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Original Article

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Quinolone Use during the First Trimester of Pregnancy and the Risk of Atopic Dermatitis, Asthma, and Allergies of Offspring during 2011 to 2020

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ABSTRACT

Background: Many pregnant women receive antibiotic treatment for infections. We investigated the association between quinolone use in the first trimester of pregnancy and the risk of adverse health outcomes for the child in Korea.
Materials and Methods: This nationwide, population-based cohort study used data on mother-child pairs from the National Health Insurance claims database. This study cohort included 2,177,765 pregnancies from January 1, 2011, to December 31, 2020, and 87,456 women were prescribed quinolones during pregnancy. After propensity score matching, the final number of study subjects was 84,365 for both quinolone and non-antibiotic users. We examined the subjects' exposure to quinolone antibiotics. The main outcome measures were absolute and relative risks of atopic dermatitis, asthma, and allergies. We adjusted for potential confounders.
Results: Quinolones were prescribed at least once during the first trimester in 4.01% of pregnancies. Quinolone users had significantly higher absolute risks than non-antibiotic users for atopic dermatitis, asthma, and allergies, with significantly elevated risk ratios (RRs) for these conditions (atopic dermatitis: RR, 1.09; 95% confidence interval [CI], 1.08–1.11, asthma: RR, 1.04; 95% CI, 1.03–1.05, and allergies: RR, 1.10; 95% CI, 1.08–1.13).
Conclusion: We found that quinolone exposure during the first trimester of pregnancy increased the risk of atopic dermatitis, asthma, and allergies. This study could provide physicians with useful information when selecting antibiotics for pregnant women.

Keywords: Antibiotics; Quinolone; Atopic dermatitis; Asthma; Allergies

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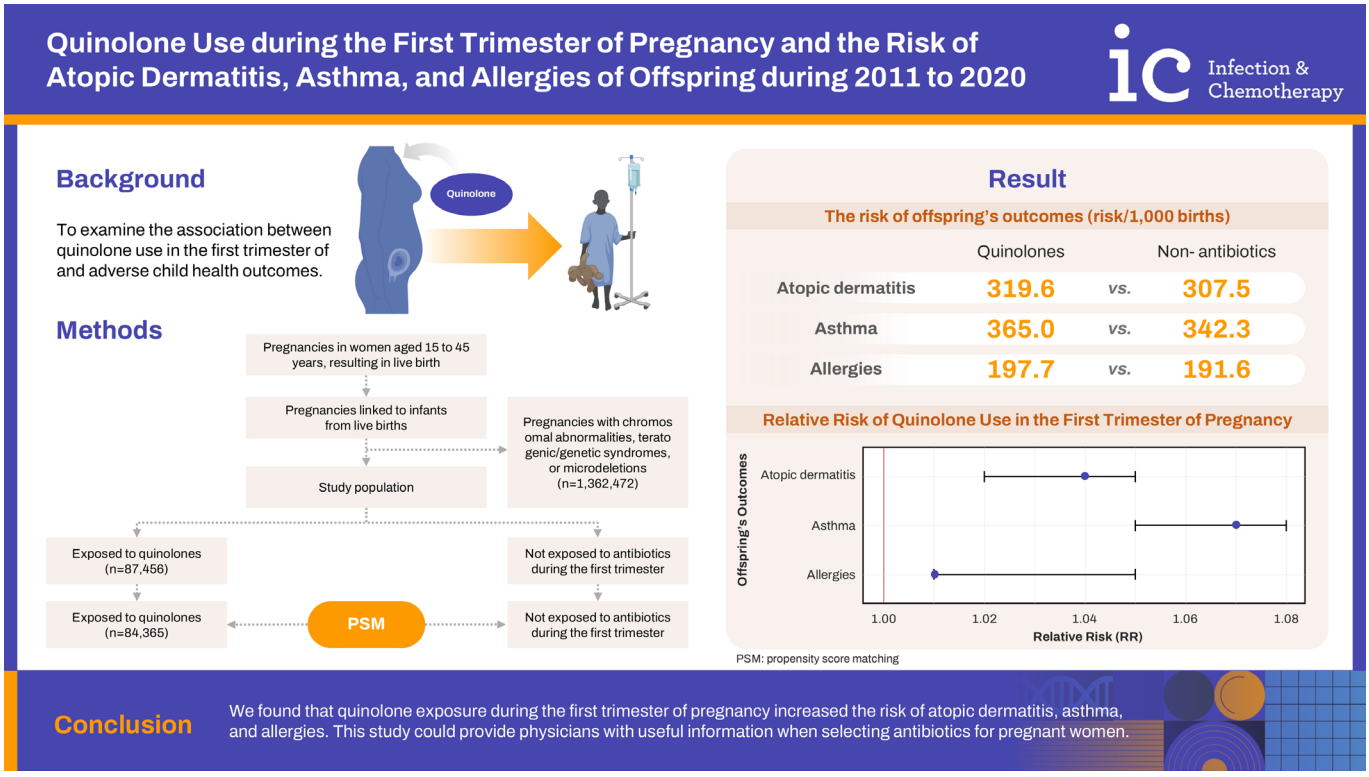
GRAPHICAL ABSTRACT



INTRODUCTION

During pregnancy, women often experience a range of infections due to physiological changes, increased susceptibility to infections, and adaptations within the immune system. Death from maternal sepsis and other pregnancy-related infections occurred at 21.2 thousands in 195 countries [1] and the evidence of literature review reported that pregnancy is associated with increased severity of some infectious diseases, such as influenza, malaria, hepatitis E, and herpes simplex virus infection [2]. Consequently, antibiotics are frequently prescribed [3], with approximately 20-60% of pregnant women receiving them [4, 5]. Although the use of antibiotics may be necessary to treat infectious diseases, the safety of macrolides, quinolones, and tetracyclines during pregnancy is still not definitively established [3, 6-10]. Furthermore, the overuse and inappropriate use of antibiotics during pregnancy can contribute to the development of antimicrobial resistance, posing risks not only to the current generation but also potentially causing adverse effects on the developing fetus, leading to various negative health outcomes such as miscarriage, birth defects, preterm birth, and low birth weight [8, 9, 11-13]. Therefore, antibiotic prescriptions should be used with caution to safeguard both maternal and fetal health.

Atopic dermatitis, asthma, and allergies are common childhood diseases, and their substantial disease burden has become a significant global public health issue [14, 15]. The prevalence of atopic diseases varies widely, ranging from approximately 6% to 25% [16]. In recent decades, the incidence has risen sharply, with reports indicating that around 13% of children and 7% of adults in the United States are affected by atopic dermatitis [17, 18]. The global prevalence of asthma defined by current wheezing and ever wheezing, is estimated to be 1181.3 million (17.9%) among individuals aged 5-69 years [19] and 11.7% within the 6- to 7-year age group [20]. Also, the prevalence of allergic diseases in childhood is significant; within a population-based cohort, 40-50% of children experienced symptoms of allergic disease within the first 4 years of life [21].

The adverse effects of quinolone use on birth, including birth defects, stillbirths, preterm births, and low birth weight are mixed [8, 22, 23]. According to recent studies, maternal antibiotic use during pregnancy increases the risk

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of atopy [24-27]. Identifying the risk of atopy from quinolone exposure during pregnancy is important because it indicates that this issue (quinolone exposure during pregnancy) should be the focus of obstetrical and neonatological attention, as well as a pediatric health concern.

However, research examining the impact of quinolones on the prevalence of atopic dermatitis, asthma, and allergic diseases is limited. Furthermore, no studies have been conducted in Korea to explore the health outcomes associated with antibiotic use during pregnancy.

The current study aimed to investigate the associations between quinolone use during the first trimester of pregnancy and the risk of atopic dermatitis, asthma, and allergic diseases in children. This investigation utilized nationwide National Health Insurance (NHI) claims data from Korea, spanning the years 2011–2020.

MATERIALS AND METHODS

1. Data source and study design

This study is a retrospective nationwide propensity-matched cohort analysis. We utilized claims data from the Korean NHI system, encompassing general hospitals, hospitals, and clinics, spanning from January 2011 to December 2020. Korea operates a single-payer insurance system, which reimburses medical service costs through a fee-for-service model accessible to all citizens. The NHI claims data employed in our research includes information on 50 million Koreans, encompassing records of surgical procedures, treatments, and prescribed medications. Since 2007, billing has been conducted electronically, with each patient receiving a unique anonymized identification number. Disease coding follows the International Classification of Diseases, 10th revision (ICD-10), with an accuracy rate of 82% for the assignment of disease codes. Medications are billed using distinct identification numbers linked to each product name. The majority of prescription drugs, such as antibiotics, require a doctor's prescription for purchase, ensuring that most medications are documented in the NHI billing data [28]. The requirement for informed consent was waived, as this study was conducted using anonymized claims data.

2. Ethics statement

This study was approved by the Institutional Review Board of Health Insurance Review & Assessment Service, Korea (2021-016).

3. Study population

This study did not involve any patient participation. We focused on a pregnancy cohort comprising women aged 15 to 45 years at the time of delivery, spanning from January 2011 to December 2020. We excluded women whose pregnancies ended in miscarriages attributed to malformation and deformity syndrome, including congenital anomalies, deformities, and chromosomal abnormalities (ICD-10 codes Q00-Q99). Additionally, we paired mothers with their children by using the health insurance identification numbers that were common within the same household. We successfully linked 3,540,227 mother-infant pairs, which represented 98.5% of the total 3,595,114 pairs (**Fig. 1**).

To calculate the pregnancy trimester, the expected date of delivery was established as the date of either vaginal delivery or cesarean section. Working backward from the date of delivery, the third trimester encompassed the period during which delivery occurred, specifically

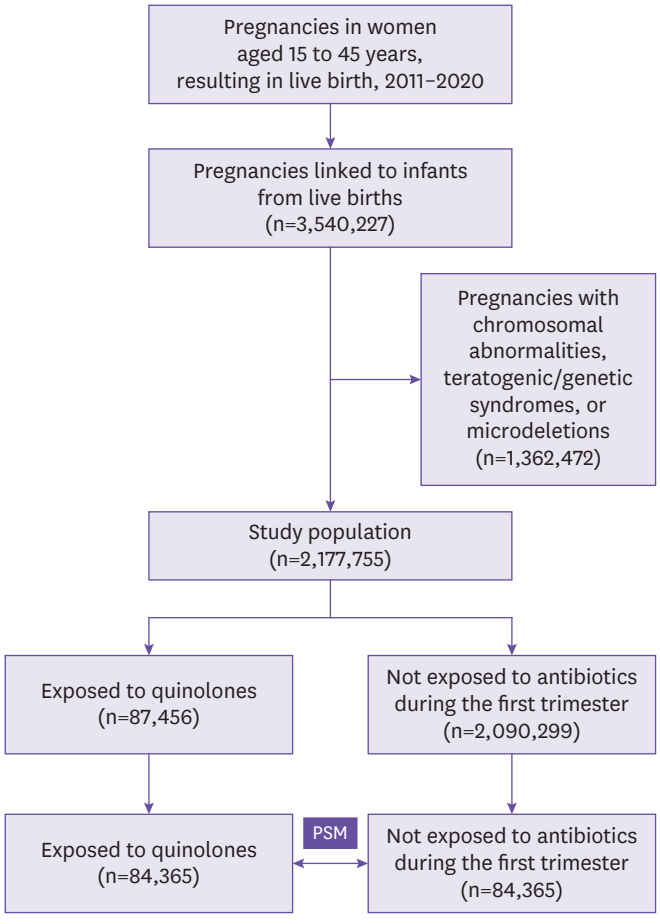

Figure 1. Flowchart of the study cohort.
PSM, propensity score matching.

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from the date of delivery to 90 days prior. The second trimester spanned the 90 days immediately preceding the third trimester, approximately 91 to 180 days before the delivery date. The first trimester covered the period starting roughly 181 days before the delivery date, extending back to the date of the last menstrual period before pregnancy.

4. Definition of exposure to quinolone antibiotics

We examined subjects' exposure to quinolones during the first trimester of pregnancy.

Therapeutic subgroups were classified according to the Anatomic Therapeutic Chemical (ATC) classification of the World Health Organization Collaborating Center [29]. For the purposes of this study, quinolone antibiotics were specifically identified as J01MA (fluoroquinolones) within the ATC classification.

We examined the subjects' exposure to quinolone antibiotics during the first trimester. Our comparison involved cases where pregnant women who gave birth had used quinolone antibiotics against those who were not prescribed any antibiotics. A subject was considered exposed to quinolones if they had been prescribed at least one quinolone prescription during the first trimester.

Each drug is registered in the NHI reimbursement list with a unique manufacturer number, individual product number, active ingredient code, dose, and formulation. We used the main active ingredient name and route of administration to map the ATC classification, and we categorized the antibiotics according to the ATC-3 level, which corresponds to the pharmacological subgroup.

Drug exposure was determined by calculating the cumulative duration of use during the first trimester. This included prescriptions for antibiotics issued after both hospital admissions and outpatient consultations. To ascertain cumulative quinolone use, we considered the prescription date and the prescribed duration of therapy. Patients were categorized based on their quinolone use (users versus non-users) and the length of time they were treated with quinolone (less than 7 days, or 7 days or more).

5. Outcomes and confounding variables

The outcome variables in this study included asthma, atopic dermatitis, and allergies in children. The specific diseases were coded according to the ICD-10 as follows: J45-46 for asthma and acute severe asthma, L20 for atopic dermatitis, H101 for acute atopic conjunctivitis, J30 for vasomotor and allergic rhinitis, T784 for unspecified allergies, and Z88 for a personal history of allergies to drugs, medicaments, and biological substances.

The study followed children born between 2011 and 2020, monitoring for the onset of asthma, atopic dermatitis, or allergies, until either the occurrence of one of these conditions, the death of the child, or the conclusion of the study period on December 31, 2020.

The confounding variables included demographic characteristics such as age, type of medical insurance, primiparity, and multifetal pregnancy. Additionally, maternal health conditions (respiratory tract infection, asthma, atopic dermatitis, allergies, high blood pressure, diabetes mellitus, renal disease, gastrointestinal disease, urinary tract infection, sexually transmitted infections, and drug dependence) and healthcare utilization (number of diagnoses, emergency department visits, hospitalizations, and outpatient visits) were considered. Diseases treated with antibiotics, including respiratory infections, pneumonia, urinary tract infections, and sexually transmitted diseases, were also accounted for. Finally, the utilization of healthcare services was factored in, which encompassed the number of distinct diagnoses, emergency room visits, hospitalizations, and the number of outpatient visits. Maternal comorbidities and the use of concomitant medications were assessed from six months prior to the last menstrual period up to the end of the first trimester.

To control for confounding factors, we calculated the propensity score for exposure to quinolones versus non-exposure by employing a logistic regression model that incorporated all covariates without further selection.

6. Statistical analysis

We used the chi-square test and the *t*-test to compare the demographic and clinical characteristics of quinolone users with those of non-antibiotic users. Standardized difference values were used to assess the disparity in quinolone exposure during pregnancy. To compare the baseline characteristics of women exposed to antibiotics during pregnancy with those who were not, we used absolute standardized differences. A value of the adjusted standard deviation of ≥0.1 was considered indicative of a significant imbalance between the groups. We calculated the absolute risk (per 1,000 pregnancies), risk difference,

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and unadjusted relative risk (RR) with a 95% confidence interval (CI) for each outcome, stratified by antibiotic exposure. Additionally, we determined the difference in risk using 1:1 propensity score matching, which accounted for demographic characteristics, diseases in pregnant women, and medical use among those using quinolones compared to those not using antibiotics during pregnancy.

Subgroup analyses and sensitivity analyses were conducted to support the findings. The subgroup analysis considered factors such as maternal age, multiple births, and the use of quinolone antibiotics. For the sensitivity analysis, we compared quinolone users with non-antibiotic users among pregnant women diagnosed with conditions like asthma, atopic dermatitis, and allergies. Additionally, we assessed the robustness of our results by examining data from quinolone users and non-users in a cohort of mothers without prior childbirth experience. In the negative control group analysis, we investigated instances where infants developed asthma, atopic dermatitis, or allergies after being exposed to quinolones within 180 days before the confirmation of the first pregnancy.

We also examined the association between the use of Penicillin in first trimester of pregnancy and the risk of atopic dermatitis, asthma, and allergic diseases in infants.

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

1. General characteristics

Our cohort included 2,177,755 pregnancies and 87,456 (4.0%) had received at least one prescription for quinolones during the first trimester. **Table 1** presents the general characteristics of both the overall cohort and the matched cohort.

In the overall cohort, the mean ages of quinolone users and antibiotic non-users were 31.8 and 32.2 years, respectively. The 31- to 35-year age group comprised approximately half of the cohort. Among quinolone users, 27.9% were in their 20s, which was higher than

Table 1. General characteristics of the overall cohort and matched cohort

Characteristics	Non-matched cohort			Propensity score-matched cohort		
	Quinolones (n=87,456)	Non-antibiotics (n=2,090,299)	aSD	Quinolones (n=84,365)	Non-antibiotics (n=84,365)	aSD
Maternal age (mean±SD), years	31.83±4.26	32.19±4.07	−0.088	31.83±4.22	31.83±4.21	0.000
Maternal age, n (%)						
20–25 years	4,374 (5.0)	77,198 (3.7)	−0.064	4,047 (4.8)	4,047 (4.8)	0.000
26–30 years	19,992 (22.9)	414,569 (19.8)	−0.074	19,246 (22.8)	19,246 (22.8)	0.000
31–35 years	40,501 (46.3)	1,022,919 (48.9)	0.053	39,442 (46.8)	39,442 (46.8)	0.000
36–40 years	19,398 (22.2)	499,900 (23.9)	0.041	18,686 (22.2)	18,686 (22.2)	0.000
41–45 years	3,191 (3.7)	75,713 (3.6)	−0.001	2,944 (3.5)	2,944 (3.5)	0.000
Obstetric classification						
Primiparity, n (%)	45,608 (52.2)	1,136,436 (54.4)	0.044	44,024 (52.2)	44,024 (52.2)	0.000
Multifetal pregnancy, n (%)	1,272 (1.5)	21,503 (1.0)	−0.038	1,085 (1.3)	1,085 (1.3)	0.000
Comorbidities, n (%)						
RTI	49,411 (56.5)	327,190 (15.7)	−0.940	47,218 (56.0)	47,218 (56.0)	0.000
Asthma	22,908 (26.2)	129,953 (6.2)	−0.563	21,854 (25.9)	21,854 (25.9)	0.000
Atopic dermatitis	792 (0.9)	11,603 (0.6)	−0.041	629 (0.8)	629 (0.8)	0.000
Allergies	2,355 (2.7)	27,510 (1.3)	−0.098	2,075 (2.5)	2,075 (2.5)	0.000
Hypertension	578 (0.7)	9,972 (0.5)	−0.024	424 (0.5)	424 (0.5)	0.000
Diabetes mellitus	576 (0.7)	7,663 (0.4)	−0.041	391 (0.5)	391 (0.5)	0.000
Renal disease	439 (0.5)	2,027 (0.1)	−0.074	238 (0.3)	238 (0.3)	0.000
Gastrointestinal disease	34,930 (39.9)	220,326 (10.5)	−0.719	30,933 (38.2)	30,933 (38.2)	0.000
Urinary tract infection	4,445 (5.1)	4,772 (0.2)	−0.305	2,672 (3.2)	2,672 (3.2)	0.000
Sexually transmitted infection	2,610 (3.0)	21,842 (1.0)	−0.138	2,166 (2.6)	2,166 (2.6)	0.000
Drug dependence	41 (0.1)	419 (0)	−0.015	17 (0)	17 (0)	0.000
Healthcare utilization						
No. of diagnoses (mean±SD)	4.55±2.95	2.79±2.30	0.666	4.44±2.79	4.43±2.78	0.002
No. of ER visits, n (%)	9,352 (10.7)	115,455 (5.5)	−0.190	8,399 (10.0)	8,399 (10.0)	0.000
No. of hospitalizations, n (%)	7,090 (8.1)	102,419 (4.9)	−0.130	6,333 (7.5)	6,333 (7.5)	0.000
No. of outpatient visits (mean±SD)	8.31±7.33	4.78±5.11	0.558	8.05±6.73	7.88±6.57	0.027

aSD, adjusted standard deviation; SD, standard deviation; RTI, respiratory tract infection; ER, emergency room.

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the 23.5% observed in non-antibiotic users. Conversely, 72.2% of quinolone users were aged 30 or older, a lower percentage than that of the non-users. Nulliparous mothers made up 52.2% of the quinolone users. Additionally, the incidence of multifetal pregnancy was 1.5% among quinolone users, slightly higher than the 1% seen in the antibiotic non-user group.

The prevalence of comorbidities was higher in quinolone users compared to non-users for conditions such as acute respiratory tract infections, asthma, atopic dermatitis, allergies, hypertension, diabetes, gastrointestinal diseases, urinary tract infections, sexually transmitted infections, and drug dependence, with the exception of renal disease. Among quinolone users, 10.7% had a history of emergency room visits and 17.1% had been hospitalized, in contrast to 5.5% and 4.4% of non-antibiotic users, respectively. Additionally, the average number of days with physician encounters was 8.31 for quinolone users, compared to 4.78 for those not using antibiotics.

After propensity score matching, the final number of study subjects was 84,356 in each group. Following the matching process, the distributions of age and comorbidities were nearly identical between the groups. The average number of physician encounters was 8.31 for quinolone users and 4.78 for those who did not use antibiotics.

2. Risk of outcomes in offspring

Table 2 presents the incidence of asthma, atopic dermatitis, and allergies in offspring of quinolone users compared to non-antibiotic users in the overall cohort and the propensity score-matched cohort. The absolute risk for atopic dermatitis was 320.2 per 1,000 births among quinolone users, versus 288.9 per 1,000 births among non-antibiotic users, with a risk difference of 31.3. For asthma, the rates were 365.6 and 321.4 per 1,000 births, respectively, resulting in a risk difference of 44.2. Allergies showed an absolute risk of 197.8 per 1,000 births in quinolone users compared to 179.6 per 1,000 births in non-antibiotic users, with a risk difference of 18.2 in the total population. Even after adjusting for propensity scores, the absolute risk remained higher in quinolone users than in non-antibiotic users.

We conducted an exploratory analysis of a matched cohort assessing the risk of various outcomes. The use of quinolones during the first trimester might be associated with an increased risk of atopic dermatitis (RR, 1.04; 95% CI, 1.02–1.05), asthma (RR, 1.07; 95% CI, 1.05–1.08), and allergies (RR, 1.01; 95% CI, 1.01–1.05).

3. Subgroup analysis

As shown in **Table 3**, when stratified by subgroup, the RR of atopic dermatitis was 1.03 for individuals under 35 years of age and 1.05 for those aged 35 and older, compared to non-users. For those experiencing their first pregnancy, the RR was 1.03, while it was 1.05 for subsequent pregnancies. The RR for those with multifetal births was 1.04, but this risk elevation was not significant; for those with singleton pregnancies, it was also 1.04.

Similarly, the RR of asthma and allergies was comparable across each subgroup, and the magnitude of the RR was larger in asthma.

4. Components of quinolones

Upon analyzing the components of various antibiotics, we found inconsistent results concerning the relationship between quinolone components and the incidence of atopic dermatitis, asthma, and allergies. There was an increased risk of atopic dermatitis associated with all quinolones studied, with RRs ranging from 1.02 to 1.09. Additionally, the risk of asthma was found to be slightly elevated with the use of ofloxacin (RR, 1.08) and levofloxacin (RR, 1.10). The risk of allergies was also higher for most quinolones, with RRs between 1.03 and 1.08, with the exception of ofloxacin and enoxacin, which did not show this increase (**Table 4**).

5. Sensitivity analysis

As shown in **Table 5** our main findings remained consistent in all sensitivity analyses when redefining

Table 2. Associations between quinolone use during the first trimester and the risk of offspring's outcomes (risk/1,000 births)

Outcomes	Non-matched cohort				Propensity score-matched cohort			
	Quinolones	Non-antibiotics	RD_{1000}	RR (95% CI)	Quinolones	Non-antibiotics	RD_{1000}	RR (95% CI)
Atopic dermatitis	320.2	288.9	31.3	1.11 (1.10–1.12)	319.6	307.5	12.1	1.04 (1.02–1.05)
Asthma	365.6	321.4	44.2	1.14 (1.13–1.15)	365.0	342.3	22.7	1.07 (1.05–1.08)
Allergies	197.8	179.6	18.2	1.10 (1.09–1.12)	197.7	191.6	6.1	1.03 (1.01–1.05)
All	372.5	406.9	−34.4	1.06 (1.05–1.06)	626.7	613.8	12.9	1.02 (1.01–1.03)

RD, risk difference; RR, relative risk; CI, confidence interval.

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Table 3. Subgroup analysis of quinolone use with the risk of offspring's outcomes (risk/1,000 births)

Characteristics	Non-matched cohort				Propensity score-matched cohort			
	Quinolone	Non-antibiotics	RD_{1000}	RR (95% CI)	Quinolone	Non-antibiotics	RD_{1000}	RR (95% CI)
Atopic dermatitis								
Maternal age								
≤35	320.1	290.1	30.0	1.10 (1.09–1.12)	319.6	309.1	10.5	1.03 (1.02–1.05)
>35	320.4	285.5	34.9	1.12 (1.10–1.14)	319.3	302.8	16.6	1.05 (1.03–1.08)
Primiparity								
No	323.2	287.8	35.4	1.12 (1.11–1.14)	322.5	308.1	14.4	1.05 (1.03–1.07)
Yes	317.4	289.8	27.7	1.10 (1.08–1.11)	316.9	306.9	10.0	1.03 (1.01–1.05)
Multifetal pregnancy								
No	319.4	288.4	31.0	1.11 (1.10–1.12)	318.9	306.9	12.0	1.04 (1.02–1.05)
Yes	374.2	338.6	35.7	1.11 (1.03–1.19)	367.7	352.1	15.7	1.04 (0.93–1.17)
Prescription length								
<7 days	318.7	288.9	29.9	1.10 (1.09–1.12)	318.2	307.5	10.7	1.03 (1.02–1.05)
≥7 days	321.9	288.9	33.0	1.11 (1.10–1.13)	321.2	307.5	13.8	1.04 (1.03–1.06)
Child age								
0–3 years	230.9	203.8	27.1	1.13 (1.09–1.18)	228.8	223.7	5.1	1.02 (0.97–1.08)
4–6 years	274.7	254.8	20.0	1.08 (1.05–1.10)	272.7	273.6	2.4	1.00 (0.97–1.03)
≥6 years	348.0	324.0	24.0	1.07 (1.06–1.09)	347.5	345.2	2.3	1.01 (0.99–1.02)
Asthma								
Maternal age								
≤35	366.9	323.8	43.1	1.06 (1.05–1.07)	366.4	345.9	20.5	1.06 (1.04–1.08)
>35	361.8	315.0	46.8	1.06 (1.05–1.07)	360.7	331.9	28.8	1.09 (1.06–1.12)
Primiparity								
No	428.2	373.8	54.4	1.06 (1.05–1.07)	427.4	397.1	30.3	1.08 (1.06–1.09)
Yes	308.2	277.4	30.8	1.05 (1.04–1.06)	307.8	292.1	15.7	1.05 (1.03–1.08)
Multifetal pregnancy								
No	365.0	320.8	44.2	1.06 (1.05–1.07)	364.4	341.3	23.1	1.07 (1.05–1.08)
Yes	406.4	380.0	26.4	1.07 (1.02–1.11)	408.3	420.3	12.0	0.97 (0.88–1.07)
Prescription length								
<7 days	367.6	321.4	46.2	1.06 (1.05–1.07)	367.3	342.3	25.0	1.07 (1.06–1.09)
≥7 days	363.3	321.4	41.9	1.06 (1.05–1.07)	362.2	342.3	19.9	1.06 (1.04–1.08)
Child age								
0–3 years	179.5	153.7	25.8	1.1 (1.07–1.12)	177.0	172.3	4.6	1.03 (0.97–1.09)
4–6 years	312.0	284.9	27.1	1.05 (1.03–1.06)	310.0	305.5	4.4	1.01 (0.99–1.04)
≥6 years	410.0	376.3	33.8	1.04 (1.04–1.05)	409.2	402.8	6.4	1.02 (1.00–1.03)
Allergies								
Maternal age								
≤35	195.5	179.1	16.4	1.09 (1.07–1.11)	195.5	191.4	4.0	1.02 (1.00–1.04)
>35	204.3	181.0	23.4	1.13 (1.10–1.16)	204.1	192.1	12.0	1.06 (1.02–1.10)
Primiparity								
No	204.7	181.7	23.0	1.13 (1.10–1.15)	204.4	195.1	9.3	1.05 (1.02–1.08)
Yes	191.5	177.9	13.6	1.08 (1.06–1.10)	191.6	188.5	3.1	1.02 (0.99–1.04)
Multifetal pregnancy								
No	197.3	179.1	18.2	1.10 (1.09–1.12)	197.2	191.1	6.1	1.03 (1.01–1.05)
Yes	235.1	231.5	3.5	1.02 (0.92–1.12)	235.9	230.4	5.5	1.02 (0.88–1.19)
Prescription length								
<7 days	196.4	179.6	16.7	1.09 (1.07–1.11)	196.2	191.6	4.6	1.02 (1.00–1.05)
≥7 days	199.5	179.6	19.9	1.11 (1.09–1.13)	199.5	191.6	7.9	1.04 (1.02–1.07)
Child age								
0–3 years	93.8	80.3	13.4	1.17 (1.09–1.25)	93.0	86.9	6.1	1.07 (0.98–1.17)
4–6 years	176.7	162.9	13.9	1.09 (1.05–1.12)	176.1	176.4	2.4	1.00 (0.96–1.04)
≥6 years	219.7	209.9	9.8	1.05 (1.03–1.06)	219.4	225.1	−5.8	0.97 (0.95–1.00)

RD, risk difference; RR, relative risk; CI, confidence interval.

the exposure and outcomes and restricting the analysis to pregnancies in women with atopic dermatitis and nulliparous pregnancies, as well as in the negative control analysis for atopic dermatitis and allergies. For

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Table 4. Associations between quinolone use during the first trimester and the risk of outcomes of offspring

Class		Non-matched			Propensity score-matched		
		Quinolones (N=87,456)		Relative risk (95% CI)	Quinolones (N=84,365)		Relative risk (95% CI)
		No. of events	Risk/1,000 births		No. of events	Risk/1,000 births	
Atopic dermatitis							
J01MA01	Ofloxacin	10,118	324.7	1.12 (1.11-1.14)	9,859	323.7	1.05 (1.03-1.07)
J01MA02	Ciprofloxacin	10,300	313.3	1.08 (1.07-1.10)	9,811	313.2	1.02 (1.00-1.04)
J01MA04	Enoxacin	887	335.2	1.16 (1.10-1.22)	849	334.6	1.09 (1.03-1.15)
J01MA06	Norfloxacin	1,188	334.8	1.16 (1.11-1.21)	1,145	333.8	1.09 (1.03-1.14)
J01MA07	Lomefloxacin	1,051	333.3	1.16 (1.10-1.21)	1,004	333.2	1.08 (1.03-1.14)
J01MA08	Fleroxacin	895	335.3	1.16 (1.10-1.22)	857	334.5	1.09 (1.03-1.15)
J01MA12	Levofloxacin	9,429	326.8	1.13 (1.11-1.15)	9,121	326.0	1.06 (1.04-1.08)
J01MA14	Moxifloxacin	1,042	330.1	1.14 (1.09-1.20)	998	329.6	1.07 (1.02-1.13)
J01MA15	Gemifloxacin	934	332.5	1.15 (1.09-1.21)	895	332.2	1.08 (1.02-1.14)
J01MA22	Tosufloxacin	1,081	334.0	1.16 (1.10-1.21)	1,028	332.1	1.08 (1.03-1.14)
Asthma							
J01MA01	Ofloxacin	11,513	369.5	1.08 (1.07-1.09)	11,243	369.2	1.08 (1.06-1.10)
J01MA02	Ciprofloxacin	11,510	350.1	1.03 (1.02-1.04)	10,947	349.4	1.02 (1.00-1.04)
J01MA04	Enoxacin	924	349.2	1.03 (0.99-1.06)	883	348.0	1.02 (0.96-1.07)
J01MA06	Norfloxacin	1,235	348.1	1.02 (1.00-1.05)	1,190	346.9	1.01 (0.97-1.06)
J01MA07	Lomefloxacin	1,119	354.9	1.04 (1.01-1.07)	1,064	353.1	1.03 (0.98-1.08)
J01MA08	Fleroxacin	931	348.8	1.02 (0.99-1.06)	891	347.8	1.02 (0.96-1.07)
J01MA12	Levofloxacin	10,893	377.5	1.07 (1.06-1.08)	10,531	376.4	1.10 (1.08-1.12)
J01MA14	Moxifloxacin	1,090	345.3	1.03 (1.00-1.06)	1,039	343.1	1.00 (0.95-1.05)
J01MA15	Gemifloxacin	979	348.5	1.03 (0.99-1.06)	938	348.2	1.02 (0.97-1.07)
J01MA22	Tosufloxacin	1,167	360.5	1.04 (1.01-1.07)	1,112	359.3	1.05 (1.00-1.10)
Allergies							
J01MA01	Ofloxacin	6,202	199.1	1.11 (1.08-1.13)	6,033	199.3	1.00 (0.98-1.03)
J01MA02	Ciprofloxacin	6,318	192.2	1.07 (1.05-1.10)	510	192.6	1.05 (0.97-1.14)
J01MA04	Enoxacin	533	201.4	1.12 (1.04-1.21)	667	201.0	1.01 (0.95-1.09)
J01MA06	Norfloxacin	693	195.3	1.09 (1.02-1.16)	618	194.5	1.07 (1.00-1.15)
J01MA07	Lomefloxacin	649	205.8	1.14 (1.07-1.23)	6,070	205.1	1.04 (1.01-1.07)
J01MA08	Fleroxacin	539	201.9	1.12 (1.04-1.21)	516	201.4	1.05 (0.97-1.14)
J01MA12	Levofloxacin	5,898	204.4	1.14 (1.11-1.16)	5,694	203.5	1.06 (1.03-1.09)
J01MA14	Moxifloxacin	629	199.2	1.11 (1.03-1.19)	600	198.2	1.03 (0.96-1.11)
J01MA15	Gemifloxacin	565	201.1	1.12 (1.04-1.20)	541	200.8	1.05 (0.97-1.13)
J01MA22	Tosufloxacin	677	209.1	1.16 (1.09-1.24)	641	207.1	1.08 (1.01-1.16)

CI, confidence interval.

Table 5. Sensitivity analysis (propensity score-matched)

Disease	Quinolones		Non-antibiotics		RD_{1000}	Relative risk (95% CI)
	No. of events	No. of births	No. of events	No. of births		
Atopic dermatitis						
Restriction to women with atopic dermatitis	251	629	212	629	62.0	1.18 (1.02-1.37)
Restriction to nulliparous women	13,952	44,024	13,512	44,024	10.0	1.03 (1.01-1.05)
Negative control analysis	26,482	82,876	19	61	8.1	1.03 (0.71-1.49)
Penicillin exposure during the first trimester of pregnancy	26,681	83,205	26,024	83,205	7.9	1.03 (1.01-1.04)
Asthma						
Restriction to women with asthma	8,657	21,854	8,050	21,854	27.8	1.08 (1.05-1.10)
Restriction to nulliparous women	13,550	44,024	12,860	44,024	15.7	1.05 (1.03-1.08)
Negative control analysis	30,309	82,876	18	61	70.6	1.24 (0.84-1.83)
Penicillin exposure during the first trimester of pregnancy	50,364	83,205	50,465	83,205	1.2	1.00 (0.99-1.01)
Allergies						
Restriction to women with allergies	499	2,075	473	2,075	12.5	1.05 (0.95-1.18)
Restriction to nulliparous women	8,434	44,024	8,297	44,024	3.1	1.02 (0.99-1.04)
Negative control analysis	16,431	82,876	12	61	1.5	1.01 (0.61-1.67)
Penicillin exposure during the first trimester of pregnancy	16,466	83,205	16,703	83,205	4.7	1.02 (1.00-1.04)

RD, risk difference; CI, confidence interval.

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asthma, consistent findings were found when redefining the exposure and outcomes and restricting the analysis to pregnancies in women with atopic dermatitis and nulliparous pregnancies, but this was not the case for the negative control analysis. Meanwhile, unlike the use of quinolones in early pregnancy, the use of penicillin during the first trimester was not associated with an increased risk of asthma or allergic diseases in infants.

DISCUSSION

This study investigated the association between quinolone use during pregnancy and the risk of asthma, atopic dermatitis, and allergies of offspring within a large, nationwide cohort comprising 2.2 million pregnancies. Our findings indicate that quinolone use during the first trimester might be significantly associated with an elevated risk of asthma, atopic dermatitis, and allergies in offspring. Based on the upper limit of the 95% CI from the adjusted estimates, the maximum observed risk was 5% for atopic dermatitis, 3% for asthma, and 5% for allergies; thus, we could rule out the possibility of about a 5% or higher increase in the risk for these outcomes in children.

Furthermore, there was a significant relationship between the duration of therapy and the risk of these outcomes; prescriptions exceeding 7 days were associated with an increased risk of atopic dermatitis and allergies in children. The results remained consistent across various sensitivity analyses, and the absence of association in the negative control analysis lends further credibility to the conclusion that the observed associations are not likely due to residual confounding.

The prevalence of atopic dermatitis, asthma, and allergic diseases in childhood is significant, and some studies have reported that the risk factors for these diseases include prenatal and postnatal exposure to various environmental risk factors. More frequent house cleaning and keeping pets at home during pregnancy were found to increase the risk of allergies and atopic dermatitis; meanwhile, infection and antibiotic use were identified as risk factors for asthma in a study from Poland [30].

Although the mechanisms by which antibiotic exposure during pregnancy increases the risk of allergic diseases in offspring remain unclear, some evidence suggests that it is mediated by the microbiome. A study of human fetuses suggested that lung microbiome colonization takes place by the 11th week of gestation. Since some antibiotics cross the placenta, their use during pregnancy can affect the maternal and fetal microbiome and cause changes in the gut microbiota of the offspring [31].

Quinolones and their newer derivatives, fluoroquinolones, are highly effective broad-spectrum antibiotics, but quinolones are contraindicated during pregnancy due to concerns about fetal malformations and carcinogenesis [32]. Their mechanism of action involves the inhibition of bacterial DNA-gyrase and topoisomerase IV, which might raise concerns about impaired DNA synthesis that could cause organ mutagenesis in fetal tissues [33]. Generally antibiotics might induce killing of commensal bacteria important for normal development of immune function [34] and especially levofloxacin is known to induce histamine secretion [35].

Several studies have been published mixed effects regarding the effects of antibiotic use, especially quinolone use, during pregnancy on atopic diseases and asthma in offspring. A meta-analysis has reported an association between maternal antibiotic exposure during pregnancy and an increased risk of asthma/wheezing and allergic diseases in childhood [9]. The studies from Japan and Switzerland reported associations between antibiotic use during pregnancy and an increased risk of asthma, atopic dermatitis, food allergy, and any allergic disease [26, 27].

Meanwhile, a study in Denmark reported no association between antibiotic exposure in the first trimester and asthma, but higher odds were observed for antibiotic exposure in the second to the third trimester, compared to unexposed children [25]. According to meta-analysis, the use of quinolones during the first trimester of pregnancy was not associated with an increased risk of birth defects, stillbirths, preterm births, or low birth weight [36]. According to two meta-analyses on risk factors for pregnancy complications, there was no association between quinolones and fetal malformations, preterm delivery, stillbirth, or miscarriage [22, 23]. The current study's findings are consistent with those from Japan and Switzerland [26, 27].

This study has several strengths. First, to our knowledge, this study is the first large-scale investigation involving approximately 2 million pregnancies to examine the association between quinolone use during the first trimester of pregnancy and the incidence of atopic

dermatitis, asthma, and allergies in children on a population-wide scale. Previous cohort studies have included fewer than 1 million subjects when researching atopic dermatitis [13], asthma [37], and allergies [27] in offspring. Second, this study compared the outcomes of interest using a quasi-experimental design involving the analysis of health insurance claims data. It utilizes data encompassing the entire population of Korea, enhancing the generalizability of the findings to other contexts, given the extensive real-world data employed in the analysis [38-40]. Third, we investigated the risk of outcomes based on the type of quinolone used and the duration of therapy. This information could be beneficial, as it would enable physicians to prescribe antibiotics with consideration for both the specific quinolone and the appropriate duration of treatment to ensure the safety of women and fetuses in clinical practice. Fourth, our findings may be subject to the influence of unmeasured confounders, despite adjustments for a wide range of known confounders. To mitigate this concern, we performed a negative control analysis. The results of this analysis showed no association, which suggests that our primary findings are unlikely to be the result of residual confounding.

Despite the strengths of this study, it has some limitations. First, this was a retrospective study, and the absence of data on genetic factors, smoking, and lifestyle habits might be a limitation. Furthermore, we relied on claims data and assumed that patients adhered to their prescribed medications. However, the prescribing records for some patients may not accurately reflect actual medication use. As this is an observational study, non-adherence to prescriptions could have potentially influenced our results. Second, since disease code information from billing data was used, the study could have underestimated the total number of prescriptions by excluding patients with diseases who did not receive medical treatment. Third, this study was limited by its inability to control for unmeasurable confounding variables. Lastly, by including only live births and excluding those with severe side effects, the study likely underestimated the actual risk. Also, we didn't include outcomes such as mortality linked to quinolone use, because we couldn't check the cause of death in our data. Nevertheless, we found an increased risk of adverse health outcomes associated with quinolone use in pregnancy. However, further studies that are larger and multinational in scope might be needed to confirm these findings.

In conclusion, quinolone use during the first trimester was associated with an increased risk of atopic dermatitis, asthma, and allergies in children. The risk was also higher for quinolone use exceeding 7 days. However, the absolute risks and population-attributable fractions were modest; therefore, these findings should be interpreted with caution. The results of this nationwide cohort study provide valuable information that can help physicians prescribe antibiotics to pregnant women in a way that reduces the risk of atopic diseases in their children.

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