Assisted reproductive techniques and subsequent risk of asthma and allergic rhinitis in offspring: a nationwide birth cohort study in South Korea

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Abstract. – **OBJECTIVE:** The relationship between assisted reproductive techniques (ART) and the risk of asthma and allergic rhinitis (AR) is controversial. Thus, we aimed to investigate the relationship between ART and the risk of asthma and AR in a nationwide, large-scale birth cohort.

PATIENTS AND METHODS: This study utilized the National Health Insurance Service data in South Korea to conduct a nationwide, large-scale, population-based birth cohort. We included all infants born between 2017 and 2018. AR, asthma, food allergies, and atopic dermatitis were defined using the International Classification of Diseases tenth edition codes. Asthma was classified as allergic or non-allergic based on accompanying allergic diseases (AR, food allergy, or atopic dermatitis). Using 1:10 propensity score matching, we compared infants conceived through ART with those conceived naturally (non-ART). After matching, logistic regression was used to compare the hazard ratio for asthma and AR between the two groups.

RESULTS: We included 543,178 infants [male infants, 280,194 (51.38%)]. After matching, 8,925 and 74,229 infants were selected for the ART and non-ART groups, respectively. The ART group showed a decreased risk of asthma in the offspring [adjusted hazard ratio (aHR), 0.45; 95% confidence interval (CI), 0.41-0.48]. Similarly, for AR, being conceived by ART was associated with a decreased risk of AR (aHR, 0.25; 95% CI, 0.12-0.37). ART offspring showed a decreased risk of asthma and AR in offspring compared to that observed in non-ART offspring.

CONCLUSIONS: Our study offers important insights for clinicians, researchers, and parents regarding the health outcomes of ART-conceived infants and enhances our understanding of ART's impact on respiratory health.

Key Words:
   Assisted reproductive techniques, ART, Allergy, Asthma, AR.

Introduction

Assisted reproductive techniques (ART), such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have become essential treatments for people with fertility problems[1,2]. Globally, approximately 3 million ART cycles are performed each year, resulting in approximately 8 million infants born over the past four decades[1]. As the use of ART has risen, extensive research has been conducted on the health status of offspring conceived through these techniques.

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Numerous studies[1,3,4] have explored the associations between ART and aspects such as growth development and the subsequent risk of cancer and chronic diseases, including allergic disorders and other health conditions. Furthermore, asthma and allergic rhinitis (AR) have been considered to be potentially associated with ART[5], but the relationship between these conditions and ART remains controversial based on previous research findings.

Thus, investigating the association of ART with asthma and AR can alleviate concerns among expectant mothers and determine the need for additional pulmonary evaluation. Using a nationwide birth cohort in South Korea, we investigated the relationship between ART and the subsequent risks of asthma and AR in children.

Patients and Methods

Data Source

This nationwide, large-scale, population-based birth cohort study utilized the National Health Insurance Service (NHIS) data in South Korea to conduct a nationwide, large-scale, population-based birth cohort[6]. The study included all infants born between January 1, 2017, and December 31, 2018, and created a mother-child paired birth cohort using a unique insurance identification number. This study was distinct in several ways: (1) the insurance service provides coverage for approximately 98% of all Koreans under a single government-based insurance service[6]; (2) a comprehensive dataset was utilized, which included detailed information on baseline characteristics, medical records for both inpatient and outpatient care, death statistics, and general health examination data for both mothers and children[7]; (3) to ensure the confidentiality of patient-related data, including the family insurance identification number, the Korean government anonymized all such information; and (4) this study includes general health examination data for children (e.g. history of breastfeeding) and mothers (e.g. body mass index and maternal smoking history during pregnancy)[8]. This study was approved by the Kyung Hee University (KHUH 2022-06-042), NHIS (NHIS-2022-1-383), and the Korea Disease Control and Prevention Agency. The requirement for written informed consent was waived by the ethics committee and the Korean government owing to the routinely collected data.

Study Design and Participants

This large-scale, population-based, nationwide birth cohort study comprising all Korean infants born between January 1, 2017, and December 31, 2018, included the first National Health Screening Program for Infants and Children at six months after birth (infant n=581,130)[9]. We performed mother-infant pairing among the included infants (mothers, n=547,032; infant-mothers, n=1,128,162). We formed mother-child pairs using a unique insurance identification number shared within a family[8]. According to a previous validation study, the combined positive predictive value for diagnostic records in claims data was 82%[10]. We excluded the following participants: (1) participants missing information of socioeconomic status or birth date (excluded n=33,014), (2) infants diagnosed with immune mechanism disorders, cystic fibrosis, chronic kidney diseases, beta-thalassemia or sickle-cell disorders, and any malignancy (excluded n=4,876), (3) infants diagnosed with an allergy within 6 months of birth (excluded n=35), and (4) mothers whose offspring were already excluded (excluded n=27). In total, 545,336 children and 525,092 mothers were included in the full unmatched cohort.

Exposures

ART was defined as individuals who underwent ART procedures before pregnancy. The group was divided into those who received ART and non-ART group[11-13]. Regarding ART treatment codes, we used R6532, R6533, R6530, R6531, R6540, and R6550. To investigate dose-dependent associations, participants were categorized into groups based on the number of ARTs received: ART <3 times or ≥3 times.

Outcomes

Asthma was defined according to the International Classification of Diseases, 10th edition (ICD-10) code (J45 or J46) with at least two claims within one year of using asthma-related medication during this study period[6,14]. AR was defined as J30.1, J30.2, J30.3, or J30.4, with at least two claims during this study period[14]. Allergic asthma was defined as asthma with at least one additional allergic disorder using the ICD-10 code, including AR, food allergy (Z91.0 or T78.0), and atopic dermatitis (L20)[6,14,15]. Non-allergic asthma was defined as asthma without any allergic disorder.

Covariates

In our analysis, we took into account various maternal covariates: maternal age at delivery (<20, 20-24, 25-29, 30-34, and ≥35 years), region of residence (rural and urban)[16-19], household income (divided into quartiles from 1st to 4th), parity (1 and ≥2 children), maternal mental illnesses (asthma, AR, food allergy, and atopic dermatitis), severe maternal morbidity (SMM; 0, 1, and ≥2 occurrences)[20], delivery type (cesarean section and vaginal delivery), and number of inpatient hospital admissions (0, 1, and ≥2) and the number of outpatient contact (0, 1, and ≥2) in a year before pregnancy. For the children, we considered the following covariates: infant sex, birth season [divided into spring (March to May), summer (June to August), autumn (September to November), and winter (December to February)], preterm birth (≤36 weeks), and low birth weight (≤2,499 g)[21-24]. All these variables were collected from eligibility data, claims codes, and child health examination data provided by the NHIS.

Propensity Score Matching Cohort

We employed an exposure-based propensity score-matched cohort to equalize the baseline demographic factors between the two groups and reduce the potential influence of confounding variables[6,25]. Infants with and without ART were matched in a 1:10 proportion *via* propensity score matching derived from the full cohort based on the following relevant factors: maternal age at delivery year, infant sex, region of residence, birth season, income, nulliparity, SMM score, delivery type, preterm birth, low birth weight, number of drug prescriptions, hospital admissions, and outpatient contacts in the year before pregnancy. The propensity score was generated using a modified logistic regression model based on the anticipated likelihood of receiving ART (n=8,925) *vs.* non-ART (n=74,229) (Figure 2). To match the offspring in the two groups, a "greedy nearest-neighbor" algorithm was applied, involving random selection without replacement of participants within specified caliper widths (0.001 standard deviations). The effectiveness of exposure-based propensity score matching was evaluated by comparing the standardized mean differences (SMDs). SMDs less than 0.2 were deemed indicative of negligible substantial disparity between the two groups[25].
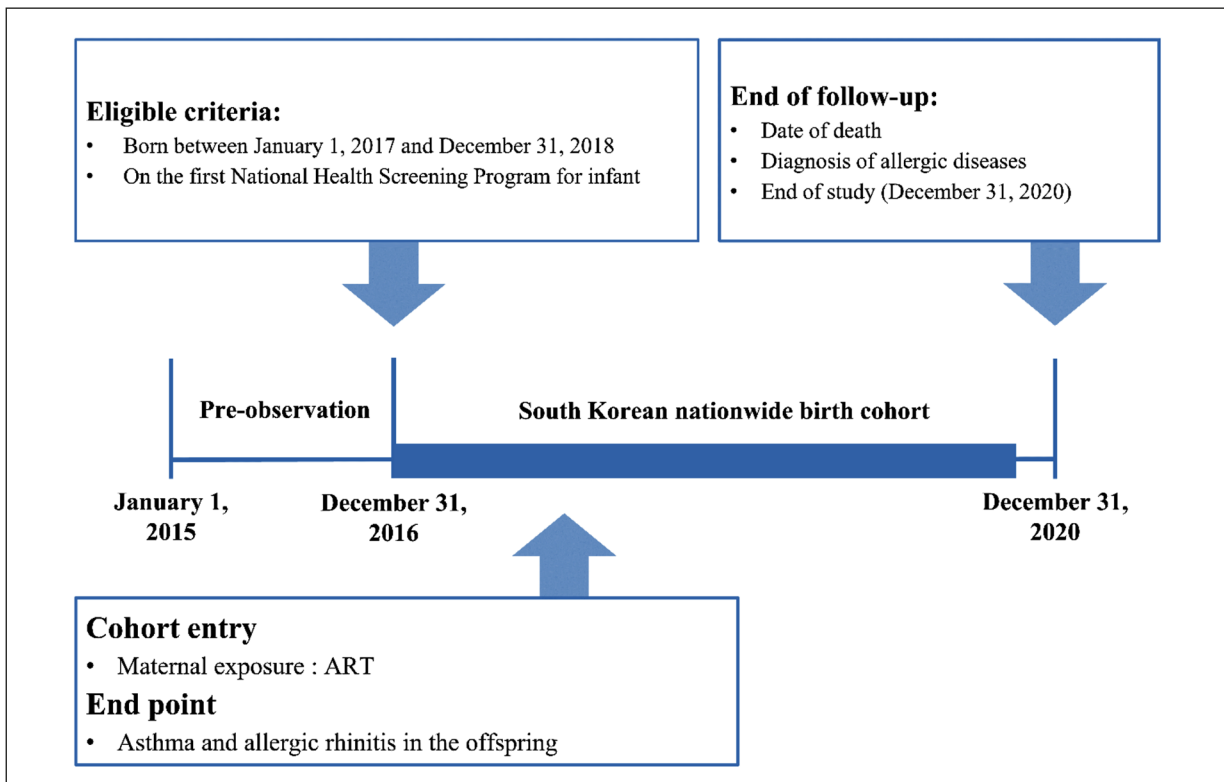

Figure 1. Study population and 1:10 propensity score-matched cohort. ART, assisted reproductive technology.

We also performed stratification analysis of the propensity score-matched cohort to mitigate unforeseeable biases or reverse causation effects: stratification analysis according to infant sex, birth season, year of delivery, delivery type, medical condition of the child (either preterm birth or low birth weight), and alternative cohort specifications (full unmatched cohort).

Patient and Public Involvement

The patients and their parents were not involved in setting the research question or outcome measures, nor were they involved in the design and implementation of the study. However, we plan to disseminate the results of this study to all study participants and wider relevant communities upon request.

Statistical Analysis

In the study dataset, the primary exposure was ART before pregnancy, and the primary outcome was asthma or AR in infants. The infant birth dates were designated as reference points and referred to as index dates. The follow-up ended on December 31, 2020, at the onset of asthma and AR, or at the death of a child. The observation period was from January 1, 2017, to December 31, 2020, and pre-observation was used to determine maternal history between January 1, 2015, and December 31, 2016 (Figure 1).

Hazard ratios (HRs) among 95% confidence intervals (CIs) were calculated using the Cox proportional hazards regression model (endpoint, occurrence of the initial allergic disease event in offspring) to evaluate the effect of conceived ART on the subsequent development of asthma and AR in the offspring[24]. For an adjusted model, we adjusted for maternal age in the delivery year, infant sex, region of residence, birth season, household income level, nulliparity, SMM score, delivery type, preterm birth, low birth weight, number of inpatient hospital admissions, and number of outpatient contacts in the year before pregnancy. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant[24].
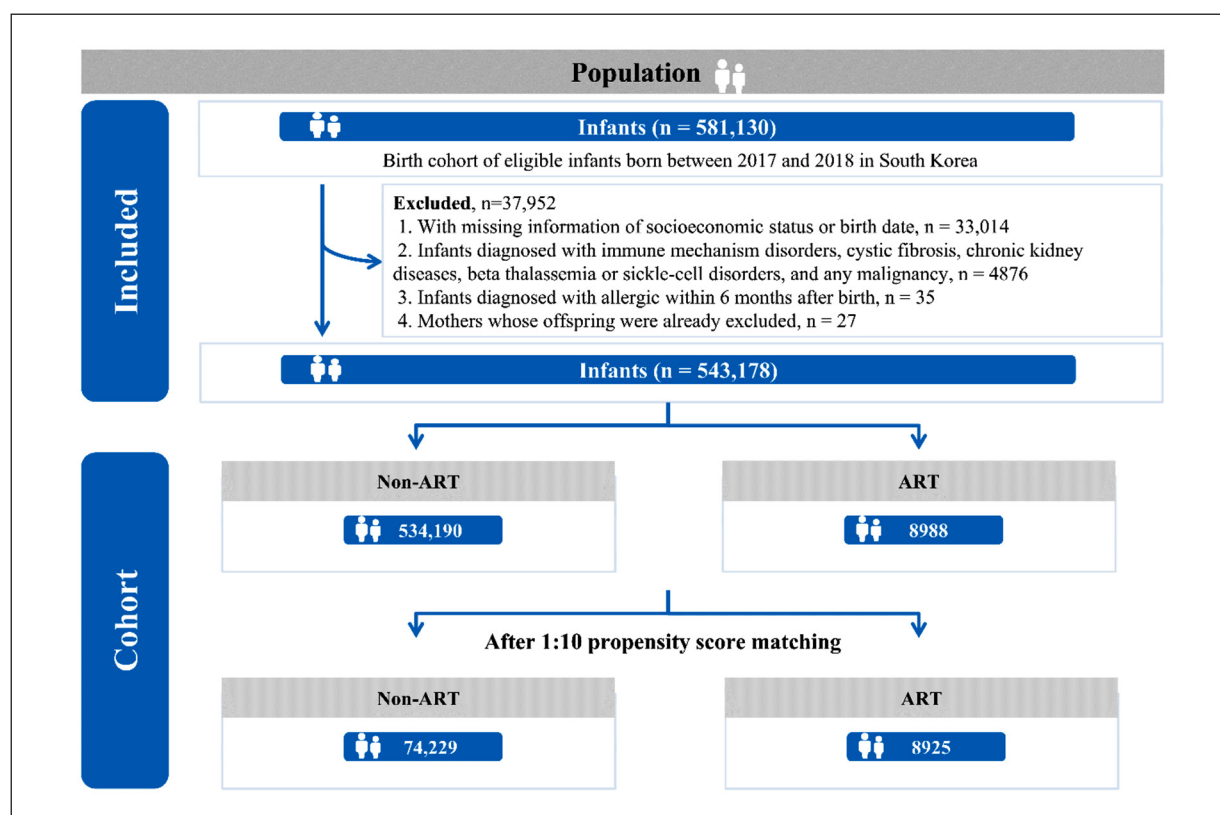

Figure 2. Disposition and study subjects. ART, assisted reproductive technology.

Results

In total, 543,178 patients were enrolled in the cohort [male infants, 280,194 (51.38%)]; 98.3% (534,190/543,178) conceived naturally (non-ART group) and 1.7% (8,988/543,178) conceived through ART (ART group). Table I presents the characteristics of the two groups.

After 1:10 propensity score matching, the differences between the non-ART and ART groups were observed. The association between conceiving through ART and asthma and AR outcomes in the offspring were indicated as the crude and adjusted HR, as shown in Table II. Conceiving through ART showed a decreased risk for asthma [adjusted HR (aHR), 0.45; 95% CI, 0.41 to 0.48] and AR (aHR, 0.25; 95% CI, 0.12 to 0.38) compared to that associated with non-ART. Furthermore, those who received ART three or more times had a more pronounced lower risk of asthma and AR.

In a stratification analysis conducted on infants conceived by ART (infant sex, birth season, delivery type, and infant conditions), the HR of asthma and AR was significantly lower in the ART group than in the non-ART group (**Supplementary Tables I** and **II**). Table III shows that ART has a more pronounced risk of allergic asthma compared to that associated with non-allergic asthma (ratio of HR, 1.46; 95% CI, 1.24-1.73) with stratification analysis (**Supplementary Tables III** and **IV**).

Discussion

Findings and Explanation

Per our results, the HR of asthma and AR in the ART group was lower than that in the non-ART group. Furthermore, those who received ART three or more times had a more pronounced lower risk of asthma and AR. Interestingly, the ART group had a higher risk of allergic asthma than that of the non-allergic asthma group. The stratification analysis yielded results similar to the main findings, indicating that ART may have a protective effect against the development of asthma and AR in the offspring. This study's results may help alleviate concerns regarding the potential risks of asthma and AR in infants conceived using ART. This also suggests that excessive evaluation for asthma and AR is not as necessary in infants conceived by ART as it is in those conceived naturally.

Comparison with Other Studies

However, the effect of ART on asthma and AR remains controversial. Studies[26] in children have shown mixed results, with some indicating a link between ART and anti-asthma medication use, while others found no significant differences in asthma and AR prevalence between IVF and naturally conceived children[27]. A study[28] in the United States on young adults conceived by IVF found them to exhibit more favorable features concerning asthma compared to that exhibited by the general population, but the study's group size was small (n=173). One large cohort study suggested a possible association between IVF and asthma. However, the age gap between birth and asthma diagnosis in this study makes the results less conclusive[29]. In a study focusing on adults born through IVF, the current asthma rates or lung function did not differ significantly from those of the general population[30].

We determined that, despite a potential relationship between ART and asthma and AR, the prevalence of these conditions was lower in the ART group. The study included a relatively large population of 8,925 infants conceived by ART out of 543,178 individuals, making it more robust than previous literature. Moreover, the study's average follow-up period of 2.46 years (900 days) focused on a relatively younger age group, which is a distinguishing factor from the literature. Additionally, using a recently collected cohort minimized bias related to advancements in ART techniques over time. These aspects enhance the reliability and relevance of our findings regarding the relationship between ART with asthma and AR.

Possible Mechanisms

We suggest two reasons why the HR for asthma and AR was higher in the non-ART group than in the ART group. First, in the ART process, GnRH antagonists and GnRH agonists are used to induce hyperovulation[31]. GnRH antagonists affect the activation and degranulation of mast cells and are also used to treat asthma. The GnRH antagonist used in the ART group may affect the systemic activation of the mast cells, thereby influencing the risk of asthma and AR[32]. Second, the ART process, including IVF and ICSI, requires *in vitro* fertilization. The egg is fertilized with sperm in a laboratory dish, and this culture media contains essential nutrients, salts, amino acids, and energy sources that support the growth and development of the embryos[33]. The fertilized

Table I. Demographics and clinical characters of patients who were non-ART and ART in a full unmatched cohort and 1:10 propensity-score-matched cohort.

	Full unmatched cohort (n=543,178)			1:10 propensity-score-matched cohort (n=83,154)			
	Total cohort	Non-ART group	ART group	PSM cohort	Non-ART group	ART group	SMD*
Total, n (%)	543,178	534,190 (98.3)	8,988 (1.7)	83,154	74,229 (89.3)	8,925 (10.7)	
Maternal age at delivery years, mean (SD)	32.7 (4.4)	32.6 (4.4)	35.5 (3.5)	35.0 (3.5)	34.9 (3.52)	35.5 (3.5)	0.18
Maternal age at delivery years, n (%)							0.08
≤19	1,008 (0.18)	1,008 (0.19)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
20-24	21,040 (3.86)	20,997 (3.93)	27 (0.30)	270 (0.32)	243 (0.33)	27 (0.30)	
35-29	100,389 (18.41)	99,832 (18.69)	379 (4.22)	4,015 (4.83)	3,636 (4.90)	379 (4.25)	
30-34	231,805 (42.51)	228,012 (42.68)	2,867 (31.90)	28,665 (34.47)	25,807 (34.77)	2,858 (32.02)	
≥35	191,094 (35.04)	184,341 (34.51)	5,715 (63.58)	50,204 (60.27)	44,543 (60.01)	5,661 (63.43)	
Infant sex, n (%)							<0.001
Male	280,194 (51.38)	274,433 (51.37)	4,674 (52.00)	43,458 (52.26)	38,814 (52.29)	4,644 (52.26)	
Female	265,142 (48.62)	259,757 (48.63)	4,314 (48.00)	39,696 (47.74)	35,415 (47.71)	4,281 (47.74)	
Region of residence, n (%)							<0.001
Rural	232,783 (42.69)	227,578 (42.60)	4,164 (46.33)	38,326 (46.09)	34,192 (46.06)	4,134 (46.32)	
Urban	312,553 (57.31)	306,612 (57.40)	4,824 (53.67)	44,828 (53.91)	40,037 (53.94)	4,791 (53.68)	
Parity, n (%)							0.13
1	391,865 (71.86)	387,501 (72.54)	3,363 (37.42)	36,389 (43.76)	33,026 (44.49)	3,363 (37.68)	
≥2	153,471 (28.14)	146,689 (27.46)	5,625 (62.58)	46,765 (56.24)	41,203 (55.51)	5,562 (62.32)	
Maternal medical conditions, n (%)							
Asthma	89,258 (16.37)	88,314 (16.53)	733 (8.16)	14,907 (17.93)	14,183 (19.11)	724 (8.11)	0.32
Allergic rhinitis	34,532 (6.33)	34,277 (6.42)	205 (2.28)	6,047 (7.27)	5,845 (7.87)	202 (2.26)	0.25
Food allergy	6,329 (1.16)	6,181 (1.16)	111 (1.23)	1,349 (1.62)	1,239 (1.67)	110 (1.23)	0.03
Atopic dermatitis	105,012 (19.26)	102,968 (6.42)	1,620 (2.28)	19,788 (23.80)	18,174 (24.48)	1,614 (18.08)	0.15
Any allergic disease (If any of the four conditions applied)	194,837 (35.73)	191,824 (35.91)	2,381 (26.49)	35,069 (42.17)	32,705 (44.06)	2,364 (26.49)	0.37
Severe maternal morbidity, n (%)							<0.001
0	509,845 (93.49)	499,505 (93.51)	8,309 (92.45)	77,244 (92.89)	68,975 (92.92)	8,269 (92.65)	
1	34,630 (6.35)	33,856 (6.34)	650 (7.23)	5,759 (6.93)	5,126 (6.91)	633 (7.09)	
≥2	861 (0.16)	829 (0.16)	29 (0.32)	151 (0.18)	128 (0.17)	23 (0.26)	

Continued

Table I *(Continued)*. Demographics and clinical characters of patients who were non-ART and ART in a full unmatched cohort and 1:10 propensity-score-matched cohort.

	Full unmatched cohort (n=543,178)			1:10 propensity-score-matched cohort (n=83,154)			
	Total cohort	Non-ART group	ART group	PSM cohort	Non-ART group	ART group	SMD*
Delivery type, n (%)							0.11
Caesarean section	269,033 (49.33)	260,693 (51.20)	6,911 (23.11)	60,217 (72,42)	53,368 (71.90)	6,849 (76.74)	
Vaginal delivery	276,303 (50.67)	273,497 (48.80)	2,077 (76.89)	22,937 (27.58)	20,861 (28.10)	2,076 (23.26)	
Conditions of infant, n (%)							
Preterm birth	26,394 (4.84)	24,166 (4.52)	1,853 (20.62)	11,332 (13.63)	9,528 (12.84)	1,,804 (20.21)	0.19
Low birth weight	20,717 (3.80)	18,852 (3.53)	1,533 (17.06)	9,199 (11.06)	7,725 (10.41)	1474 (16.52)	0.17
Number of inpatient hospital admissions in a year before pregnancy, n (%)							0.05
0	446,800 (81.93)	438,104 (82.01)	6,867 (76.40)	65,465 (58,609)	58,609 (78.96)	6,856 (76.82)	
1	79,554 (14.59)	77,739 (14.55)	1,560 (17.36)	13,461 (16.19)	11,922 (16.06)	1,539 (17.24)	
≥2	18,992 (3.48)	18,347 (3.43)	561 (6.24)	4,228 (5.08)	3,698 (4.98)	530 (5.94)	
Number of outpatient contacts in a year before pregnancy, n (%)							<0.001
0	28,221 (5.17)	28,171 (5.27)	48 (0.53)	432 (0.52)	384 (0.52)	48 (0.54)	
1	23,733 (4.35)	23,654 (4.43)	55 (0.73)	569 (0.68)	503 (0.68)	66 (0.74)	
≥2	493,382 (90.47)	482,365 (90.3)	8,874 (98.73)	82,153 (98.8)	73,342 (98.81)	8,811 (98.72)	
Birth season, n (%)							0.09
Spring (March to May)	143,224 (26.26)	143,067 (26.78)	130 (1.45)	1,283 (1.54)	1,153 (1.55)	130 (1.46)	
Summer (June to August)	134,779 (24.71)	130,772 (24.48)	3,258 (36.25)	30,450 (36.62)	27,213 (36.66)	3,237 (36.27)	
Autumn (September to November)	129,452 (23.74)	124,140 (23.24)	4,268 (47.49)	37,143 (44.67)	32,913 (44.34)	4,230 (47.39)	
Winter (December to February)	137,881 (25.28)	136,211 (25.5)	1,332 (14.82)	14,278 (17.17)	12,950 (17.45)	1,328 (14.88)	
Income level, n (%)							0.04
1st quartile	121,606 (22.30)	119,887 (22.44)	1,383 (15.39)	13,520 (16.26)	12,147 (16.36)	1,373 (15.38)	
2nd quartile	133,897 (24.55)	131,824 (24.68)	1,626 (18.09)	15,865 (19.08)	14,248 (19.19)	1,617 (18.12)	
3rd quartile	138,002 (25.31)	135,071 (25.29)	2,333 (25.96)	21,656 (26.04)	19,334 (26.05)	2,322 (26.02)	
4th quartile	151,831 (27.84)	147,408 (27.59)	3,646 (40.57)	32,113 (38.62)	28,500 (38.39)	3,613 (40.48)	

ART, assisted reproductive technology; SD, standard deviation; SMD, standardized mean difference; PSM, propensity score matching. *SMD <0.2 corresponds to no major imbalance.

Table II. Hazard ratio for the risk of asthma and allergic rhinitis between non-ART group and ART group after 1:10 propensity-score-matching.

| | Allergy disease | N (%) | Allergy disease events (%) | Person-years | Allergy disease incidence rate* | Hazard ratio (95% CI) | | | |
						Crude	p-value	Adjusted†	p-value
Non-ART group	Asthma	74,229 (89.27)	14,183 (19.11)	158,325	8.96	1.0 (reference)		1.0 (reference)	
ART group		8,925 (10.73)	724 (8.11)	16,701	4.36	**0.433 (0.401-0.466)**	<0.001	**0.448 (0.414-0.481)**	<0.001
<3		8,688 (97.34)	708 (8.15)	16,261	4.35	**0.435 (0.403-0.469)**	<0.001	**0.450 (0.417-0.485)**	<0.001
≥3		237 (2.66)	16 (6.75)	440	3.64	**0.381 (0.233-0.621)**	<0.001	**0.382 (0.234-0.624)**	<0.001
Non-ART group	Allergic rhinitis	74,229 (89.27)	5,845 (7.88)	172,391	3.39	1.0 (reference)		1.0 (reference)	
ART group		8,925 (10.73)	202 (2.26)	17,390	1.16	**0.246 (0.131-0.361)**	<0.001	**0.247 (0.117-0.376)**	<0.001
<3		8,688 (97.34)	199 (2.29)	16,930	1.18	**0.287 (0.249-0.331)**	<0.001	**0.295 (0.256-0.340)**	<0.001
≥3		237 (2.66)	3 (1.27)	460	0.65	**0.162 (0.052-0.501)**	<0.001	**0.156 (0.050-0.483)**	<0.001

ART, assisted reproductive technology; CI, confidence interval. †Adjusted: Adjustment for maternal age at delivery years, infant sex, region of residence, birth season, income, parity, year of delivery, severe maternal morbidity (SMM), delivery type, preterm birth, low birth weight, number of inpatient hospital admissions in a year before pregnancy, and number of outpatient contact in a year before pregnancy. *Allergic disease incidence rate is expressed per 100 person-years. Numbers in boldface correspond to significant differences ($p<0.05$).

Table III. Hazard ratio for the risk of allergic asthma and non-allergic asthma between non-ART group and ART group after 1:10 propensity- score-matching.

| | | Allergic asthma | | | Non-allergic asthma | | | Hazard ratio (95% CI) | | | | | Ratio of hazard ratio | |
| | | | | | | | | Allergic asthma | | Non-allergic asthma | | | | |
	N (%)	Events (%)	Person-years	Allergic asthma incidence rate*	Events (%)	Person-years	Non-allergic asthma incidence rate*	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†	p-value
Non-ART group	74,229 (89.27)	4,497 (6.06)	178,108	2.52	9,686 (13.05)	167,512	5.78	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)			
ART group	8,925 (10.73)	170 (1.90)	17,501	0.97	554 (6.21)	16,935	3.27	**0.337 (0.285-0.389)**	**0.348 (0.297-0.399)**	**0.493 (0.450-0.535)**	**0.509 (0.469-0.553)**	**1.463 (1.224-1.748)**	**1.463 (1.235-1.732)**	<0.001
<3	8,688 (97.34)	165 (1.90)	17,044	0.97	543 (6.25)	16,486	3.29	**0.336 (0.287-0.392)**	**0.347 (0.297-0.405)**	**0.496 (0.455-0.541)**	**0.513 (0.470-0.560)**	**1.476 (1.235-1.764)**	**1.478 (1.237-1.767)**	<0.001
≥3	237 (2.66)	5 (2.11)	457	1.09	11 (4.64)	449	2.45	**0.397 (0.165-0.953)**	**0.388 (0.162-0.934)**	**0.385 (0.213-0.696)**	**0.392 (0.217-0.708)**	**0.970 (0.337-2.793)**	**1.010 (0.351-2.907)**	<0.001

ART, assisted reproductive technology; CI, confidence interval. †Adjusted: Adjustment for maternal age at delivery years, infant sex, region of residence, birth season, income, parity, year of delivery, severe maternal morbidity (SMM), delivery type, preterm birth, low birth weight, number of inpatient hospital admissions in a year before pregnancy, and number of outpatient contact in a year before pregnancy. * Allergic and non-allergic asthma incidence rate is expressed per 100 person-years. Numbers in boldface correspond to significant differences ($p<0.05$).

embryo is cultured outside the body for several days before implantation in the uterus. In this process, the culture medium does not contain sex hormones, and embryos implanted through ART are less exposed to sex hormones, especially estrogen, than embryos implanted through the normal pregnancy process. Estrogen enhances antigen-presenting cell function, polarize T cells to type 2 T helper cell response, and promote the degranulation of mast cells/basophils, leading to allergic diseases and asthma[34]. These two proposed mechanisms explain that ART may have a protective effect on asthma and AR.

A study[35] comparing cytokine levels between children conceived by ART and naturally conceived children found that children born after ART had increased levels of interferon-gamma and interleukine-4, which are associated with elevated estradiol levels. However, this study focused on children, and the influence of maternal sex hormone changes on infant cytokine levels remains unclear.

Strengths and Limitations of the Study

Findings from the present study must be interpreted in light of its limitations. First, the definitions of asthma and AR relied on ICD codes from patient records, which may be less accurate than direct clinical diagnosis. Additionally, the distinction between allergic and non-allergic asthma was made based on ICD codes owing to the lack of laboratory data, which could introduce potential misclassification bias. However, previous large cohort studies[9,36,37] have used similar claims-based definitions and demonstrated good reliability. Second, although the study used a large pediatric dataset, the follow-up period was relatively short. The relationship between ART and asthma in children can vary depending on age and sometimes increases or decreases over time. Moreover, no association has been found between ART and asthma in adults. Therefore, a longer follow-up period in this cohort may have yielded additional meaningful results. However, since the data collection period was from 2017 to 2020, this represents the maximum follow-up period available from the dataset used for this study. Third, although this study analyzed a large cohort, different perspectives were presented in the literature. An increased hazard ratio for asthma in children conceived using ART has been suggested. Therefore, research from other countries and perspectives would be valuable. Lastly, further research is needed to investigate the immunological status of pregnant women and infants in relation to ART and its potential effects on asthma and AR. A biological study focusing on maternal and infant immunological factors could provide further insights into the mechanisms underlying these observed associations.

Despite these limitations, this study provides additional insights into the relationships among ART, asthma, and AR. Previous literature has mainly focused on various health aspects of infants born *via* ART, often suggesting higher prevalence rates of several diseases compared to those of naturally conceived infants. However, this study found a lower risk of allergic disorders, including asthma and AR, in infants conceived *via* ART than in naturally conceived infants. Considering the increasing trend of delayed childbearing and the rising number of pregnancies due to ART, this study's results could help alleviate maternal concerns regarding the health status of ART-conceived infants. Moreover, this suggests that excessive pulmonary evaluations may not be necessary for infants conceived using ART, potentially reducing unnecessary medical interventions. Overall, this study provides valuable information to clinicians, researchers, and parents regarding the health outcomes of ART-conceived infants and contributes to a more comprehensive understanding of the implications of ART on respiratory health. However, further research is required to confirm and explore the mechanisms underlying these associations.

Conclusions

In this nationwide birth cohort study, conception through ART was associated with increased risks of asthma and AR in offspring. Infants conceived using ART had a lower risk of asthma and AR than infants conceived naturally. Furthermore, those who received ART three or more times had a more pronounced lower risk of asthma and AR. The hazard ratio for allergic asthma was significantly lower than that for non-allergic asthma among infants conceived *via* ART. In conclusion, our study offers important insights for clinicians, researchers, and parents regarding the health outcomes of ART-conceived infants and enhances our understanding of ART's impact on respiratory health. However, further research is required to confirm and explore the mechanisms underlying these associations.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval

This study was approved by Kyung Hee University (KHUH 2022-06-042) and NHIS (NHIS-2022-1-383). The study was conducted in accordance with the Declaration of Helsinki and its later amendments.

Informed Consent

The requirement for written informed consent was waived by the ethics committee and the Korean government owing to the routinely collected data.

Authors' Contributions

Dr. Dong Keon Yon had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript prior to submission. Study concept and design: Seok Hyun Kim, Minji Kim, Hye Kyu Min, Jin-Young Min, and Dong Keon Yon; Acquisition, analysis, and interpretation of data: Seok Hyun Kim, Minji Kim, Hye Kyu Min, Jin-Young Min, and Dong Keon Yon; Drafting of the manuscript: Seok Hyun Kim, Minji Kim, Hye Kyu Min, Jin-Young Min, and Dong Keon Yon; Critical revision of the manuscript for important intellectual content: Seok Hyun Kim, Minji Kim, Hayeon Lee, Selin Woo, Hyeon Jin Kim, Ai Koyanagi, Lee Smith, Min Seo Kim, Hye Kyu Min, Jin-Young Min, and Dong Keon Yon; Study supervision: Dong Keon Yon. Dong Keon Yon supervised the study and served as a guarantor. Dong Keon Yon is a senior author. Minji Kim and Seok Hyun Kim contributed equally to this work as first authors. Dong Keon Yon, Hye Kyu Min, and Jin-Young Min contributed equally to this work as corresponding authors. The corresponding author attests that all listed authors meet the authorship criteria and that no one who meets the criteria has been omitted.

Availability of Data and Materials

Data are available upon reasonable request. The study protocol and statistical code are available from Dong Keon Yon (e-mail: yonkkang@gmail.com). The data set is available from the National Health Insurance Service (NHIS) data in South Korea through a data use agreement.

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