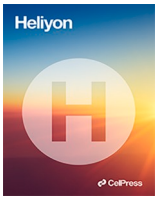
Heliyon 10 (2024) e37547

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Pregnancy related adverse events and congenital disorders associated with fluoroquinolones: A real-world pharmacovigilance study of the FDA adverse event reporting system (FAERS)

Dao-chun Xiang [a,1], Wen-long Xie [a,1], Gang-ying Cheng [a], Ming Yue [a], Xiao-yi Du [b,*], Jue Jiang [c,**]

[a] *Department of Pharmacy, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430014, China*
[b] *Department of Pediatrics, Maternal and Child Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430070, China*
[c] *Institute of Infection, Immunology and Tumor Microenvironment, School of Medicine, Wuhan University of Science and Technology, Wuhan 430065, China*

ARTICLE INFO

Keywords:
Fluoroquinolone
Pharmacovigilance
FAERS
Disproportionality analysis
Spontaneous abortion
Congenital disorders

ABSTRACT

Background: Fluoroquinolones, including ciprofloxacin, levofloxacin, and moxifloxacin, are extensively employed as broad-spectrum antibacterial agents. However, their use is discouraged during pregnancy due to potential adverse events (AEs). The aim of this study is to systematically investigate the association between fluoroquinolones (specifically ciprofloxacin, levofloxacin, and moxifloxacin) and AEs related to pregnancy, as well as their potential impact on congenital disorders.

Methods: A disproportionality analysis was conducted utilizing FDA Adverse Event Reporting System (FAERS) data spanning from the first quarter of 2004 to September 2023. The objective was to identify potential AEs signatures associated with fluoroquinolones through conducting reporting odds ratios (RORs) and Bayesian confidence propagation neural networks (BCPNN). Assessing the potential risk of pregnancy-associated AEs involved comparing each fluoroquinolone with all other medications. Additionally, in-depth comparative analyses were carried out between various fluoroquinolones and a reference drug (azithromycin).

Results: A total of 1159 cases were identified, involving AEs related to pregnancy and congenital disorders. Obvious disproportionate association of abortion spontaneous and other nine AEs was identified for fluoroquinolone during gestation. Upon comparison with all the other drugs, ciprofloxacin exhibited an elevated risk of spontaneous abortion, non-site specific bone disorders congenital and 10 other significant signals. Levofloxacin demonstrated an increased risk of congenital tongue disorders and three other significant signals. Moxifloxacin displayed a noteworthy signal indicating multiple congenital cardiac abnormalities.

Conclusions: We present compelling evidence regarding pregnancy-related AEs and congenital disorders linked to fluoroquinolones. Considering perinatal and genotoxicity aspects, we explore

* Corresponding author.
** Corresponding author.
E-mail addresses: duxy166@126.com (X.-y. Du), juejiang@wust.edu.cn (J. Jiang).
[1] These authors contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.heliyon.2024.e37547
Received 19 April 2024; Received in revised form 2 September 2024; Accepted 4 September 2024
Available online 7 September 2024

whether levofloxacin or moxifloxacin might be preferable when fluoroquinolones are deemed necessary to balance the benefits of pregnant women and fetuses.

1. Introduction

Fluoroquinolones are synthetic broad-spectrum antimicrobial agents that act by inhibiting DNA cyclase and topoisomerase IV. This direct inhibition of bacterial DNA synthesis [1] makes fluoroquinolones highly effective antibiotics. They possess favorable pharmacokinetic properties, including high oral bioavailability, a large volume of distribution, and a broad antimicrobial spectrum. Consequently, they are widely used in treating gastrointestinal, respiratory, genitourinary, and ophthalmic infections [2]. The third to fourth generation of fluoroquinolones such as ciprofloxacin, levofloxacin, and moxifloxacin, demonstrate significantly increased antimicrobial activity compared to previous generations. They are commonly used in clinical practice due to their strong antimicrobial capacity against Gram-positive and anaerobic bacteria [3]. The decision to use them for relatively serious infections must be carefully weighed against the associated benefits and risks. Although fluoroquinolones are well-tolerated most of the time, certain adverse events (AEs) have been reported. The common AEs are generally mild and may include gastrointestinal discomfort, headache, dizziness, or temporary altered states of mind or sleep. Although the exact incidence is not known, it has been estimated that the incidence of gastrointestinal and central nervous system AEs to fluoroquinolones is three times higher than that of other antibiotics [4].

While fluoroquinolones demonstrate efficacy against numerous pathogenic bacteria, their administration during pregnancy poses significant concerns. Their mechanism of action, which inhibits DNA synthesis, can lead to fetal organ failure or malformations. Extensive clinical research has underscored various AEs associated with fluoroquinolones, such as tendonitis or tendon rupture, phototoxicity, QT interval prolongation, anaphylaxis, and teratogenic effects [5]. Notably, fluoroquinolones exhibit a high rate of placental penetration [6]. Studies on Beagles indicated that maternal exposure to these drugs caused irreversible cartilage damage in offspring [7]. Furthermore, a nested case-control study linked quinolone use in early pregnancy to a heightened risk of spontaneous abortion [8]. Given these findings, the general recommendation is to avoid fluoroquinolones during pregnancy and lactation unless there are no alternative therapies available. Nevertheless, clinical observations reveal a rising trend in administering this class of drugs to women of childbearing age. This trend can be attributed to the prevalent nature of urinary tract infections among women, with a high recurrence rate [9]. Additionally, *Mycoplasma genitalium* which affects up to 80 % of sexually mature women, is sensitive to fluoroquinolones [10]. The statistic that nearly half of pregnancies in the United States are unplanned [11],suggests a potential for inadvertent exposure of pregnant women to fluoroquinolones. This highlights the pressing need to address the risks associated with fluoroquinolone exposure during pregnancy. Alarmingly, women exposed to these drugs often opt for therapeutic abortions due to perceived significant risks [12]. Yet, it's essential to note the scarcity of comprehensive clinical data regarding the safety of fluoroquinolone use in pregnant women. Harnessing pharmacovigilance analyses, particularly those derived from real-world sources of the FDA adverse event reporting system (FAERS) database, can offer pivotal insights for optimizing clinical medication practices.

Here, we prioritized extracted AEs with potential safety implications based on clinical significance. We obtained real-world fluoroquinolone-related data from the FAERS database to identify preventive measures and their clinical importance. By the disproportionality analyses of AEs associated with various fluoroquinolones for pregnancy-related and congenital disorders, we assessed the safety profiles of different medication regimens. We also conducted a comparative analysis between azithromycin and fluoroquinolones as equivalent drugs. Our data supplies crucial insights into antibiotics choices for pregnant women or those with suspected pregnancies. Additionally, it offers substantial guidance on the judicious use of fluoroquinolones in necessary medical conditions.

2. Materials and methods

2.1. Data source and study design

All AE data for this study were obtained from the FAERS database. The Medical Dictionary for Regulatory Activities (MedDRA) standardizes medical terminology for clinical trials, and AEs in the FAERS are recorded as preferred terms (PTs) or lowest level terms (LLTs), and the PTs or LLTs are coded according to High Level Terms (HLTs) in the MedDRA terminology. These HLTs can be attributed and associated based on their primary system organ classes (SOCs). In this manuscript, we choose two SOCs for analysis, which were "pregnancy, puerperium and perinatal conditions" (SOC code: 10036585) and "congenital, familial and genetic disorders" (SOC code: 10010331). We conducted a retrospective pharmacovigilance study on fluoroquinolone spanning from the first quarter of 2004 (Q1 2004) to the third quarter of 2023 (Q3 2023). Fluoroquinolone was considered as the primary focus, and only data reaching a predefined quality level were included in our analysis. The data de-duplication rules are the same as previous study [13]: as the instruction of FAERS database, PRIMARYlD is the primary key between data files, the unique number for identifying a FAERS report. In this study, the most recent FDA DT (the date FDA received the case) with the same CASElD (the abbreviation of number for identifying a FAERS case) was selected, or when the CASElD and FDA DT were the same, the higher PRIMARYID was selected to deduplicate reports as FDA's recommendations. The target drugs and related trade names are detailed in Supplementary Table S1. The drug's role in the AE is coded with "role_code", which specifically coding as "PS" (primary suspect), "SS" (secondary suspect), "C" (concomitant) and "I" (interacting) for each drug in event. In this analysis, the "role_code" was chosen as "PS" and those reported as "SS", "C" or "I" were excluded.

2.2. Data analysis

Disproportionality analysis based on individual case safety reports are widely used to detect safety signals [14–16]. Specific analysis applied in our study include the reporting odds ratio (ROR), and Bayesian confidence propagation neural network method (BCPNN) [17]. BCPNN is a classic technique used for data mining of AEs by the World Health Organization Uppsala Monitoring Centre since 1998 [18], and ROR is more sensitivity for detecting uncommon AEs compare to BCPNN [19]. In order to identify each possible AE signal, and discuss the credibility, these two methods were used for analysis. The total number of AE for each HLT of the target drug constituted the 'a' value, 'b' represented the number of reports containing other AEs of the target drug, 'c' represented the number of reports containing the target AE of other drugs; and 'd' represented the number of reports containing other drugs and other AEs. Detail equations and criteria can be found in Supplementary Table S2. A significant disproportionality should meet the criteria listed as: (1) the number of cases greater than or equal to 3 (a $\geq$3); (2) the lower limit of 95 % confidence interval (CI) of ROR should be greater than 1 (ROR_{025} > 1), or the lower end of 95 % CI of the information component higher than 0 (IC025 > 0). When a signal was significant by two methods, the credibility increases. In this study, we adopted the HLT and SOC in the MedDRA version 26.1 to categorize and describe AEs. All data processing and statistical analyses were performed using SAS 9.4, Microsoft EXCEL 2019 and GraphPad Prism 8.0.1. The flow diagram is presented in Fig. 1.

To investigate the potential risks of fluoroquinolones, three comparisons were employed in the study. First, each fluoroquinolone was compared with all the other drugs. Second, each fluoroquinolone was compared with all the other fluoroquinolones. Third, with a determination that benefits outweigh potential harms, azithromycin administration is recommended for pregnant women [20], it was supposed to have a low risk of pregnancy-related AEs. Each specific fluoroquinolone was compared to azithromycin, which and were taken as the reference drugs for relative comparison.

3. Results

3.1. General characteristics

During the study period (Q1 2004-Q3 2023), 20,340,254 reports were collected from the FAERS database. After excluding duplicates, 11,743 case reports implicated fluoroquinolone as the PS resulting in 73,709 associated AEs with fluoroquinolone. Among these, 1159 were related to the "pregnancy, puerperium, and perinatal conditions", and "congenital, familial and genetic disorders". Demographic characteristics are detailed in Table 1. Health professionals submitted 82.47 % of the related AEs to the FAERS. The

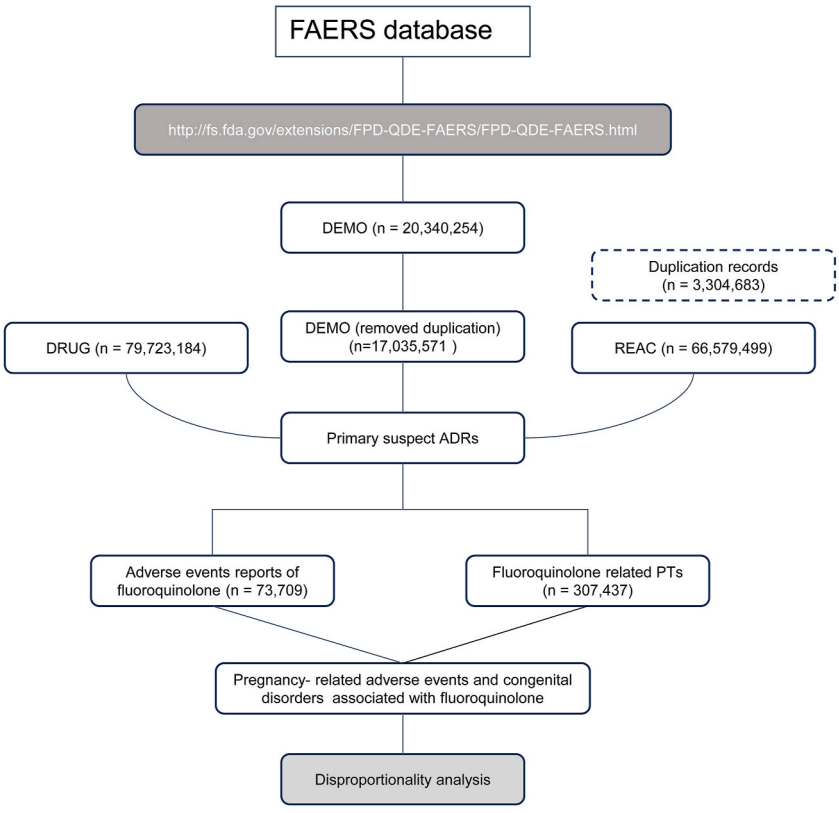


Fig. 1. The flow diagram of selecting Fluoroquinolone-related AEs from FAERS database.

majority of reports originated from Canada (49.63 %), followed by Germany (10.42 %) and the United States (9.59 %). Notably, Ciprofloxacin accounted for 75.28 % of AEs, followed by levofloxacin. The data reveals an increase in fluoroquinolone-related AEs reported between 2018 and 2020 (15.41 %, 30.54 %, and 16.70 %, respectively). Despite initial contraindications during pregnancy, fluoroquinolone-associated pregnancy-related AEs have been reported from Q1 2004 to Q3 2023, reflecting their potential clinical application in pregnant women in real world. A study on antibiotics (including quinolones) in pregnancy initiated in Canada was published in 2017 [8], possibly explaining why Canada contributed the most reports in later years.

3.2. Signals associated with fluoroquinolones compared with all the other drugs

When comparing fluoroquinolones with all the other drugs (Table 2), disproportionality analysis showed an increased risk of spontaneous abortions, with ROR values of 2.61 (95 % CI, 2.40–2.84). Moreover, fluoroquinolones were concerned with a higher rate of AEs in congenital, familial and genetic disorders compared to all other drugs. The significant HLT included "coagulation disorders congenital" (N = 46; ROR 4.43; 95 % CI, 3.31–5.94; IC025, 0.45), "genetic mitochondrial abnormalities" (N = 32; ROR 6.51; 95 % CI, 4.57–9.27; IC025, 0.99), "skin and subcutaneous tissue disorders congenital" (N = 26; ROR 1.60; 95 % CI, 1.09–2.36; IC025, -0.99), "connective tissue disorders congenital" (N = 21; ROR 4.50; 95 % CI, 2.92–6.95; IC025, 0.47), "tongue disorders congenital" (N = 21; ROR 6.76; 95 % CI, 4.37–10.45; IC025, 1.04), "ocular disorders congenital" (N = 19; ROR 1.71; 95 % CI, 1.09–2.69; IC025, -0.9), "respiratory tract disorders congenital" (N = 15; ROR 6.97; 95 % CI, 4.16–11.69; IC025, 1.08), "inborn errors of amino acid metabolism" (N = 9; ROR 2.67; 95 % CI, 1.38–5.15; IC025, -0.27), and "inborn errors of metabolism" (N = 5; ROR 2.65; 95 % CI, 1.09–6.40;

Table 1
Clinical characteristics of reports with fluoroquinolone from the FAERS database (Q1 2004 to Q3 2023).

Characteristics	Case number, n	Case proportion, %
Total	**1084**	
Reported countries (the top ten)		
Canada	538	49.63
Germany	113	10.42
United States of America	104	9.59
United Kingdom	91	8.39
Italy	26	2.40
Netherlands	22	2.03
France	19	1.75
China	17	1.57
Spain	16	1.48
India	14	1.29
Medication n (%)		
Ciprofloxacin	816	75.28
Levofloxacin	179	16.51
Moxifloxacin	89	8.21
Reported person		
Health profession	**894**	**82.47**
Physician	148	13.65
Pharmacist	26	2.40
Other health-professional	720	66.42
Non-healthcare professional	**190**	**17.53**
Consumer	149	13.75
Others	41	3.78
Reporting year		
2004	12	1.11
2005	11	1.01
2006	10	0.92
2007	12	1.11
2008	16	1.48
2009	6	0.55
2010	12	1.11
2011	4	0.37
2012	17	1.57
2013	8	0.74
2014	35	3.23
2015	19	1.75
2016	29	2.68
2017	26	2.40
2018	167	15.41
2019	331	30.54
2020	181	16.70
2021	64	5.90
2022	77	7.10
2023 (Q1, Q2 and Q3)	47	4.34

Table 2
Signal strength of reports of fluoroquinolones at the High Level Terms (HLTs) level in FAERS database.

HLT	N	ROR(95%,CI)	IC025
Abortions spontaneous	553	2.61(2.40-2.84)*	-0.30
Gestational age and weight conditions	63	0.27(0.21-0.35)	-3.54
Coagulation disorders congenital	46	4.43(3.31-5.94)*	0.45*
Labour onset and length abnormalities	34	0.24(0.17-0.34)	-3.71
Genetic mitochondrial abnormalities	32	6.51(4.57-9.27)*	0.99*
Stillbirth and foetal death	31	0.49(0.35-0.70)	-2.68
Skin and subcutaneous tissue disorders congenital	26	1.60(1.09-2.36)*	-0.99
Connective tissue disorders congenital	21	4.50(2.92-6.95)*	0.47*
Tongue disorders congenital	21	6.76(4.37-10.45)*	1.04*
Ocular disorders congenital	19	1.71(1.09-2.69)*	-0.90
Gene mutations and other alterations	18	0.25(0.16-0.40)	-3.65
Musculoskeletal and connective tissue disorders of limbs congenital	18	0.30(0.19-0.47)	-3.42
Central nervous system disorders congenital	15	0.45(0.27-0.75)	-2.82
Respiratory tract disorders congenital	15	6.97(4.16-11.69)	1.08*
Maternal complications of pregnancy	13	0.24(0.14-0.42)	-3.70
Cardiac disorders congenital	13	0.37(0.21-0.63)	-3.10
Neurological disorders congenital	11	0.79(0.44-1.44)	-2.00
Male reproductive tract disorders congenital	11	0.37(0.21-0.68)	-3.08
Abortions not specified as induced or spontaneous	10	0.28(0.15-0.52)	-3.50
Inborn errors of porphyrin metabolism	10	1.23(0.66-2.29)	-1.37
Foetal growth complications	9	0.24(0.13-0.47)	-3.70
Cardiac septal defects congenital	9	0.10(0.05-0.20)	-4.95
Inborn errors of amino acid metabolism	9	2.67(1.38-5.15)*	-0.27
Normal pregnancy, labour and delivery	7	0.04(0.02-0.09)	-6.17
Gastric disorders congenital	7	1.30(0.62-2.73)	-1.29
Congenital disorders	7	0.09(0.04-0.20)	-5.07
Foetal complications	7	0.26(0.12-0.55)	-3.59
Non-site specific muscle disorders congenital	7	1.62(0.77-3.41)	-0.98
Non-site specific bone disorders congenital	7	1.25(0.59-2.62)	-1.35
Pulmonary and bronchial disorders congenital	6	0.16(0.07-0.35)	-4.33
Hypertension associated disorders of pregnancy	6	0.17(0.07-0.37)	-4.25
Musculoskeletal and connective tissue disorders of spine congenital	6	0.91(0.41-2.03)	-1.81
Vascular anomalies congenital	6	0.32(0.14-0.71)	-3.31
Persistent foetal circulation disorders	5	0.18(0.08-0.44)	-4.12
Cardiovascular disorders congenital	5	0.59(0.24-1.42)	-2.43
Renal disorders congenital	5	0.18(0.07-0.42)	-4.16
Inborn errors of metabolism	5	2.65(1.09-6.40)*	-0.28
Unintended pregnancies	4	0.02(0.01-0.07)	-6.98
Multiple cardiac abnormalities congenital	4	0.60(0.23-1.61)	-2.40

* Indicates statistically significant signals in algorithm. N, the number of cases; the ROR, reporting odds ratio; CI, confidence interval; IC025, the lower end of 95 % CI of the information component.

Table 3
Signal strength of reports of each specific fluoroquinolone at the High Level Terms (HLTs) level in FAERS database.

HLT	Ciprofloxacin			Moxifloxacin			Levofloxacin		
	N	ROR(95%,CI)	IC025	N	ROR(95%,CI)	IC025	N	ROR(95%,CI)	IC025
Abortions spontaneous	486	4.61(4.21-5.04)*	0.52*	7	0.18(0.08-0.35)	-4.27	60	0.93(0.72-1.20)	-1.77
Gestational age and weight conditions	48	0.41(0.31-0.55)	-2.93	8	0.17(0.09-0.35)	-4.18	7	0.10(0.05-0.21)	-4.98
Coagulation disorders congenital	27	5.16(3.53-7.55)*	0.68*	0			19	5.99(3.81-9.42)*	0.90*
Labour onset and length abnormalities	25	0.36(0.24-0.53)	-3.15	3	0.11(0.03-0.33)	-4.88	6	0.14(0.06-0.31)	-4.49
Genetic mitochondrial abnormalities	26	10.54(7.13-15.58)*	1.69*	2	1.99(0.50-7.97)	-0.68	4	2.62(0.98-6.99)	-0.29
Stillbirth and foetal death	17	0.54(0.34-0.87)	-2.55	11	0.89(0.49-1.60)	-1.84	3	0.16(0.05-0.49)	-4.32
Skin and subcutaneous tissue disorders congenital	22	2.71(1.78-4.13)*	-0.23	3	0.93(0.30-2.88)	-1.77	1	0.20(0.03-1.44)	-3.97
Connective tissue disorders congenital	16	6.84(4.17-11.22)*	1.08*	0			5	3.49(1.45-8.42)*	0.13*
Tongue disorders congenital	8	5.04(2.51-10.12)*	0.64*	0			13	13.70(7.90-23.75)*	2.07*
Ocular disorders congenital	12	2.16(1.22-3.81)*	-0.56	3	1.36(0.44-4.21)	-1.23	4	1.19(0.44-3.17)	-1.42
Gene mutations and other alterations	14	0.39(0.23-0.66)	-3.02	1	0.07(0.01-0.50)	-5.49	3	0.14(0.04-0.43)	-4.51
Musculoskeletal and connective tissue disorders of limbs congenital	11	0.36(0.20-0.66)	-3.13	2	0.17(0.04-0.67)	-4.25	5	0.27(0.11-0.66)	-3.54
Central nervous system disorders congenital	12	0.72(0.41-1.27)	-2.14	3	0.45(0.15-1.41)	-2.80	0		
Respiratory tract disorders congenital	9	8.25(4.26-15.99)*	1.34*	0			6	9.04(4.04-20.27)*	1.48*
Maternal complications of pregnancy	5	0.19(0.08-0.45)	-4.08	0			8	0.50(0.25-0.99)	-2.67
Cardiac disorders congenital	2	0.11(0.03-0.45)	-4.80	4	0.57(0.22-1.53)	-2.47	7	0.66(0.31-1.38)	-2.27
Neurological disorders congenital	5	0.72(0.30-1.74)	-2.14	1	0.36(0.05-2.59)	-3.12	5	1.20(0.50-2.88)	-1.41
Male reproductive tract disorders congenital	8	0.55(0.27-1.09)	-2.54	1	0.17(0.02-1.22)	-4.20	2	0.23(0.06-0.90)	-3.81
Abortions not specified as induced or spontaneous	4	0.22(0.08-0.60)	-3.82	4	0.57(0.21-1.51)	-2.49	2	0.19(0.05-0.74)	-4.09
Inborn errors of porphyrin metabolism	10	2.46(1.32-4.59)*	-0.37	0			0		
Foetal growth complications	1	0.05(0.01-0.38)	-5.87	8	1.10(0.55-2.19)	-1.53	0		
Cardiac septal defects congenital	1	0.02(0.00-0.16)	-7.11	5	0.29(0.12-0.69)	-3.46	3	0.11(0.04-0.35)	-4.80
Inborn errors of amino acid metabolism	5	2.95(1.22-7.12)*	-0.12	2	2.96(0.74-11.88)	-0.11	2	1.95(0.49-7.80)	-0.71
Normal pregnancy, labour and delivery	3	0.04(0.01-0.12)	-6.39	3	0.10(0.03-0.30)	-5.06	1	0.02(0.00-0.15)	-7.25
Gastric disorders congenital	6	2.23(1.00-4.98)	-0.52	0			1	0.61(0.09-4.36)	-2.37
Congenital disorders	3	0.08(0.03-0.25)	-5.29	2	0.14(0.03-0.54)	-4.54	2	0.09(0.02-0.36)	-5.15
Foetal complications	4	0.30(0.11-0.80)	-3.40	3	0.57(0.18-1.78)	-2.48	0		
Non-site specific muscle disorders congenital	5	2.32(0.96-5.59)	-0.46	1	1.16(0.16-8.28)	-1.45	1	0.76(0.11-5.43)	-2.06
Non-site specific bone disorders congenital	7	2.50(1.19-5.26)*	-0.35	0			0		
Pulmonary and bronchial disorders congenital	5	0.26(0.11-0.63)	-3.60	0			1	0.09(0.01-0.62)	-5.19
Hypertension associated disorders of pregnancy	4	0.22(0.08-0.59)	-3.83	2	0.28(0.07-1.12)	-3.50	0		
Musculoskeletal and connective tissue disorders of spine congenital	5	1.52(0.63-3.65)	-1.07	1	0.76(0.11-5.43)	-2.06	0		
Vascular anomalies congenital	3	0.32(0.10-0.99)	-3.31	0			3	0.53(0.17-1.64)	-2.59
Persistent foetal circulation disorders	0			5	0.92(0.38-2.21)	-1.79	0		
Cardiovascular disorders congenital	5	1.18(0.49-2.85)	-1.43	0			0		
Renal disorders congenital	3	0.21(0.07-0.66)	-3.90	1	0.18(0.03-1.27)	-4.15	1	0.12(0.02-0.83)	-4.75
Inborn errors of metabolism	3	3.17(1.02-9.87)*	-0.02	0			2	3.49(0.87-14.00)	0.12
Unintended pregnancies	1	0.01(0.00-0.09)	-7.98	0			3	0.06(0.02-0.19)	-5.67
Multiple cardiac abnormalities congenital	0			4	3.05(1.14-8.14)*	-0.06	0		
Musculoskeletal disorders congenital	2	0.18(0.05-0.74)	-4.10	1	0.23(0.03-1.66)	-3.77	0		
Chromosomal abnormalities	1	0.21(0.03-1.49)	-3.92	1	0.53(0.07-3.76)	-2.58	1	0.35(0.05-2.47)	-3.19
Cerebellar disorders congenital	0			3	2.28(0.73-7.08)	-0.48	0		
Palate disorders congenital	0			3	0.86(0.28-2.68)	-1.88	0		
Cardiac valve disorders congenital	1	0.12(0.02-0.84)	-4.75	2	0.60(0.15-2.39)	-2.41	0		
Multiple pregnancies	3	1.05(0.34-3.27)	-1.80	0			0		
Great vessel disorders congenital	1	0.10(0.01-0.73)	-4.95	2	0.52(0.13-2.07)	-2.62	0		
Peripheral nervous system disorders congenital	0			1	4.10(0.57-29.22)	0.35	2	5.40(1.34-21.75)	0.74

* Indicates statistically significant signals in algorithm. N, the number of cases; ROR, reporting odds ratio; CI, confidence interval; IC025, the lower end of 95 % CI of the information component.

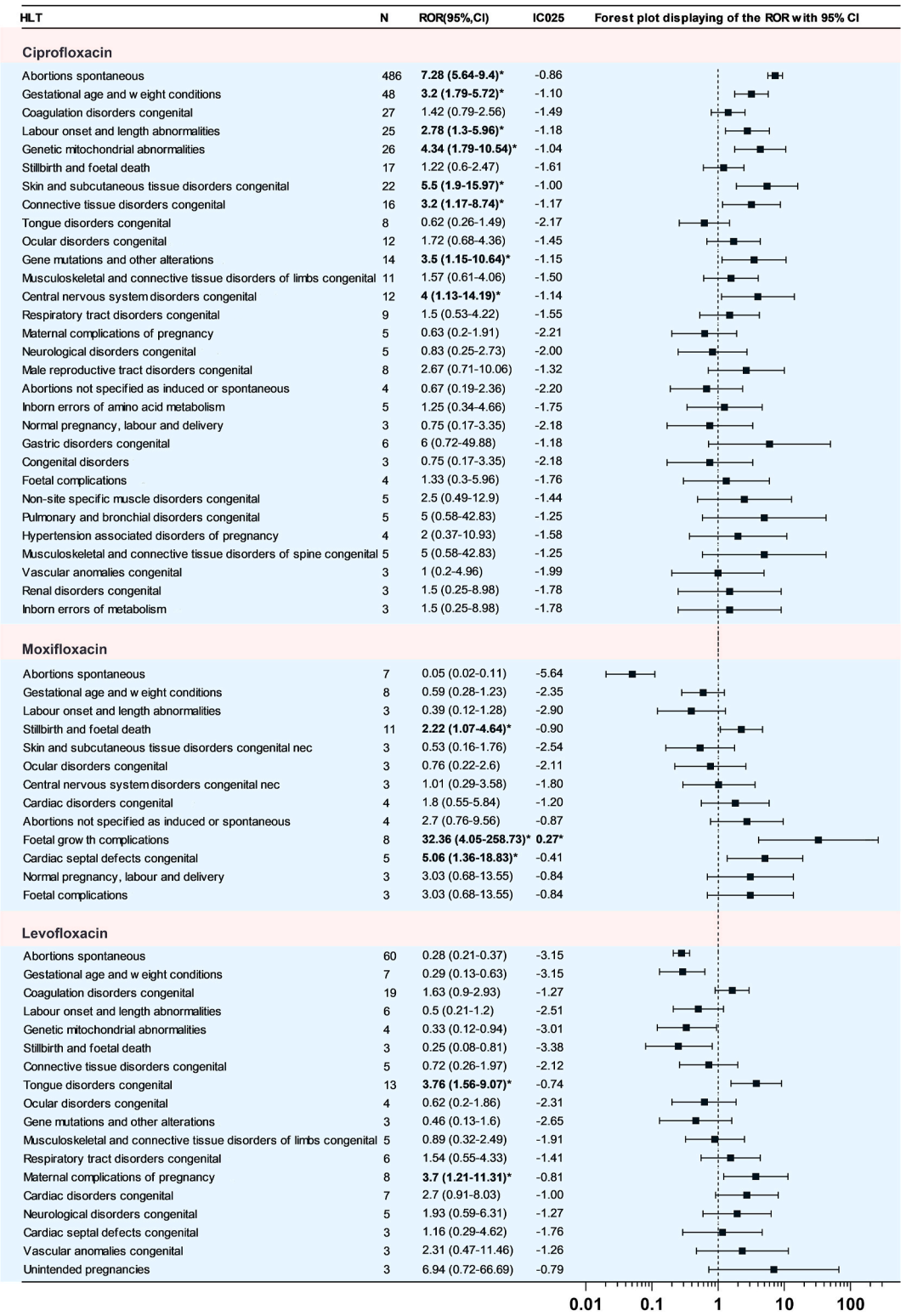


Fig. 2. Disproportionality analysis of pregnancy-related AEs for specific fluoroquinolone at the High Level Terms (HLTs) level, compared with all the other fluoroquinolones.

Emerging findings of specific fluoroquinolone associated AEs from FAERS database. The figure shows data with the number of cases (N) greater than or equal to 3 ($N \geq 3$). * Indicates statistically significant signals in algorithm. ROR, reporting odds ratio; CI, confidence interval; IC025, the lower end of 95 % CI of the information component.

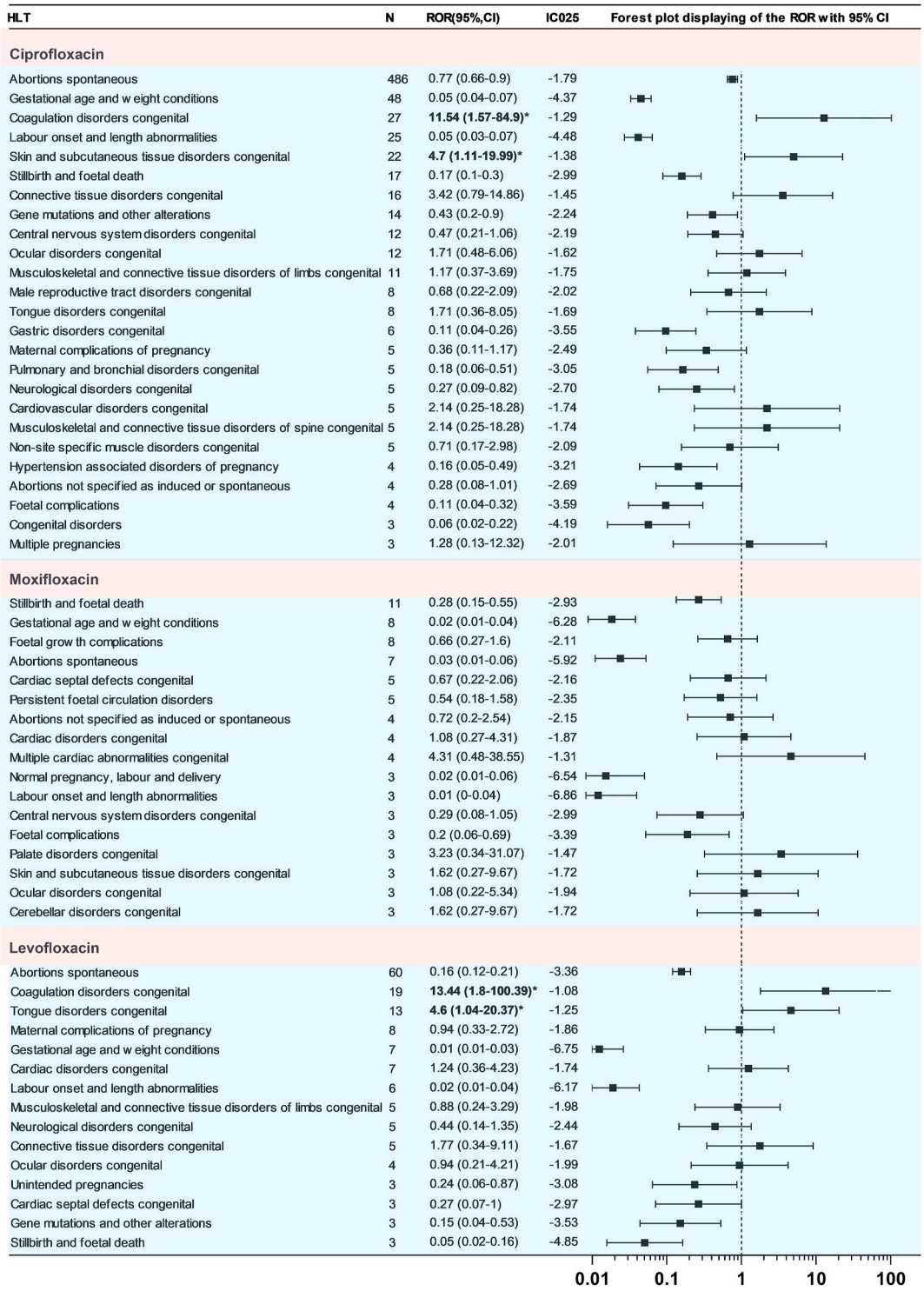


Fig. 3. Disproportionality analysis of pregnancy-related AEs for fluoroquinolone at the High Level Terms (HLTs) level, compared with azithromycin.

Emerging findings of specific fluoroquinolone associated AEs from FAERS database. The figure shows data with the number of cases (N) greater than or equal to 3 ($N \geq 3$).* Indicates statistically significant signals in algorithm. ROR, reporting odds ratio; CI, confidence interval; IC025, the lower end of 95 % CI of the information component.

IC025, -0.28).

3.3. Signals associated with each single fluoroquinolone compared with all the other drugs

Considering that different fluoroquinolone have their distinct characteristics, we conducted an analysis of each drug in related SOCs (Table 3). Ciprofloxacin has 12 significant signals compared to all other drugs, including "abortions spontaneous" (ROR 4.61; 95 % CI, 4.21–5.04; IC025, 0.52), "coagulation disorders congenital" (ROR 5.16; 95 % CI, 3.53–7.55; IC025, 0.68), "genetic mitochondrial abnormalities" (ROR 10.54; 95 % CI, 7.13–15.58; IC025, 1.69), "skin and subcutaneous tissue disorders congenital" (ROR 2.71; 95 % CI, 1.78–4.13; IC025, -0.23), "connective tissue disorders congenital" (ROR 6.84; 95 % CI, 4.17–11.22; IC025, 1.08), "tongue disorders congenital" (ROR 5.04; 95 % CI, 2.51–10.12; IC025, 0.64), "ocular disorders congenital" (ROR 2.16; 95 % CI, 1.22–3.81; IC025, -0.56), "respiratory tract disorders congenital" (ROR 8.25; 95 % CI, 4.26–15.99; IC025, 1.34), "inborn errors of porphyrin metabolism" (ROR 2.46; 95 % CI, 1.32–4.59; IC025, -0.37), "inborn errors of amino acid metabolism" (ROR 2.95; 95 % CI, 1.22–7.12; IC025, -0.12), "non-site specific bone disorders congenital" (ROR 2.50; 95 % CI, 1.19–5.26; IC025, -0.35), and "inborn errors of metabolism" (ROR 3.17; 95 % CI, 1.02–9.87; IC025, -0.02). Moxifloxacin demonstrated a single unique significant signal, "multiple cardiac abnormalities congenital" (N = 4; ROR 3.05; 95 % CI, 1.14–8.14; IC025, -0.06). Levofloxacin shared four significant signals with ciprofloxacin, which were "coagulation disorders congenital" (ROR 5.99; 95 % CI, 3.81–9.42; IC025, 0.9), "connective tissue disorders congenital" (ROR 3.49; 95 % CI, 1.45–8.42; IC025, 0.13), "tongue disorders congenital" (ROR 13.70; 95 % CI, 7.90–23.75; IC025, 2.07, and "respiratory tract disorders congenital" (ROR 9.04; 95 % CI, 4.04–20.27; IC025, 1.48).

3.4. Disproportionality analysis of related AEs for specific fluoroquinolone compared with all the other fluoroquinolones

To mitigate confounding biases arising from disease conditions, direct comparisons were conducted between a specific fluoroquinolone and all other fluoroquinolones to assess rates of pregnancy-related AEs and congenital disorders (Fig. 2). The analysis uncovered significant signals when comparing ciprofloxacin with other fluoroquinolones, indicating elevated risks for "abortions spontaneous" (ROR 7.28; 95 % CI, 5.64–9.4; IC025, -0.86), "gestational age and weight conditions" (ROR 3.2; 95 % CI, 1.79–5.72; IC025, -1.1), "labour onset and length abnormalities" (ROR 2.78; 95 % CI, 1.3–5.96; IC025, -1.18), "genetic mitochondrial abnormalities " (ROR 4.34; 95 % CI, 1.79–10.54; IC025, -1.04), "skin and subcutaneous tissue disorders congenital " (ROR 5.5; 95 % CI, 1.9–15.97; IC025, -1), "connective tissue disorders congenital" (ROR 3.2; 95 % CI, 1.17–8.74; IC025, -1.17), "gene mutations and other alterations " (ROR 3.5; 95 % CI, 1.15–10.64; IC025, -1.15), and "central nervous system disorders congenital" (ROR 4; 95 % CI, 1.13–14.19; IC025, -1.14). These findings suggest a higher risk of ciprofloxacin administration in pregnancy compare with the other fluoroquinolones, especially in the risk of spontaneous abortions and some congenital disorders. Similarly, comparisons involving moxifloxacin revealed a significant disproportionality in "stillbirth and foetal death" (ROR 2.22; 95 % CI, 1.07–4.64; IC025, -0.9), "foetal growth complications" (ROR 32.36; 95 % CI, 4.05–258.73; IC025, 0.27), and "cardiac septal defects congenital" (ROR 5.06; 95 % CI, 1.36–18.83; IC025, -0.41). Levofloxacin, when compared to other fluoroquinolones, exhibited greater significance in "tongue disorders congenital" (ROR 3.76; 95 % CI, 1.56–9.07; IC025, -0.74), and "maternal complications of pregnancy" (ROR 3.7; 95 % CI, 1.21–11.31; IC025, -0.81)". These outcomes suggested that the safety profiles of ciprofloxacin during pregnancy might be relatively lower due to higher reporting proportion of AEs.

3.5. AEs during pregnancy for each fluoroquinolone compared with azithromycin

As shown in Fig. 3, the disproportionality analysis revealed an increased risk of ciprofloxacin-associated "coagulation disorders congenital" (ROR 11.54; 95 % CI, 1.57–84.9; IC025, -1.29) and "skin and subcutaneous tissue disorders congenital" (ROR 4.7; 95 % CI, 1.11–19.99; IC025, -1.38) when compared to azithromycin. Reports of spontaneous abortions or other congenital disorders were either lower or similar between ciprofloxacin and azithromycin, showing no disproportionality in higher risk for these AEs. Furthermore, levofloxacin exhibited significant disproportionality linked to "coagulation disorders congenital" (ROR 13.44; 95 % CI, 1.8–100.39; IC025, -1.08), and "tongue disorders congenital" (ROR 4.6; 95 % CI, 1.04–20.37; IC025, -1.25). Moxifloxacin, in terms of pregnancy-related AEs, including abortion and congenital disorders, did not show significance compared to azithromycin. In addition, certain congenital disorders were not evaluated due to insufficient quantity of azithromycin-related cases, such as "genetic mitochondrial abnormalities", "inborn errors of porphyrin metabolism", "respiratory tract disorders congenital", "non-site specific bone disorders congenital", "inborn errors of amino acid metabolism", and "inborn errors of metabolism".

4. Discussion

Our investigation into congenital AEs associated with fluoroquinolones reveal a substantial proportion of adult cases, resulting in data recording bias due to various circumstances. Approximately 34 % of these cases did not have age information recorded; however, some of them could be indirectly inferred from weight data related to adverse reactions observed in neonates. Notably, certain congenital AEs may go unnoticed during the early stages and only become apparent after several years or even in adulthood. Consequently, a small number of EVENT_DT entries in the Demo table capture birth times, while a larger portion remains empty and only includes FDA_DT information. This discrepancy may arise from the recorded individual's birthdate falling outside the system's configuration range. Such limitations are inherent to the self-reporting system of FAERS, which, despite its benefit of extensive real-world data, is susceptible to data bias and lacks callback availability. In this study, although precise quantification was unfeasible, we

successfully conducted qualitative analysis utilizing disproportionality analysis to ascertain the correlation between fluoroquinolones and the occurrence of congenital AEs, thus enabling conclusions and providing guidance for clinical drug selection. Additionally, to further reduce bias, we used azithromycin as a reference drug.

Owing to instances of unintended pregnancies and the accumulation of clinical data, the application of fluoroquinolones in pregnant women emerged. This study observed an increase in spontaneous abortions associated particularly with ciprofloxacin among fluoroquinolones. Nonetheless, significant AEs like fetal and neonatal toxicity, including congenital defects, due to intrauterine exposure to fluoroquinolones were not identified. Therefore, termination of pregnancy due to fluoroquinolones exposure is not recommended, necessitating further analysis of the situation. In consistent with systematic review by Acar et al. [21] and Muanda et al. [22], none of these three drugs showed the risk of major congenital malformations. Our analysis of congenital, familial, and hereditary disorders from our database highlighted notable AEs such as congenital coagulation disorders, hereditary mitochondrial abnormalities, congenital skin and subcutaneous tissue disorders, and congenital connective tissue disorders.

The question of whether fluoroquinolones induce toxicity during pregnancy has been a longstanding subject to debate in published research. Some evidence suggests that fluoroquinolones exposure in the first trimester does not correlate with any specific pattern of birth defects [23]. Meta-analytical studies have further indicated that fluoroquinolone exposure, including ciprofloxacin, is not significantly associated with an increased risk of major malformations or adverse pregnancy outcomes [24], nor with other unfavorable pregnancy outcomes [25]. On the contrary, a cohort study has reported an elevated risk of spontaneous abortion, particularly in early pregnancy associated with quinolone use [8]. Preclinical studies have also indicated significant pregnancy toxicity of fluoroquinolones, with ciprofloxacin causing oxidative damage in fetal liver tissue [26], and uterine exposure to quinolones being linked to organ-specific malformations [27].

Our study revealed that pregnancy-related AEs associated with ciprofloxacin exceeded those of other fluoroquinolones. Interestingly, signals of spontaneous abortions were not significantly related to either levofloxacin or moxifloxacin. These results suggested that, in situations where fluoroquinolones are deemed necessary, levofloxacin or moxifloxacin might be preferable choices. Additionally, based on the available data, we identified crucial signals of fluoroquinolone exposure pertaining to perinatal conditions and genotoxicity. Specifically, ciprofloxacin and levofloxacin were associated with congenital coagulation dysfunction, congenital connective tissue dysfunction, congenital tongue dysfunction and congenital respiratory dysfunction. Understanding these findings enables a more informed estimation when administering fluoroquinolones to pregnant women and addressing potential pregnancy-related risks for prevention.

Recent studies connected fluoroquinolones, especially ciprofloxacin and levofloxacin, to coagulation disorders and congenital malformations, which likely due to their transplacental passage and potential DNA damage [6,27,28]. Our research supports these findings, showing a strong association between ciprofloxacin exposure and congenital connective tissue disorders, with levofloxacin following closely. The teratogenic effects may be attributed to fluoroquinolones' cytotoxicity, which converting topoisomerase II to cellular poison, triggering DNA damage, cell death and then possibly fetal malformations or loss [29,30]. Additionally, studies also reveals that these drugs induce oxidative damage on the embryos [31], disrupting development and enhancing stem cell marker expression, which may lead to increased cell apoptosis [32]. The constant placental transfer and accumulation of ciprofloxacin could extend fetal exposure, intensifying these effects [28].

Furthermore, our study identifies a significant correlation between ciprofloxacin and tendonitis, as well as bone malformations [33–35]. Despite a study in foals showing no gross lesions from ciprofloxacin exposure [34], the risk of subtle, undetectable lesions persists. A Danish cohort study also points to an increased prevalence of bone malformations with fluoroquinolone exposure during pregnancy though it was not significant due to sample size [35]. Our finding on "non-site specific bone disorders congenital" associated with ciprofloxacin is consistent with evidence of dose-dependent fluoroquinolone-induced DNA damage leading to visceral and skeletal defects [30,36–38]. Quinolones disturb the adherence mechanism of chondrocytes and lead to cytoskeleton changes [37], caused a lack of functionally available magnesium in immature joint cartilage, and inhibit proteoglycan and procollagen syntheses in embryo limbs [38]. Beyond this, fluoroquinolones are implicated in metabolic errors during pregnancy, encompassing inborn errors of metabolism and genetic mitochondrial abnormalities, among other disorders [34,35].

The link between fluoroquinolone (ciprofloxacin or levofloxacin) and coagulation disorders, notably acquired hemophilia, is clinically significant as previous studies suggested [39,40]. Historically, the FDA's description of 'temafloxacin syndrome,' leading to market withdrawal, underscores the severity of fluoroquinolone-related complications [41]. Ciprofloxacin has also been tied to the development of factor V inhibitor, antiphospholipid antibodies, and von Willebrand syndrome [42,43]. The structurally similarity to quinine to quinine suggests a risk of quinine-type immune thrombocytopenia [44]. The cardiac hyperplasia was consistent with the previous studies, which showed that the fluoroquinolones caused QT prolongation at rather low doses thus increasing the risk for severe arrhythmia [45,46]. Fluoroquinolones block cardiac potassium channel, which led to prolonged QT interval with cardiac arrhythmia and consequently cardiac hyperplasia [46]. In conclusion, our research underscores the multifaceted risks of fluoroquinolone use during pregnancy, underscoring the need for vigilant maternal and fetal health monitoring. As study showed that, autogenic infection in pregnant rats induced the myocardial changes in fetal rats [47], we also cannot rule out the possibility that the infection itself may cause fetal birth defects.

Azithromycin has a good pharmacokinetic profile and additional immunomodulatory, anti-inflammatory, and potential antiviral properties, is commonly prescribed during pregnancy [48]. Pregnant women face an elevated risk of infection, necessitating prompt and decisive treatment to prevent complications [49]. *Mycoplasma genitalium* independently heightens the risk of female cervicitis and pelvic inflammatory disease, potentially causing salpingitis, which can result in infertility, ectopic pregnancy, or an increased incidence of preterm birth in late pregnancy [50]. Due to limited options for safe antibiotic use during pregnancy, as conducting clinical trials to assess the potential benefit-risk profile in pregnant mother and fetuses is challenging, the macrolide antimicrobial drug

azithromycin is recommended for treating mycoplasma infections during pregnancy [20,48,51]. But azithromycin resistance may be occurred and fluoroquinolone was sensitivity [20,51]. Due to the potential reproductive toxicity of fluoroquinolones, clinical medication choice trapped in a dilemma. While medications carry potential hazardous, misconceptions and suboptimal treatment of the mother might pose greater harm to the unborn child [49]. Here, we compared AE data for azithromycin extracted from the FAERS database with that of fluoroquinolones. No significant difference in the incidence of spontaneous abortion was observed between azithromycin and fluoroquinolones. Both ciprofloxacin and levofloxacin exhibited disproportionate reporting for congenital coagulation disorders. Ciprofloxacin exerted significant disproportionality with congenital skin and subcutaneous tissue disorders, while levofloxacin showed significant disproportionality with congenital tongue disorders. These findings align with the risk comparison between fluoroquinolones and all other drugs. Based on literature data and our results, in cases of azithromycin resistance, use of fluoroquinolones with caution for anti-infection therapy can be considered after weighing the pros and cons. In view of the fact that a certain percentage of birth defects occur in normal pregnancies, it is recommended to have regular obstetric check-ups and to closely monitor the condition of the pregnant woman and the fetus.

This study investigates pregnancy-related AEs associated with fluoroquinolone use during pregnancy utilizing real world data from one of the largest pharmacovigilance databases. Conducting large clinical trials on pregnant women is ethically challenging, making real-world data crucial for exploring the safety of this vulnerable population. However, the study also has limitations, including incomplete information, and missing data in the FAERS database. As the guideline mentioned, "exposure dates are important, as susceptible periods for specific malformations may be less than one week" [52]. Thus, there is flaw in the current database that as we are unable to determine the accurate gestational week, and there is no information provided regarding the results of the autopsy conducted on the stillborn baby. Consequently, the results about the congenital disorders were need to be treated more cautiously. While the FAERS database can capture multiple adverse events resulting from a single exposure to a drug during pregnancy, attributing them to a single individual can be challenging when these events do not occur concurrently. Although this aspect is advantageous for investigating the occurrence of various AEs, the lack of overall medication data makes it difficult to calculate the incidence rate of adverse events. In addition, due to the fact that FAERS is a spontaneous reporting system and the individual differences in understanding of AEs, there must be situations of underreporting of related AEs or some reporting bias during the reporting process, which may lead to the underestimation of some given AEs. Results may be influenced by confounding factors, including the concurrent use of other medications and the patient's disease state. Despite these limitations, the cases submitted in the FAERS database offer a broadly representative sample. Application of disproportionality analysis allows for an accurate comparison of the likelihood of AEs, offering valuable insights for future pharmaceutical selection. Therefore, when applying the results of this article in clinical practice, it is essential to do so under professional guidance. This involves considering the results in conjunction with the sensitive periods of fetal organ development during gestation and assessing factors such as the patient's willingness for pregnancy and likelihood of conception. In view of this, well-designed clinical trials, including retrospective controlled studies, play an irreplaceable role in evaluating AEs during pregnancy and childbirth. Furthermore, we anticipate further research adhering to these guidelines to provide a more comprehensive understanding of the topic.

5. Conclusion and clinical recommendations

Ciprofloxacin use in our data showed an association with spontaneous abortion, while none of the three drugs studied increased the risk of major congenital malformations. However, each drug was linked to specific congenital malformations, highlighting the importance of long-term monitoring for fluoroquinolone risks. Despite potential hazards, pregnant women with infections require early and decisive treatment to prevent complications for both mother and baby. While absolute risks remain small, physicians should prioritize safer antibiotics for maternal infections when possible. If fluoroquinolones are deemed necessary, (e.g. atypical pathogen infections that are resistant to macrolides but sensitive to fluoroquinolones) moxifloxacin or levofloxacin may be safer alternatives to ciprofloxacin in most of time, and as low a dose exposure and as short a course of treatment as possible. As susceptible periods for specific malformations may be less than one week, if unintentionally exposure of a pregnant woman to a specific fluoroquinolone, elective abortion might not be a well-informed option. Only if the fluoroquinolone with high organ-specific teratogenic potential is taken concurrently during the period of specific organogenesis, the pregnant women may need to make more prudent choices with the help of professionals (e.g., moxifloxacin administration coincides with a sensitive period of fetal cardiac development, ciprofloxacin administration coincides with a sensitive period of bone development). Considering the inherent risk of birth defects in normal pregnancies, regular maternity checkups are strongly recommended following the use of these drugs, and coagulation monitoring is recommended for routine checkups of pregnant women.

Data availability statement

The data that support the findings of this study are available in FAERS database and details in https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The search terms and calculation methods for the research presented in the study are included in the Supplementary Material. Other requests about the data in the manuscript can be submitted in writing to the corresponding author.

Ethics statement

The study is a secondary analysis of publicly available summary statistics and requires no specific ethical approval.

Funding

This work was supported by the grants from Hubei Provincial Natural Science Foundation of China (2021CFB035).

CRediT authorship contribution statement

Dao-chun Xiang: Writing – review & editing, Writing – original draft, Software, Methodology. **Wen-long Xie:** Writing – original draft, Software, Methodology. **Gang-ying Cheng:** Data curation. **Ming Yue:** Data curation. **Xiao-yi Du:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis. **Jue Jiang:** Writing – original draft, Supervision, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Jue Jiang reports financial support and writing assistance were provided by Hubei Provincial Natural Science Foundation of China (2021CFB035). Jue Jiang reports a relationship with Hubei Provincial Natural Science Foundation of China (2021CFB035). that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37547.

References

[1] T. Chan, P.E. Bunce, Fluoroquinolone antimicrobial drugs, CMAJ (Can. Med. Assoc. J.) 189 (2017) E638, https://doi.org/10.1503/cmaj.160938.
[2] Y. Jia, L. Zhao, The antibacterial activity of fluoroquinolone derivatives: an update (2018-2021), Eur. J. Med. Chem. 224 (2021) 113741, https://doi.org/10.1016/j.ejmech.2021.113741.
[3] A.R. Millanao, A.Y. Mora, N.A. Villagra, S.A. Bucarey, A.A. Hidalgo, Biological effects of quinolones: a family of broad-spectrum antimicrobial agents, Molecules 26 (2021) 7153, https://doi.org/10.3390/molecules26237153.
[4] M. Tandan, M. Cormican, A. Vellinga, Adverse events of fluoroquinolones vs. other antimicrobials prescribed in primary care: a systematic review and meta-analysis of randomized controlled trials, Int. J. Antimicrob. Agents 52 (2018) 529–540, https://doi.org/10.1016/j.ijantimicag.2018.04.014.
[5] P.P. Majalekar, P.J. Shirote, Fluoroquinolones: blessings or curses, Curr. Drug Targets 21 (2020) 1354–1370, https://doi.org/10.2174/1389450121666200621193355.
[6] O. Ozyuncu, E. Nemutlu, D. Katlan, S. Kir, M.S. Beksac, Maternal and fetal blood levels of moxifloxacin, levofloxacin, cefepime and cefoperazone, Int. J. Antimicrob. Agents 36 (2010) 175–178, https://doi.org/10.1016/j.ijantimicag.2010.03.011.
[7] A.W. Gough, O.B. Kasali, R.E. Sigler, V. Baragi, Quinolone arthropathy–acute toxicity to immature articular cartilage, Toxicol. Pathol. 20 (1992) 436–450, https://doi.org/10.1177/019262339202000313.
[8] F.T. Muanda, O. Sheehy, A. Berard, Use of antibiotics during pregnancy and risk of spontaneous abortion, CMAJ (Can. Med. Assoc. J.) 189 (2017) E625–E633, https://doi.org/10.1503/cmaj.161020.
[9] S.P. Mclaughlin, C.C. Carson, Urinary tract infections in women, Med. Clin. 88 (2004) 417–429, https://doi.org/10.1016/s0025-7125(03)00148-2.
[10] M.J. Redelinghuys, M.M. Ehlers, A.W. Dreyer, H.A. Lombaard, M.M. Kock, Antimicrobial susceptibility patterns of Ureaplasma species and Mycoplasma hominis in pregnant women, BMC Infect. Dis. 14 (2014) 171, https://doi.org/10.1186/1471-2334-14-171.
[11] L.B. Finer, M.R. Zolna, Unintended pregnancy in the United States: incidence and disparities, 2006, Contraception 84 (2011) 478–485, https://doi.org/10.1016/j.contraception.2011.07.013.
[12] R. Loebstein, A. Addis, E. Ho, R. Andreou, S. Sage, A.E. Donnenfeld, et al., Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study, Antimicrob. Agents Chemother. 42 (1998) 1336–1339, https://doi.org/10.1128/AAC.42.6.1336.
[13] D.C. Xiang, W. Chen, Z.W. Fu, X.H. Wu, P. Gao, Y. Wu, Adverse events of guselkumab in the real world: emerging signals to target preventive strategies from the FDA adverse event reporting system, Expet Opin. Drug Saf. 22 (2023) 943–955, https://doi.org/10.1080/14740338.2023.2223956.
[14] M. Fusaroli, F. Salvo, B. Begaud, T.M. Alshammari, A. Bate, V. Battini, et al., The reporting of a disproportionality analysis for drug safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): development and statement, Drug Saf. 47 (2024) 575–584, https://doi.org/10.1007/s40264-024-01421-9.
[15] Y.K. Loke, Not just another reporting guideline? Here's why READUS-PV is a major step forward, Drug Saf. 47 (2024) 571–573, https://doi.org/10.1007/s40264-024-01441-5.
[16] M. Fusaroli, F. Salvo, B. Begaud, T.M. Alshammari, A. Bate, V. Battini, et al., The REporting of A disproportionality analysis for DrUg safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): explanation and elaboration, Drug Saf. 47 (2024) 585–599, https://doi.org/10.1007/s40264-024-01423-7.
[17] J. Slattery, Y. Alvarez, A. Hidalgo, Choosing thresholds for statistical signal detection with the proportional reporting ratio, Drug Saf. 36 (2013) 687–692, https://doi.org/10.1007/s40264-013-0075-1.
[18] A. Bate, Bayesian confidence propagation neural network, Drug Saf. 30 (2007) 623–625, https://doi.org/10.2165/00002018-200730070-00011.
[19] T. Wu, Y. Shi, B. Zhu, D. Li, Z. Li, Z. Zhao, et al., Pregnancy-related adverse events associated with statins: a real-world pharmacovigilance study of the FDA Adverse Event Reporting System (FAERS), Expet Opin. Drug Saf. 23 (2024) 313–321, https://doi.org/10.1080/14740338.2023.2251888.
[20] A.T.N. Tita, W.A. Carlo, E.M. Mcclure, M. Mwenechanya, E. Chomba, J.J. Hemingway-Foday, et al., Azithromycin to prevent sepsis or death in women planning a vaginal birth, N. Engl. J. Med. 388 (2023) 1161–1170, https://doi.org/10.1056/NEJMoa2212111.
[21] A. Ziv, R. Masarwa, A. Perlman, D. Ziv, I. Matok, Pregnancy outcomes following exposure to quinolone antibiotics - a systematic-review and meta-analysis, Pharm. Res. (N. Y.) 35 (2018) 109, https://doi.org/10.1007/s11095-018-2383-8.
[22] F.T. Muanda, O. Sheehy, A. Berard, Use of antibiotics during pregnancy and the risk of major congenital malformations: a population based cohort study, Br. J. Clin. Pharmacol. 83 (2017) 2557–2571, https://doi.org/10.1111/bcp.13364.

[23] S. Padberg, E. Wacker, R. Meister, M. Panse, C. Weber-Schoendorfer, M. Oppermann, et al., Observational cohort study of pregnancy outcome after first-trimester exposure to fluoroquinolones, Antimicrob. Agents Chemother. 58 (2014) 4392–4398, https://doi.org/10.1128/aac.02413-14.
[24] S. Acar, E. Keskin-Arslan, H. Erol-Coskun, T. Kaya-Temiz, Y.C. Kaplan, Pregnancy outcomes following quinolone and fluoroquinolone exposure during pregnancy: a systematic review and meta-analysis, Reprod. Toxicol. 85 (2019) 65–74, https://doi.org/10.1016/j.reprotox.2019.02.002.
[25] E. Yefet, N. Schwartz, B. Chazan, R. Salim, S. Romano, Z. Nachum, The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis, Bjog 125 (2018) 1069–1076, https://doi.org/10.1111/1471-0528.15119.
[26] Z. Dogan, H. Elbe, E. Taslidere, H. Soysal, A. Cetin, S. Demirtas, Effects of ciprofloxacin on fetal rat liver during pregnancy and protective effects of quercetin, Biotech. Histochem. 92 (2017) 481–486, https://doi.org/10.1080/10520295.2017.1356469.
[27] J.W. Corbett, S.S. Ko, J.D. Rodgers, L.A. Gearhart, N.A. Magnus, L.T. Bacheler, et al., Inhibition of clinically relevant mutant variants of HIV-1 by quinazolinone non-nucleoside reverse transcriptase inhibitors, J. Med. Chem. 43 (2000) 2019–2030, https://doi.org/10.1021/jm990580e.
[28] M. Noergaard, P.B. Jensen, D Resendal Gotfredsen, T. Bergholt, J Trærup Andersen, L. Mathiesen, Therapeutic concentration of ciprofloxacin and transfer across the human term placenta, Am. J. Obstet. Gynecol. 225 (2021) 670.e1–670.e9, https://doi.org/10.1016/j.ajog.2021.05.032.
[29] S.H. Elsea, P.R. Mcguirk, T.D. Gootz, M. Moynihan, N. Osheroff, Drug features that contribute to the activity of quinolones against mammalian topoisomerase II and cultured cells: correlation between enhancement of enzyme-mediated DNA cleavage in vitro and cytotoxic potential, Antimicrob. Agents Chemother. 37 (1993) 2179–2186, https://doi.org/10.1128/aac.37.10.2179.
[30] M. Aboubakr, M. Elbadawy, A. Soliman, M. El-Hewaity, Embryotoxic and teratogenic effects of norfloxacin in pregnant female albino rats, Adv Pharmacol Sci 2014 (2014) 924706, https://doi.org/10.1155/2014/924706.
[31] J.R. Rosas-Ramírez, J.M. Orozco-Hernández, G.A. Elizalde-Velázquez, D. Raldúa, H. Islas-Flores, L.M. Gómez-Oliván, Teratogenic effects induced by paracetamol, ciprofloxacin, and their mixture on Danio rerio embryos: oxidative stress implications, Sci. Total Environ. 806 (2022) 150541, https://doi.org/10.1016/j.scitotenv.2021.150541.
[32] J. Xi, J. Liu, S. He, W. Shen, C. Wei, K. Li, et al., Effects of norfloxacin exposure on neurodevelopment of zebrafish (Danio rerio) embryos, Neurotoxicology 72 (2019) 85–94, https://doi.org/10.1016/j.neuro.2019.02.007.
[33] Y. Shu, Q. Zhang, X. He, Y. Liu, P. Wu, L. Chen, Fluoroquinolone-associated suspected tendonitis and tendon rupture: a pharmacovigilance analysis from 2016 to 2021 based on the FAERS database, Front. Pharmacol. 13 (2022) 990241, https://doi.org/10.3389/fphar.2022.990241.
[34] R.E. Ellerbrock, I.F. Canisso, R.J. Larsen, K.S. Garrett, M.C. Stewart, K.K. Herzog, et al., Fluoroquinolone exposure in utero did not affect articular cartilage of resulting foals, Equine Vet. J. 53 (2021) 385–396, https://doi.org/10.1111/evj.13295.
[35] P. Wogelius, M. Nørgaard, M. Gislum, L. Pedersen, H.C. Schønheyder, H.T. Sørensen, Further analysis of the risk of adverse birth outcome after maternal use of fluoroquinolones, Int. J. Antimicrob. Agents 26 (2005) 323–326, https://doi.org/10.1016/j.ijantimicag.2005.06.017.
[36] A. Pino, A. Maura, F. Villa, L. Masciangelo, Evaluation of DNA damage induced by norfloxacin in liver and kidney of adult rats and in fetal tissues after transplacental exposure, Mutat. Res. 264 (1991) 81–85, https://doi.org/10.1016/0165-7992(91)90049-a.
[37] I. Walter, M. Egerbacher, B. Wolfesberger, G. Seiberl, Confocal laser scanning microscopy of chondrocytes in vitro: cytoskeletal changes after quinolone treatment, Scanning 20 (1998) 511–515, https://doi.org/10.1002/sca.1998.4950200705.
[38] E. Yefet, R. Salim, B. Chazan, H. Akel, S. Romano, Z. Nachum, The safety of quinolones in pregnancy, Obstet. Gynecol. Surv. 69 (2014) 681–694, https://doi.org/10.1097/ogx.0000000000000122.
[39] L.T. Mor, K. Holley, A case report of anticoagulation management in acquired hemophilia associated with levofloxacin, J. Pharm. Pract. 33 (2020) 378–381, https://doi.org/10.1177/0897190018799186.
[40] T. Psarros, T. Trammell, K. Morrill, C. Giller, H. Morgan, B. Allen, Abnormal coagulation studies associated with levofloxacin. Report of three cases, J. Neurosurg. 100 (2004) 710–712, https://doi.org/10.3171/jns.2004.100.4.0710.
[41] P. Campi, W.J. Pichler, Quinolone hypersensitivity, Curr. Opin. Allergy Clin. Immunol. 3 (2003) 275–281, https://doi.org/10.1097/00130832-200308000-00007.
[42] W. Miesbach, J. Voigt, D. Peetz, I. Scharrer, Massive bleeding symptoms in two patients with factor V inhibitor and antiphospholipid antibodies after treatment with ciprofloxacin, Med. Klin. 98 (2003) 339–343, https://doi.org/10.1007/s00063-003-1268-7.
[43] J.J. Michiels, U. Budde, M. Van Der Planken, H.H. Van Vliet, W. Schroyens, Z. Berneman, Acquired von Willebrand syndromes: clinical features, aetiology, pathophysiology, classification and management, Best Pract. Res. Clin. Haematol. 14 (2001) 401–436, https://doi.org/10.1053/beha.2001.0141.
[44] R. Santucci, K. Bouayad-Agha, F. Maloisel, F. Couturier, Ciprofloxacin-induced thrombopenia, Med Mal Infect 42 (2012) 175–176, https://doi.org/10.1016/j.medmal.2012.02.008.
[45] R. Stahlmann, Clinical toxicological aspects of fluoroquinolones, Toxicol. Lett. 127 (2002) 269–277, https://doi.org/10.1016/s0378-4274(01)00509-4.
[46] J. Kang, L. Wang, X.L. Chen, D.J. Triggle, D. Rampe, Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG, Mol. Pharmacol. 59 (2001) 122–126, https://doi.org/10.1124/mol.59.1.122.
[47] G.I. S Maior, G.V. Mascena, V. Marquis, C.A. Figueiredo Filho, A.R. D Paz, L. Moura, et al., Role of moxifloxacin-dexamethasone in cardiac histomorphometric findings among Wistar rats from infected mothers, Acta Cir. Bras. 33 (2018) 744–752, https://doi.org/10.1590/s0102-865020180090000002.
[48] R. Antonucci, L. Cuzzolin, C. Locci, F. Dessole, G. Capobianco, Use of azithromycin in pregnancy: more doubts than certainties, Clin. Drug Invest. 42 (2022) 921–935, https://doi.org/10.1007/s40261-022-01203-0.
[49] T.H. Vu, E. Adhel, K. Vielfort, N T Ha Duong, G. Anquetin, K. Jeannot, et al., Modified fluoroquinolones as antimicrobial compounds targeting Chlamydia trachomatis, Int. J. Mol. Sci. 23 (2022) 6741, https://doi.org/10.3390/ijms23126741.
[50] J. Yu, Y. Zhou, H. Luo, X. Su, T. Gan, J. Wang, et al., Mycoplasma genitalium infection in the female reproductive system: diseases and treatment, Front. Microbiol. 14 (2023) 1098276, https://doi.org/10.3389/fmicb.2023.1098276.
[51] L.E. Manhart, J.M. Broad, M.R. Golden, Mycoplasma genitalium: should we treat and how? Clin. Infect. Dis. 53 (Suppl 3) (2011) S129–S142, https://doi.org/10.1093/cid/cir702.
[52] E.M. Agency, Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data, in: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf, 2006.