contraceptives and tocolysis drugs. Contraceptives are mainly levonorgestrel, and antitocolic drugs include hydroxyprogesterone, etogestrel, mifepristone and dinoprostone. Studies have shown that a shorter duration of estrogen exposure may increase the risk of early miscarriage, even if it achieves the desired endometrial thickness. On the contrary, a longer duration of estrogen exposure is not beneficial to the general patient, but may increase the incidence of adverse events such as vaginal bleeding [20-21]. However, there is no evidence that levonorgestrel emergency contraception affects fetal development, miscarriage or stillbirth [22-24]. In addition, tocolysis progestins have little or no effect on the live birth rate of women with threatened or recurrent miscarriage [25].

3.4.6 Musculoskeletal drugs include bisphosphonates such as alendronate, zoledronic acid and pamidronate. Data available in the literature suggest that such drugs have no significant teratogenic effects, but women with systemic disease have a higher rate of neonatal complications and women with bone disease have an increased rate of miscarriage. This may be related to the severity of the underlying disease and concomitant medication [26]. Studies have shown that the use of bisphosphonates before and during early pregnancy may not pose a significant risk to the fetus [27]. However, the potential harm to the mother and fetus should be weighed when using bisphosphonates during pregnancy. In cases where there is a clear or relative indication for bisphosphonate use before pregnancy, close monitoring of the mother and baby is essential, especially during the first two weeks after delivery, to ensure a successful pregnancy [28].

3.4.7 Cardiovascular drugs: Antihypertensive drugs are one of the most commonly used drugs during pregnancy. Methyldopa, labetalol, and nifedipine are considered safe for use during pregnancy and are recommended in international guidelines for the treatment of hypertension[29]. However, this study shows that antihypertensive drugs show high signal in adverse events of pregnancy caused by cardiovascular system drugs, so attention should be paid to the dosage of antihypertensive drugs and the balance of advantages and disadvantages.

3.4.8 Administration of blood and hematopoietic organs: According to the relevant literature, this paper mainly discusses aspirin and low molecular weight heparin drugs. Pregnancy is a prothrombotic state that increases the risk of thromboembolic events. Venous thromboembolism events are one of the leading causes of maternal death in developed countries. In addition, the literature suggests that exposure to enoxaparin during the first trimester

is not associated with an increased risk of major congenital malformations, nor is exposure during the third trimester associated with an increased risk of low birth weight [30]. The study also showed that the use of aspirin combined with low molecular weight heparin during pregnancy was associated with a lower rate of miscarriage than the use of aspirin alone during pregnancy.

In conclusion, when using drugs during pregnancy, the pros and cons should be weighed and the dosage should be mastered. Finally, drugs with low signal and low frequency in each ATC system are also studied in this paper, but these low signal drugs have not been discussed due to research limitations.

4 Summary

This study conducted a real-world data analysis of drugs that may cause adverse reactions during pregnancy based on FAERS database, which provided some guidance for clinical medication. The occurrence of adverse pregnancy events related to drug exposure may be due to a variety of factors, such as drug accumulation caused by long-term medication in patients with chronic diseases, drug treatment in early pregnancy when women are unaware of their pregnancy, and long-term use of tocolysis drugs. Therefore, it is necessary to weigh the pros and cons and make reasonable decisions when selecting drugs. However, this study has some limitations because FAERS data belong to a spontaneous reporting system, and the database cannot accurately calculate the probability of adverse effects of pregnancy caused by specific drugs. Further prospective studies and large-scale clinical trials are needed to verify the findings of this study and obtain more convincing evidence.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationship that could be interpreted as a potential conflict of interest.All participants agreed to participate.

Author contributions

FuXu contributed to literature searching and wrote the manuscript.WU Ai-lin2,Ye Ding-xun 1, FAN Ke-lin1designed figures and a table. Meng Xia and Di Wei supervised the study and revised the manuscript.All authors contributed to the article and approved the submitted version.

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