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RESEARCH ARTICLE

Ciprofloxacin exposure and adverse pregnancy outcomes: A Danish nationwide cohort study

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Abstract

Objective: To examine the association between maternal exposure to ciprofloxacin and the risk of miscarriage and major malformations.

Design: A nationwide register-based cohort study.

Setting: Data were obtained from the Medical Birth Registry, the National Hospital Registry, the Danish National Prescription Registry and Statistics Denmark.

Population: Data were collected in the period between 1997 and 2016 and included all registered pregnancies that ended in an elective termination, miscarriage, stillbirth or a live birth. Exposure was defined as redeeming one or more prescriptions of ciprofloxacin.

Methods: Miscarriage was defined as a diagnosis given before 22 weeks without any medical intervention. Major malformations were classified according to EUROCAT 1.4. We matched ciprofloxacin-exposed pregnancies to unexposed pregnancies on the propensity score in a ratio 1:4. To estimate the hazard ratio (HR) of miscarriage a Cox proportional hazard regression model was used. A log binomial model was used to estimate the relative risk ratio (RR) of major malformations.

Main outcome measures: HR of miscarriage and the RR of major malformations.

Results: A total of 1 650 649 pregnancies were identified. Of these, 10 250 (2050 ciprofloxacin-exposed) and 6100 (1220 ciprofloxacin-exposed) were included in the miscarriage and major malformation analysis, respectively. The HR of miscarriage was 0.99 (95% confidence interval [CI] 0.84–1.17). For major malformation, the RR was 1.01 (95% CI 0.72–1.40). For the organ-specific major malformations and the sensitivity analyses, no significant increased risks were identified.

Conclusion: We demonstrated no association between miscarriage and maternal ciprofloxacin exposure within the first 22 weeks of pregnancy, or between major malformations and maternal exposure during the first trimester.

Tweetable abstract: No association between maternal ciprofloxacin exposure and adverse pregnancy outcomes.

KEYWORDS
ciprofloxacin, early exposure, major malformation, miscarriage

1 | INTRODUCTION

Is there an association between adverse pregnancy outcomes and maternal exposure to ciprofloxacin during early pregnancy? This important question needs to be elucidated, especially due to the increase in bacterial resistance, as more treatment interventions are essential.[1]

Ciprofloxacin is a second-generation quinolone classified as a broad-spectrum antibiotic.[2] It features in the World Health Organization (WHO) List of Essential Medicines and it is used to treat a variety of infections.[2,3] The mechanism of action involves inhibition of the bacterial DNA gyrase and topoisomerase IV and therefore, theoretically, ciprofloxacin can impair the fetus's DNA synthesis and hence cause organ agenesis and mutagenesis.[4]

Safety concerns of quinolones were initially raised in animal studies where arthropathy of weight-bearing joints was reported.[5] Evidence regarding adverse pregnancy outcomes from human studies is sparse and conflicting. Some studies indicates no increased risk,[6–9] whereas others demonstrate an increased risk of miscarriage or major malformations.[10–12] A recently published *ex vivo* placental study investigated the extent of transport across the human term placenta and concluded that the fetus is exposed to ciprofloxacin to a moderate degree when administered to the mother at therapeutic concentration.[13] This result represents a higher level than previously detected.[14]

The conflicting fetal safety data on the use of ciprofloxacin during pregnancy increases the risk of sub-optimal treatment in pregnant women and consequently increases the risk of both maternal and neonatal complications.[15,16] In this study, the aim is to examine the association between the risk of miscarriage and maternal exposure to ciprofloxacin during the first 22 weeks of pregnancy, and between the risk of major malformations and maternal exposure to ciprofloxacin during the first trimester.

2 | METHODS

2.1 | Data sources and study cohort

All registered pregnancies resulting in an elective termination, miscarriage, stillbirth or live birth were included from 1 January 1997 to 31 December 2016. Data were obtained from the Danish nationwide registries and an exact individual linkage was enabled using the unique personal identification number (CPR number) assigned to all Danish residents at birth or immigration.[17] The *Danish Medical Birth Register* contains information on all live births and stillbirths in Denmark since 1973 and has a high validity and a data completeness of more than 99%.[18,19] Data on elective terminated pregnancies, miscarriages and major malformations were obtained from the *Danish National Patient Registry* and are based on diagnoses

assigned by hospital physicians. The registry records diagnoses according to the International Classification of Disease 10th revision (ICD-10) and has a high positive predictive value.[19–21] Information on filled prescriptions was collected from The Danish Prescription Registry.[22] This registry contains information on prescriptions redeemed at community pharmacies in Denmark and has a high quality and completeness, as patients received reimbursement from all redeemed prescriptions. Information on drugs is recorded in accordance with the Anatomical Therapeutic Chemical (ATC) coding system and includes, but is not limited to, the date the prescription was filled, strength and package size. Information concerning maternal socio-demographic and economic characteristics was obtained from Statistics Denmark.[17,23,24] The study was approved by the Danish Data Protection Agency (P-2021–113).

2.2 | Ciprofloxacin exposure

In the analyses of miscarriage and late elective termination after week 12, maternal exposure to ciprofloxacin was defined as redeeming one or more prescriptions of systemic ciprofloxacin (ATC-code J01MA02) within the first 22 weeks of pregnancy. For the analysis of major malformations, the exposure period was restricted to the first 12 weeks of pregnancy. The pregnancy start date was based on the first day of the last menstrual period (LMP), calculated by subtracting the gestational age at delivery from the pregnancy end date. The unexposed pregnant women were defined as women with no redemption of a prescription of any quinolones (ATC-code J01 M) in the period of 3 months before the LMP date to the pregnancy end date.

2.3 | Outcomes

Cases of miscarriage were defined as pregnancies ending in fetal death before the end of gestational week 22 without any medical intervention (ICD-10 codes O021 and O03). Major malformations, diagnosed within the first year of life, were classified according to the European Surveillance of Congenital Anomalies (EUROCAT) guide 1.4 and 12 organ-specific major malformations were included.[25] Chromosomal anomalies and malformation syndromes with known causes, e.g. Down syndrome and fetal alcohol syndrome, were excluded, and subgroups with less than three individuals were not presented due to Danish legal requirements for anonymity (Table S1).

For both outcomes, a sensitivity analysis of accumulated ciprofloxacin dose was conducted. The accumulated dose was divided in two categories: ciprofloxacin >5 g (high dose) and ≤5 g (low dose), with the latter reflecting the standard dose regimen of 500 mg × 2 for 5 days. Furthermore, we conducted analyses of singleton pregnancies and late elective

terminated pregnancies due to malformations after 12 weeks of gestation (ICD-10 codes O053 and O054).

2.4 | Covariates

A broad range of covariates were identified and, for example, included maternal age, previous history of miscarriage and/or major malformations. Furthermore, we included characteristics regarding co-morbidity based on the redemption of selected drugs. To ensure uniformity of the teratogenic drugs, we used the list published by Padberg et al.[9] As a proxy for current health status, we used concomitant drug use. The drugs included were antiviral drugs for the treatment of herpes virus, drugs used in *in vitro* fertilisation (IVF) treatment, hypnotics, NSAIDs, opioids and oral corticosteroids. The antibiotics, extended-spectrum penicillins and macrolides, were also included as an indicator of current infection-status. As a general marker of co-morbidity, the number of drugs used and the number of outpatient visits and hospital admissions were included. All the covariates were measured in the period of 1 year prior to the LMP date and throughout the entire pregnancy. The definitions and data sources are presented in Table S2.

2.5 | Statistics analysis

To account for confounders, we matched each ciprofloxacin-exposed pregnant woman with four unexposed pregnant women. Matching was conducted based on the propensity score, a summary score reflecting the probability of receiving the treatment, ciprofloxacin, given the covariates. The propensity score was calculated using a binary logistic regression model, and all covariates were included (Table S2). In the matching procedure, we used greedy nearest neighbour-matching and a caliper width of 0.02. In the analysis of miscarriage, controls were conditioned to still be pregnant at the index date (for the cases: the day of the filled prescription of ciprofloxacin). To assess balance with respect to covariates between the matched groups, we used the mean standardised difference. We considered the matching to be balanced if the mean standardised difference was <10%.[26] Missing values were present in 0–3.9% of cases and were imputed using the mode value (Table S3). A sensitivity analysis restricted to complete cases was also conducted (Table S5).

A Cox proportional hazard regression model was used to estimate the hazard ratio (HR) of miscarriage and elective termination of pregnancy. We conducted a graphic and numerical test to ensure that the proportional hazard assumption was fulfilled. To estimate the relative risk ratio (RR) of major malformations, a log binomial model was used. The effect estimates were calculated with the corresponding 95% confidence interval (CI). All statistical tests were two-sided and the estimates were considered statistically insignificant if the 95% CI overlapped 1. Analyses were performed with SAS, version 9.4.

3 | RESULTS

3.1 | Study cohort

A flowchart of the two study cohorts is presented in Figure 1. A total of 1 650 649 pregnancies and 1 192 539 live births were identified. Before matching, women exposed to ciprofloxacin had a higher parity and a higher burden of co-morbidity and were more likely to have a multiple birth pregnancy. The unexposed pregnant women were more likely to be married, have a higher education and a higher household income (Table S4). After propensity score-matching, the study cohorts were trimmed, and three ciprofloxacin-exposed pregnant women were pruned due to a lack of match. All the covariates were well balanced with a mean standardised difference of less than 10% (Table 1). The final cohorts for the analyses of miscarriage and major malformations included 10 250 (2050 ciprofloxacin-exposed) and 6100 (1220 ciprofloxacin-exposed) pregnant women, respectively (Table 1).

3.2 | Outcomes

A total of 171 (8.3%) miscarriages were identified among the ciprofloxacin-exposed pregnancies. The prevalence in the unexposed group was 714 (8.7%), corresponding to HR of 0.99 (95% CI 0.84–1.17). Regarding major malformations, 42 (3.4%) children exposed to maternal ciprofloxacin were diagnosed with a major malformation compared with 167 (3.4%) among the unexposed. The RR was 1.01 (95% CI 0.72–1.40; Figure 2). For the organ-specific major malformations, no significant increased risks were identified (Figure 2).

3.3 | Prespecified sensitivity analyses

Dividing ciprofloxacin-exposed pregnancies into low (≤5 g) and high (>5 g) dose exposure, 8.1% and 8.8% miscarriages were identified. The corresponding HRs were 0.96 (95% CI 0.78–1.17) and 1.05 (95% CI 0.80–1.37; Figure 3) compared with unexposed pregnancies. As for major malformations, 3.5% and 3.4% were diagnosed among the low dose- and high dose-exposed women, corresponding to an RR of 1.01 (95% CI, 0.69–1.49) and 1.00 (95% CI 0.75–1.31), respectively (Figure 3). Among singleton pregnancies, 3.4% of the ciprofloxacin-exposed pregnancies were identified with a major malformation, with an RR of 1.00 (95% CI 0.70–1.42). Finally, late elective termination of pregnancy was identified in 0.4% of the ciprofloxacin-exposed pregnancies compared with 0.3% among the unexposed, corresponding to an HR of 1.11 (95% CI 0.51–2.43; Figure 3).
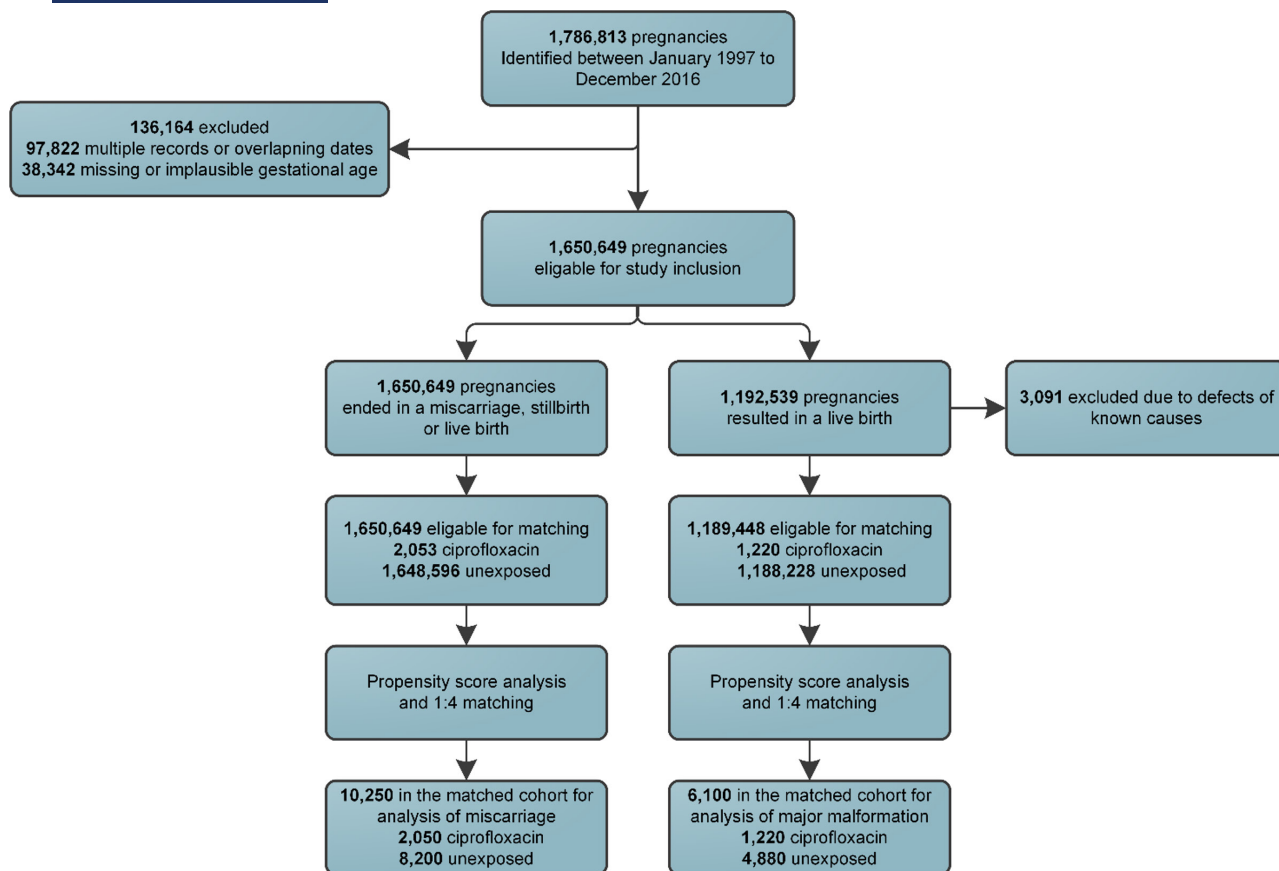
FIGURE 1 Flowchart of the study design

4 | DISCUSSION

4.1 | Main findings

In this large nationwide cohort study, a total of 2050 pregnancies exposed to maternal ciprofloxacin were identified. Among these, no increased risk of a miscarriage or a major malformation was detected. The same applies to the organ-specific major malformations and the sensitivity analyses.

4.2 | Interpretation

In contrast to our results, three previous studies identified an increased risk of adverse pregnancy outcomes among women exposed to quinolones.[10–12] In a nested case–control study, Muanda et al. found an adjusted odds ratio (aOR) of 2.45 (95% CI 1.98–3.03) for miscarriage. The study was based on 114 women exposed to ciprofloxacin during the first 20 weeks of pregnancy.[10] A limitation of the study, despite the small study size, was a significant difference in characteristics among controls and cases, e.g. cases being older, having a higher prior history of abortions and a higher degree of co-morbidities. Furthermore, confounding by severity could have influenced the result, although the underlying infection was considered (by using penicillin as an active

comparator). Among women with a urinary tract infection or a respiratory tract infection, the aORs for miscarriages were 8.73 (95% CI 3.08–24.77) and 1.83 (95% CI 0.50–6.70), respectively. Despite the small numbers, the divergent results might suggest that the adverse events were not caused by the quinolones.

In a cohort study, Muanda et al. investigated the association between major malformations and first-trimester exposure to antibiotics. Contrary to our results, a significant aOR of 1.89 (95% CI 1.09–3.28) for urinary system malformations among women exposed to quinolones was identified.[11] This result was not confirmed among the women exposed to ciprofloxacin (*n* = 608), despite accounting for 75% of the quinolone cases. In addition, the study applied multiple testing without adjusting.

In line with our results, a cohort study by Padberg et al. demonstrated no significantly increased risk of miscarriage (adjusted HR [aHR] was 1.01 [95% CI 0.8–1.3]) among women exposed to fluoroquinolones.[9] This was also evident for major malformations among women exposed to fluoroquinolones and the subgroup restricted to use of ciprofloxacin (aOR 0.91 [95% CI 0.6–1.5] and crude OR 2.4 [95% CI 1.0–4.6]). The study included a total of 949 pregnancies, of which ciprofloxacin exposure was the most prevalently used (*n* = 407). The only significant estimate was the increased risk of elective terminated pregnancies (aHR 1.32 [95% CI 1.03–1.7]); however, the

TABLE 1 Baseline characteristics of the propensity scored-matched cohorts

	Miscarriage			Major malformations		
	No. (%) of pregnancies			No. (%) of pregnancies		
	Ciprofloxacin	Unexposed	Mean standardised difference (%)	Ciprofloxacin	Unexposed	Mean standardised difference (%)
Pregnancies	2050	8200		1220	4880	
Year of pregnancy						
1997–2001	227 (11.1)	825 (10.1)	3.3	118 (9.7)	410 (8.4)	4.4
2002–2006	400 (19.5)	1573 (19.2)	0.8	219 (18.0)	896 (18.4)	1.1
2007–2011	714 (34.8)	2871 (35.0)	0.4	414 (33.9)	1716 (35.2)	2.6
2012–2016	709 (34.6)	2931 (35.7)	2.4	469 (38.4)	1858 (38.1)	0.8
Maternal condition						
Age at pregnancy, year						
<20	83 (4.1)	315 (3.8)	1.1	21 (1.7)	72 (1.5)	2.0
20–24	315 (15.4)	1242 (15.2)	0.6	173 (14.2)	694 (14.2)	0.1
25–29	568 (27.7)	2205 (26.9)	1.8	363 (29.8)	1452 (29.8)	0.0
30–34	649 (31.7)	2709 (33.0)	3.0	422 (34.6)	1726 (35.4)	1.6
>35	435 (21.2)	1729 (21.1)	0.3	241 (19.8)	936 (19.2)	1.5
Smoking	NA	NA	NA	203 (16.6)	784 (16.1)	1.6
Multiple birth pregnancy	NA	NA	NA	29 (2.4)	74 (1.5)	6.2
Previous pregnancies with same fetal outcome	268 (13.1)	1040 (12.7)	1.2	29 (2.4)	117 (2.4)	0.1
Parity						
1	NA	NA	NA	623 (51.1)	2571 (52.7)	3.2
2	NA	NA	NA	373 (30.6)	1478 (30.3)	0.6
≥3	NA	NA	NA	224 (18.4)	831 (17.0)	3.5
Maternal co-morbidity						
Prescription of drugs 1 year prior to conception and during the entire pregnancy						
Antidepressant	210 (10.2)	808 (9.9)	1.3	114 (9.3)	379 (7.8)	5.6
Antidiabetics	42 (2.1)	155 (1.9)	1.1	32 (2.6)	114 (2.3)	1.8
Antiepileptic	41 (2.0)	129 (1.6)	3.2	21 (1.7)	77 (1.6)	1.1
Antihypertension	86 (4.2)	317 (3.9)	1.7	55 (4.5)	173 (3.6)	4.9
Antipsychotic	35 (1.7)	111 (1.4)	2.9	17 (1.4)	61 (1.3)	1.3
Antiviral drugs	94 (4.6)	352 (4.3)	1.4	64 (5.3)	229 (4.7)	2.6
Drug used in IVF treatment	101 (4.9)	382 (4.7)	1.3	74 (6.1)	270 (5.5)	2.3
Extended-spectrum penicillins	831 (40.5)	3399 (41.5)	1.9	537 (44.0)	2180 (44.7)	1.3
Hypnotics	130 (6.3)	492 (6.0)	1.4	75 (6.2)	268 (5.5)	2.8
Macrolides	502 (24.5)	1993 (24.3)	0.4	291 (23.9)	1117 (22.9)	2.3
NSAIDs	525 (25.6)	1912 (23.3)	5.3	306 (25.1)	1119 (22.9)	5.0
Opioids	201 (9.8)	714 (8.7)	3.8	116 (9.5)	436 (8.9)	2.0
Oral corticosteroids	110 (5.4)	370 (4.5)	3.9	70 (5.7)	281 (5.8)	0.1
Suspected teratogens[a]	8 (0.4)	33 (0.4)	0.2	1 (0.1)	0 (0.0)	4.1
Thyroid drugs	45 (2.2)	197 (2.4)	1.4	32 (2.6)	126 (2.6)	0.3
No. of drug filled						
None	534 (26.1)	2176 (26.5)	1.1	297 (24.3)	1213 (24.9)	1.2
1–2 drugs	1134 (55.3)	4651 (56.7)	2.8	696 (57.1)	2894 (59.3)	4.6

(Continues)

TABLE 1 (Continued)

	Miscarriage No. (%) of pregnancies			Major malformations No. (%) of pregnancies		
	Ciprofloxacin	Unexposed	Mean standardised difference (%)	Ciprofloxacin	Unexposed	Mean standardised difference (%)
3–4 drugs	314 (15.3)	1143 (13.9)	3.9	181 (14.8)	607 (12.4)	7.0
≥5 drugs	68 (3.3)	230 (2.8)	3.0	46 (3.8)	166 (3.4)	2.0
No. of hospital admissions						
1	238 (11.6)	904 (11.0)	1.9	133 (10.9)	496 (10.2)	2.4
2	66 (3.2)	229 (2.8)	2.5	40 (3.3)	133 (2.7)	3.2
≥3	29 (1.4)	101 (1.2)	1.6	15 (1.2)	44 (0.9)	3.2
No. of outpatient visits						
1	309 (15.1)	1260 (15.4)	0.8	187 (15.3)	722 (14.8)	1.5
2	111 (5.4)	445 (5.4)	0.1	65 (5.3)	263 (5.4)	0.3
≥3	63 (3.1)	199 (2.4)	4.0	34 (2.8)	118 (2.4)	2.3
Maternal socio-economic status						
Married or cohabit	1515 (73.9)	6107 (74.5)	1.3	969 (79.4)	3899 (79.9)	1.2
Place of birth						
Denmark	1743 (85.0)	6993 (85.3)	0.7	1040 (85.3)	4191 (85.9)	1.8
Europe	98 (4.8)	345 (4.2)	2.8	58 (4.8)	207 (4.2)	2.5
Outside of Europe	209 (10.2)	862 (10.5)	1.0	122 (10.0)	482 (9.9)	0.4
Region of residence						
The Capital Region of Denmark	1099 (53.6)	4298 (52.4)	2.4	429 (35.2)	1766 (36.2)	2.1
Region Zealand	197 (9.6)	827 (10.1)	1.6	171 (14.0)	674 (13.8)	0.6
The Region of Southern Denmark	246 (12.0)	946 (11.5)	1.4	205 (16.8)	751 (15.4)	3.9
Central Denmark Region	382 (18.6)	1617 (19.7)	2.8	311 (25.5)	1283 (26.3)	1.8
The North Denmark Region	126 (6.2)	512 (6.2)	0.4	104 (8.5)	406 (8.3)	0.7
Educational level, year						
<12	658 (32.1)	2607 (31.8)	0.7	354 (29.0)	1372 (28.1)	2.0
12–13	313 (15.3)	1252 (15.3)	0.0	179 (14.7)	764 (15.7)	2.7
14–15	380 (18.5)	1544 (18.8)	0.8	240 (19.7)	955 (19.6)	0.3
>15	699 (34.1)	2797 (34.1)	0.0	447 (36.6)	1789 (36.7)	0.0
Household income, quartile						
Lowest	630 (30.7)	2519 (30.7)	0.0	374 (30.7)	1491 (30.6)	0.2
Low	482 (23.5)	1886 (23.0)	1.2	282 (23.1)	1106 (22.7)	1.1
Medium	431 (21.0)	1738 (21.2)	0.4	268 (22.0)	1059 (21.7)	0.6
High	507 (24.7)	2057 (25.1)	0.8	296 (24.3)	1224 (25.1)	1.9

Note: For miscarriages, the ciprofloxacin exposure period was within the first 22 weeks of pregnancy. For major malformations, the exposure period was restricted to the first 12 weeks of pregnancy.

Abbreviations: IVF, *in vitro* fertilisation; NA, not available.

[a]Acitretin, carbamazepine, isotretinoin, lenalidomide, methotrexate, mycophenolate, phenobarbital, phenprocoumon, phenytoin, thalidomide, valproate, warfarin, angiotensin type-1 antagonist, angiotensin-converting enzyme inhibitor.

underlying indication (social, embryopathology, maternal or unknown) did not differ between the exposed and unexposed.

Finally, a review and meta-analysis by Yefet et al. investigated the safety of quinolones and fluoroquinolones during pregnancy and their conclusions align with ours.[4] A total of nine cohort studies and four case–control studies were included. For first trimester exposure, based on five studies, the pooled OR for miscarriage was 1.78 (95% CI 0.93–3.38). Based on seven studies, a nonsignificant increased risk of

OUTCOME	Ciprofloxacin	Unexposed	
Miscarriage	n = 2,050	n = 8,200	Hazard ratio (95% CI)
	171 (8.3%)	714 (8.7%)	0.99 (0.84-1.17)
Major malformations	n = 1,220	n = 4,880	Relative risk (95% CI)
All major malformations	42 (3.4%)	167 (3.4%)	1.01 (0.72-1.40)
Organ-specific malformations			
Nervous system	3 (0.2%)	7 (0.1)	1.71 (0.44-6.62)
Congenital Heart Defects	14 (1.1%)	49 (1.0)	1.14 (0.63-2.06)
Digestive system	3 (0.2%)	15 (0.3)	0.80 (0.23-2.76)
Genital	3 (0.2%)	15 (0.3)	0.80 (0.23-2.76)
Limb	7 (0.6%)	32 (0.7)	0.88 (0.39-1.98)
Other major malformations	4 (0.3%)	13 (0.3)	1.23 (0.40-3.77)
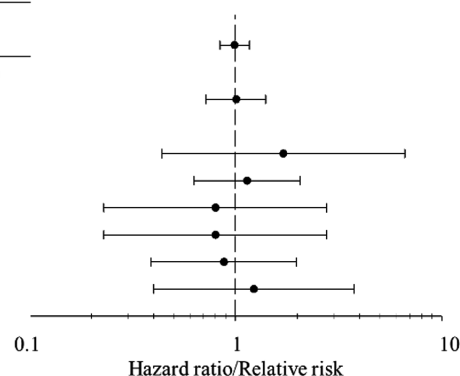
FIGURE 2 The association between maternal ciprofloxacin exposure and the risk of miscarriage and major malformations. Propensity score-matched analyses (1:4). Data are presented as n (%). CI: confidence interval. Subgroups of major malformations with fewer than three cases are not presented

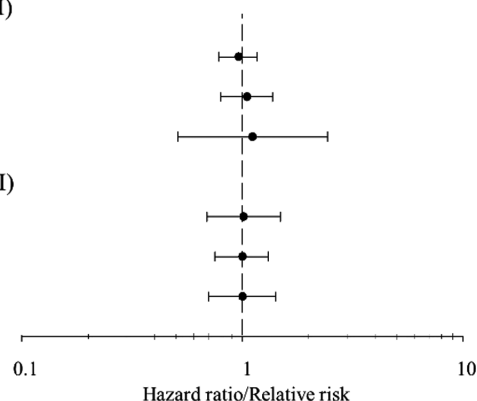|	Ciprofloxacin	Unexposed	
	No. with outcome/total no.		
Miscarriage			Hazard ratio (95% CI)
Low dose vs. none	112/1,377	714/8,200	0.96 (0.78-1.17)
High dose vs. none	59/673	714/8,200	1.05 (0.80-1.37)
Termination of pregnancy	8/2,050	30/8,200	1.11 (0.51-2.43)
Major malformations			Relative risk (95% CI)
Low dose vs. none	29/837	167/4,880	1.01 (0.69-1.49)
High dose vs. none	13/383	167/4,880	1.00 (0.75-1.31)
Singleton pregnancies	40/1,191	162/4,806	1.00 (0.70-1.42)

FIGURE 3 Sensitivity analyses. Data are presented as n. Low dose and high dose are defined as accumulated ciprofloxacin exposure of ≤5 g and >5 g, respectively

major malformation was estimated (pooled OR 1.08 [95% CI 0.90–1.29]). The authors find that quinolones are not associated with adverse pregnancy outcomes but acknowledged the lack of homogeneity among the included studies. They therefore advocated for the need for larger studies before the safety of ciprofloxacin during pregnancy could be established.

4.3 | Strengths and limitations

A major strength of our study is the large sample size including 2050 pregnancies exposed to ciprofloxacin. Furthermore, data were collected over a 20-year period from nationwide registries covering the entire Danish population with a high validity and completeness.[19,20] By conducting analyses based on these registries, selections bias and recall bias are eliminated and loss to follow-up is minimised.

A limitation of the study is the definition of drug exposure. This was based on filled drug prescriptions identified in the Danish Prescription Registry. In Denmark, all

pharmacies are required by law to register all redeemed drug prescriptions, and the quality and completeness of the data are high;[22] however, a filled drug prescription may not reflect actual drug use. For drugs used to manage chronic diseases, compliance is high among pregnant women compared with drugs used for short treatment courses.[27] Nevertheless, as the pregnant woman goes to the physician, receives a prescription, goes to the pharmacy and buys the drug, a high degree of adherence is expected. Furthermore, in Denmark, ciprofloxacin is mainly used to treat complicated infections, that is, an infection not responding sufficiently to the initial antibiotic treatment; hence an even higher compliance is therefore likely. Nevertheless, non-adherence to the dispensed drug would bias the result toward the null effect. For the unexposed, the risk of misclassification is limited, as women redeeming ciprofloxacin 3 months prior to conception were excluded. Medication borrowed from another patient or bought abroad is possible but less likely.

Miscarriages and malformations were identified in the Danish National Patient Registry, a registry with a

high positive predictive value and high completeness.[19-21] However, the use of ICD-10 codes and EUROCAT classification system has some limitations, e.g. rarely occurring malformations do not have a specific ICD-10 code, making them difficult to identify. Therefore, we cannot rule out the occurrence of these rare malformations and a possible association with ciprofloxacin exposure; more importantly, we do not have the power to detect the rarely occurring malformations. Furthermore, the ICD-10 code definitions are not 100% identical between countries, even in Europe, although to our knowledge this is the best standardised method available.

To ensure proper matching, we used the propensity score. We included both true confounders (associated with both exposure and outcome) and potential confounders (related to outcome). Although important covariates were included, body mass index (BMI), alcohol consumption and folic acid supplements were not available and therefore residual confounding has not been fully eliminated. Fortunately, as Danish pregnant women have a high folic acid consumption (70%) and a low prevalence of abundant alcohol intake (>7 units per week) or severe obesity, we expect that residual confounding is reduced to a minimal.[28,29]

Finally, confounding by indication (the underlying indication for being treated) and/or confounding by severity (the severity of the infections) could have influenced our estimates. However, as no increased risks were identified in either the main analysis or in the sensitivity analyses, we believe that our estimates was not biased by the presence of the infection.

4.4 | Indications/contraindications for ciprofloxacin in pregnancy

Based on the WHO List of Essential Medicines, ciprofloxacin should be used as first line of treatment for various infectious diseases, e.g. paratyphoid fever, typhoid fever, acute pyelonephritis, and gastroenteritis without specification of the infectious agent.[30] These recommendations do not, however, account for selected populations, e.g. pregnant women. The current recommendation states that ciprofloxacin should be avoided during pregnancy based on evidence from animal studies,[4,5] but based on our results and other previous human studies,[6-9,31] we argue that there is no association between exposure to ciprofloxacin and adverse events. Nevertheless, penicillins and other small-spectrum antibiotics should be the preferred choice during pregnancy. Only when intolerance to first-line antibiotics, allergy or bacterial resistance is apparent, should ciprofloxacin be recommended in order to avoid suboptimal therapy or treatment failure.

5 | CONCLUSION

In this large nationwide cohort study, we demonstrated no association between ciprofloxacin and an increased risk of miscarriage and major malformations, suggesting that a moderate to large increase of these is unlikely.

AUTHOR CONTRIBUTIONS

MN contributed to the design of the study and drafted the manuscript. DRG and AMSS contributed to the interpretation of the results and critically reviewed the manuscript. JTA contributed to the design of the study, conducted the statistical analyses and critically reviewed the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

The study was approved by the Danish Data Protection Agency on 11 February 2020. Reference number: P-2021–113.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available with the permission of Danish Protection Agency (P-2021–113).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.