ORIGINAL REPORT

Birth Outcomes of Infants Born to Mothers with Alopecia Areata: A Nationwide Population-based Study in Korea

Jung-Won SHIN[1,2], Taeuk KANG[3], Heather SWAN[4], Kyungho PAIK[1], Chang-Hun HUH[1,2] and Hyun Jung KIM[4]
[1]Department of Dermatology, Seoul National University Bundang Hospital, Gyeonggi, [2]Department of Dermatology, Seoul National University College of Medicine, Seoul, [3]College of Natural Sciences, Sungshin Women's University, Seoul, [4]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

Data on pregnancy outcomes in patients with alopecia areata (AA) are limited. The aim of this study is to determine the association between maternal AA and risk of adverse birth outcomes in children. A retrospective cohort study was conducted on 45,328 children born to mothers with AA and 4,703,253 controls born to mothers without AA using the Korean National Health Insurance Claims database from 2002 to 2016. Multivariate logistic regression analyses were performed to evaluate the association between maternal AA and the birth outcomes of their children. Infants born to mothers with AA exhibited a significantly higher risk of preterm birth (odds ratio [OR] 1.39, 95% CI 1.33–1.45; adjusted OR [aOR] 1.07, 95% CI 1.01–1.13), low birthweight (OR 1.36, 95% CI 1.30–1.42; aOR 1.11, 95% CI 1.05–1.17), and Caesarean section birth (OR 1.24, 95% CI 1.22–1.26; aOR 1.12, 95% CI 1.08–1.15) than controls. In addition, the risk of congenital malformations was also significantly higher in infants born to mothers with AA (OR 1.19, 95% CI 1.15–1.22; aOR 1.10, 95% CI 1.07–1.14), especially for malformations of the urinary (OR 1.33, 95% CI 1.19–1.48; aOR 1.16, 95% CI 1.04–1.29) and musculoskeletal (OR 1.19, 95% CI 1.12–1.27; aOR 1.12, 95% CI 1.05–1.19) systems, than controls. Maternal AA is associated with an increased risk of adverse birth outcomes in infants.

Key words: alopecia areata; birth outcome; pregnancy; preterm birth; low birthweight; congenital malformations.

Submitted Oct 14, 2024. Accepted after revision Dec 9, 2024

Published Jan 8, 2025. DOI: 10.2340/actadv.v105.42248

Acta Derm Venereol 2025; 105: adv42248

Corr: Hyun Jung Kim, MPH, PhD, Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea, 73, Goryeodae-ro, Seongbuk-gu, Seoul, 02841, Republic of Korea. E-mail: moole02@naver.com

SIGNIFICANCE

This study investigates the effects of alopecia areata on pregnancy outcomes using nation-wide data. Findings reveal an increased risk of adverse outcomes, including preterm birth, low birth weight, and congenital malformations, in infants born to mothers with alopecia areata. By highlighting these risks, the study underscores the importance of recognizing alopecia areata not only as a dermatological condition but also as one with potential syste-mic effects on maternal and infant health. These insights aim to guide healthcare providers in improving prenatal care for affected mothers, ultimately promoting better outcomes for both mothers and their babies.

Alopecia areata (AA) is a common polygenic, T cell-mediated autoimmune disorder presenting with non-scarring hair loss (1). AA is known to be associated with other autoimmune diseases or immune-related inflammatory conditions, including thyroiditis, vitiligo, psoriasis, and systemic lupus erythematosus (SLE) (2–4). Although the collapse of local immune privilege of the hair bulb is thought to be the main pathogenic mechanism of AA, some evidence has shown elevation of inflammatory cytokines or markers in the peripheral blood of patients with AA, indicating that systemic inflammation might be associated with AA development and progression (5–7).

Systemic autoimmune or inflammatory diseases have been demonstrated to affect the course of pregnancy and trigger birth complications in offspring. For example, SLE, autoimmune thyroid disease, and inflammatory bowel diseases increase the risk of preterm birth, low birthweight (LBW), Caesarean section, congenital heart disease, or congenital malformations (8–14). However, despite the possible role of systemic inflammation in AA and the highest incidence of AA in women aged 20–40 years, no studies have investigated the neonatal outcomes in maternal AA.

Our study aimed to determine the association between maternal AA and birth outcomes of offspring, including preterm delivery, LBW, delivery by Caesarean section, and congenital malformations, using the Korean National Health Insurance (NHI) claims database.

MATERIALS AND METHODS

Data sources

This study used the Korean NHI database linked to the National Health Screening Program for Infants and Children (NHSIC) database. The NHI is a government-operated service that provides mandatory insurance to South Korea's entire population of more than 50 million people. It includes inpatient and outpatient healthcare utilization data, which each medical facility must submit for reimbursement purposes according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes.

The NHSIC database records screening data on the growth and development of all the children in Korea. All children are eligible to participate in the NHSIC programme up to a maximum of 7 times from the age of 4–71 months. At every visit, a physician assesses the children's overall condition, including height, weight, nutritional status, and visual acuity, and the results are submitted to the NHI Service. The questionnaire used for history taking in this programme includes questions regarding children's gestational age, mode of delivery, weight at birth, and nutritional habits, such as breastfeeding. Currently, the programme covers 80% of children in Korea.

Employed or self-employed individuals become NHI beneficiaries by paying a certain percentage of their income, and their family members become dependents. The children of beneficiaries enrol in the NHI programme as dependents immediately after the registration of their birth. Using familial relationship information from the NHI data, we created a nationwide mother–child database. This database includes disease history based on ICD-10 codes of mothers during pregnancy, NHSIC screening data, and disease history based on ICD-10 codes of infants during the first year of life.

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-1811-507-005).

Study population

The study population consisted of all live singleton infants born between 1 January 2002, and 31 December 2016, and who had information matching with their mothers (n=4,804,806).

Mothers with AA were defined as those who had 3 or more documented physician visits per year with diagnostic codes for AA, alopecia totalis, alopecia universalis, or alopecia ophiasis (ICD-10 code L63.9, L63.0, L63.1, or L63.2, respectively). The diagnosis was validated using previously described methodology, with a sensitivity of 90.6% and a specificity of 90.8% (15). If the diagnostic code for AA began to be used before the date of delivery, it was defined as a case diagnosed with AA before delivery. When the diagnostic code for AA was used for the first time after delivery, it was considered a case of AA after delivery. If the diagnostic code for AA was not used during the study period, it was considered a case that was unexposed to AA.

Among the 4,804,806 infants, 45,328 and 56,225 were born to mothers diagnosed with AA before and after delivery, respectively. We excluded those born to women diagnosed with AA after delivery to investigate the association between *in utero* exposure to AA and birth outcomes. The remaining 4,703,253 infants were born to mothers without AA and were defined as the control group.

Assessment of morbidities of mothers during pregnancy

The morbidities of mothers during pregnancy that could affect birth outcomes were assessed based on the currently available scientific literatures (16–20) and determined using ICD-20 codes. These include hypertension (O10.X, O13, O16) and diabetes mellitus (DM) (O24.X), comprising both pre-existing and complicated pregnancy cases and pregnancy-induced cases, and pre-eclampsia (O11.X, O14.X), eclampsia (O15.X), and genitourinary infections during pregnancy (O23.X). Morbidities were defined as mothers having 3 or more documented visits in outpatient physician contacts or 1 or more documented hospitalizations with a principal diagnostic code from the codes already mentioned.

Assessment of maternal autoimmune diseases

Autoimmune or autoinflammatory diseases commonly associated with alopecia areata and known to potentially impact pregnancy outcomes were evaluated. These include autoimmune thyroiditis (E05.9, E06.3), SLE (M32.X), vitiligo (L80.X), and psoriasis (L40.X) (2–4). Diseases were defined as mothers having 3 or more documented visits in outpatient physician contacts or 1 or more documented hospitalizations with a principal diagnostic code from the codes already mentioned.

Study outcomes

The main outcomes of interest in this study were the birth outcomes of the children, including preterm birth, LBW, Caesarean section birth, and congenital malformations. Children were followed up from the time of birth until the age of 1 year for the ICD diagnostic codes and for the NHSIC, which includes the first 2 checkups. Using the NHSIC questionnaire, preterm birth was defined as a gestational age < 37 weeks, and LBW was defined as a birthweight < 2,500 g. For cases that did not complete the NHSIC questionnaire during the follow-up period, preterm (P07.2, P7) and LBW (P7.0, P7.1) were determined by referring to ICD-10 codes. Caesarean section birth was determined using the procedure code of the mother (ICD-10 code O82). Congenital malformations were determined using the diagnostic codes of children (ICD-10 codes Q00–Q99). These were further classified according to the affected system and several specific diseases (Table SI).

Statistical analysis

The characteristics of mothers with and without AA were compared using Student's *t*-test for continuous variables and standardized mean differences (SMD) for categorical variables. SMD provides a standardized measure of effect size that is not influenced by sample size alone, allowing for more meaningful comparisons between groups. A standard difference that is less than 0.1 was regarded as indicating a negligible difference. We used multivariate logistic regression analyses to investigate the association between maternal AA and birth outcomes in their children. The dependent variables were birth outcomes of infants, including preterm birth, LBW, Caesarean section birth, and congenital malformations.

Potential confounders for adjustment included maternal age, morbidity during pregnancy (hypertension, pre-eclampsia, eclampsia, DM, and genitourinary infection), as well as maternal autoimmune or autoinflammatory diseases (autoimmune thyroiditis, systemic lupus erythematosus, vitiligo, and psoriasis). Crude odds ratios (ORs), adjusted ORs (aORs), and 95% confidence intervals (CIs) were reported. All statistical analyses were performed using the STATA statistical package version 15.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Characteristics of infants and mothers

Table I indicates the characteristics of the infants and their mothers, including maternal morbidity during pregnancy and associated autoimmune diseases. The mean ages of the mothers were 31.76 and 30.98 years in infants born to mothers with and without AA, respectively. DM (6.53% in mothers with AA vs 5.03% in mothers without AA) and genitourinary infection (5.53% vs 4.51%, respectively) showed a tendency to be worse in mothers with AA than in those without AA (all p<0.05), although the differences were not sufficiently large as to be clinically significant (all SMDs <0.1). Other morbidities, such as hypertension during pregnancy, pre-eclampsia,

Table I. Characteristics of infants born to mothers with and without alopecia areata (AA)

Characteristics	Children born to mothers with AA (*n* = 45,328)	Children born to mothers without AA (*n* = 4,703,253)	*p*-value	SMD
Sex, *n* (%)			0.706	0.002
Male	23,343 (51.50)	2,426,295 (51.59)		
Female	21,985 (48.50)	2,276,958 (48.41)		
Age of mothers, mean years±SD	31.76±3.82	30.98±3.97	0.019	–0.201
Maternal autoimmune disease, *n* (%)				
Autoimmune thyroiditis	1,587 (3.50)	111,313 (2.37)	0.000	0.067
SLE	141 (0.31)	5,618 (0.12)	0.000	0.041
Vitiligo	391 (0.86)	18,240 (0.39)	0.000	0.060
Psoriasis	443 (0.98)	23,044 (0.49)	0.000	0.057
Morbidity of mothers during pregnancy, *n* (%)				
Hypertension	579 (1.28)	54,474 (1.16)	0.019	0.011
Pre-eclampsia	459 (1.01)	51,228 (1.09)	0.121	0.008
Eclampsia	34 (0.08)	5,233 (0.11)	0.022	0.012
Diabetes mellitus	2,961 (6.53)	236,405 (5.03)	0.000	0.065
Genitourinary infection	2,508 (5.53)	211,929 (4.51)	0.000	0.047

SLE: systemic lupus erythematosus; SD: standardized difference.

and eclampsia, showed little difference between mothers with and without AA.

Maternal autoimmune diseases including autoimmune thyroiditis (3.50% in mothers with AA vs 2.37% in mothers without AA), SLE (0.31% vs 0.12%, respectively), vitiligo (0.86% vs 0.39%, respectively), and psoriasis (0.98% vs 0.49 %, respectively) showed a tendency to be more prevalent in mothers with AA than in those without AA (all $p<0.05$). However, the differences were not sufficiently large as to be clinically significant (all SMDs < 0.1).

Prenatal outcomes

Infants born to mothers with AA had a higher incidence of adverse outcomes compared with controls (**Table II**). Preterm birth and LBW were more frequent in the AA group (preterm birth: 4.90% vs 33.58%, OR 1.39; 95% CI 1.33–1.45; LBW: 5.35% vs 3.98%, OR 1.36; 95% CI 1.31–1.42). After adjusting for maternal age, pregnancy-related morbidity, and associated autoimmune diseases, these risks were attenuated but remained elevated (aOR for preterm birth: 1.07; 95% CI 1.01–1.13; aOR for LBW: 1.11; 95% CI 1.05–1.17). Additionally, the Caesarean section rate was significantly higher in the AA group compared with controls, both before and after adjustment (OR 1.24; 95% CI 1.22–1.26, aOR 1.12; 95% CI 1.08–1.15).

Congenital malformations

Infants born to mothers with alopecia areata (AA) had a significantly higher incidence of congenital malformations compared with controls (11.28% vs 9.68%; OR 1.19; 95% CI 1.15–1.22), with the risk remaining elevated after adjustment (aOR,1.10; 95% CI 1.07–1.14) (Table II).

Table III displays the incidence of congenital malformation according to systematic classification, including several specific diseases. Specifically, the risks of congenital malformation of the urinary system, including cystic kidney disease (aOR 1.16; 95% CI 1.04–1.29); malformation of the circulatory system, including cardiac septal defect (aOR 1.07; 95% CI 1.01–1.14); and malformation of the musculoskeletal system, including polydactyly (aOR 1.12; 95% CI 1.05–1.19) were higher in infants from mothers with AA than in controls.

DISCUSSION

In this nationwide study, we observed that infants born to mothers with AA had an increased risk of preterm birth, LBW, and Caesarean section birth. Furthermore, maternal AA was associated with an increased risk of congenital malformations, including those of the urinary, circulatory, nervous, and musculoskeletal systems. To the best of our knowledge, this is the first study to investigate the birth outcomes of offspring of mothers with AA.

Although active studies have been conducted on the effect of maternal systemic autoimmune or autoinflammatory diseases on the birth outcomes of their offspring (14, 21, 22), there is little information regarding autoimmune or autoinflammatory skin diseases, and most of

Table II. Birth outcomes of children of mothers with AA compared with those of children of mothers without alopecia areata (AA)

	Incidence		Univariate analysis	Multivariate analysis	
Outcomes	Children born to mothers with AA (*n* = 45,328)	Children born to mothers without AA (*n* = 4,703,253)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Preterm birth (< 37 wk)	4.90% (2,223/45,328)	3.58% (168,325/4,703,253)	1.39 (1.33–1.45)	1.15 (1.10–1.20)	1.07 (1.01–1.13)
Low birthweight (< 2,500 g)	5.35% (2,424/45,328)	3.98% (187,194/4,703,253)	1.36 (1.30–1.42)	1.15 (1.11–1.20)	1.11 (1.05–1.17)
Caesarean section birth	41.04% (18,601/45,328)	35.99% (1,692,727/4,703,253)	1.24 (1.22–1.26)	1.10 (1.08–1.12)	1.12 (1.08–1.15)
Congenital malformation	11.28% (5,112/45,328)	9.68% (455,352/4,703,253)	1.19 (1.15–1.22)	1.12 (1.09–1.16)	1.10 (1.07–1.14)

[a]Adjusted for maternal age and morbidities of the mothers during pregnancy. [b]Adjusted for maternal age, morbidities of the mothers during pregnancy, and associated autoimmune diseases of the mothers.
OR: odds ratio; 95% CI: 95% confidence interval.

Table III. Systematic congenital malformations based on the presence or absence of alopecia areata (AA) in mothers

Type	Incidence		Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
	Children born to mothers with AA (n = 45,328)	Children born to mothers without AA (n = 4,703,253)		
Congenital malformations of the nervous system	0.39% (153/45,328)	0.27% (12,636/4,703,253)	1.26 (1.07–1.48)	1.11 (0.95–1.31)
Spina bifida	0.11% (48/45,328)	0.10% (4,493/4,703,253)	1.11 (0.834–1.474)	0.93 (0.70–1.23)
Congenital malformations of the eye, ear, face, and neck	1.82% (823/45,328)	1.67% (78,644/4,703,253)	1.09 (1.02–1.17)	1.13 (1.05–1.21)
Cleft lip and cleft palate	0.07% (31/45,328)	0.07% (3,275/4,703,253)	0.98 (0.69–1.40)	0.93 (0.67–1.33)
Congenital malformations of the circulatory system	2.96% (1,340/45,328)	2.33% (109,478/4,703,253)	1.28 (1.21–1.35)	1.07 (1.01–1.14)
Congenital malformations of the cardiac septa	2.80% (1,268/45,328)	2.13% (100,292/4,703,253)	1.32 (1.25–1.40)	1.08 (1.02–1.14)
Congenital malformations of the respiratory system	0.18% (82/45,328)	0.20% (9,342/4,703,253)	0.91 (0.73–1.13)	0.98 (0.78–1.21)
Congenital malformations of the digestive system	2.70% (1,222/45,328)	2.37% (111,695/4,703,253)	1.14 (1.08–1.21)	1.08 (1.02–1.14)
Congenital absence, atresia, and stenosis of the large intestine	0.06% (26/45,328)	0.05% (2,334/4,703,253)	1.16 (0.79–1.70)	1.06 (0.71–1.54)
Congenital malformations of the genital organs	1.04% (469/45,328)	0.86% (40,438/4,703,253)	1.21 (1.10–1.32)	1.10 (1.00–1.20)
Undescended testicles	0.92% (415/45,328)	0.80% (37,541/4,703,253)	1.15 (1.04–1.27)	1.06 (0.96–1.16)
Hypospadias	0.10% (45/45,328)	0.80% (4,387/4,703,253)	1.06 (0.79–1.43)	0.97 (0.72–1.30)
Congenital malformations of the urinary system	0.74% (337/45,328)	0.56% (26,419/4,703,253)	1.33 (1.19–1.48)	1.16 (1.04–1.29)
Cystic kidney disease	0.07% (30/45,328)	0.07% (3,387/4,703,253)	0.91 (0.64–1.32)	0.87 (0.61–1.25)
Congenital malformations of the musculoskeletal system	2.26% (1,025/45,328)	1.90% (89,503/4,703,253)	1.19 (1.12–1.27)	1.12 (1.05–1.19)
Polydactyly	0.21% (96/45,328)	0.19% (9,023/4,703,253)	1.10 (0.90–1.35)	1.13 (0.93–1.39)
Other congenital malformations	0.53% (239/45,328)	0.48% (22,679/4,703,253)	1.09 (0.96–1.24)	1.09 (0.96–1.24)
Chromosomal abnormalities, NEC	0.13% (61/45,328)	0.15% (6,955/4,703,253)	0.91 (0.71–1.17)	0.89 (0.69–1.14)

[a]Adjusted for maternal ages, morbidities of the mothers during pregnancy, and associated autoimmune diseases.
OR: odds ratio; 95% CI: 95% confidence interval; NEC: not elsewhere classified.

them are limited to psoriasis. A Taiwanese record-linkage study demonstrated an increased risk of LBW in infants from mothers with severe psoriasis (23), and a Swedish population-based study demonstrated that infants with maternal psoriasis had an increased risk of congenital malformation (24). Cho et al. (25) recently reported that maternal AA increased the risk of abortion and ectopic pregnancy. Nevertheless, the results of this study focused only on maternal outcomes and not on the outcomes of offspring. The present study used big data based on the NHI and created a unique mother–child database using familial relationship information. In this way, we obtained a large sample size, allowing us to have sufficient statistical power to analyse birth outcomes, including specific congenital malformations by the affected system.

Although the ORs of birth complications were not dramatically higher in infants from AA mothers, our results are expected to have certain clinical significance considering that AA is a common autoimmune disease, with a lifetime risk of approximately 2% that frequently affects women of childbearing ages. We believe our data provide evidence for the necessity of preconception counselling, active surveillance during pregnancy, and thorough neonatal care of offspring in pregnant women with AA.

Meanwhile, in our results, mothers with AA showed a tendency to have worse maternal obstetric outcomes compared with mothers without AA, particularly for gestational DM and genitourinary infection. Moreover, as expected, mothers with AA showed a tendency to be more commonly associated with other autoimmune or autoinflammatory diseases such as autoimmune thyroiditis, SLE, vitiligo, and psoriasis. Considering that the strengths of association for birth outcome of the study group were attenuated after adjusting for these comorbid maternal obstetric conditions and associated autoimmune diseases, close monitoring and thorough management of pregnancy morbidity and associated diseases of mothers with AA might improve the outcomes of their children.

The exact mechanism underlying the worse outcomes in infants from AA mothers is unclear. Previous studies have shown significantly higher T helper 1 (Th 1) and Th 17 cytokines and lower regulatory T-cell cytokine levels not only in the lesional skin of patients with AA but also in the peripheral blood (26, 27). Excessive immunity of effector T cells causes pathological inflammation at the maternal–foetal interface and may lead to preterm labour and birth, spontaneous abortion, intrauterine growth retardation, and pre-eclampsia (28–31). On the other hand, regulatory T cells regulate maternal alloreactive T cells and induce foeto-maternal immune tolerance, which may reduce perinatal complications caused by effector T cells (32). An inadequate number or functional deficiency of regulatory T cells is associated with spontaneous abortion and pre-eclampsia (33). Taken together, abnormal regulation of particular T-cell cytokines in mothers with AA might be an important pathogenetic mechanism that causes worse birth outcomes of the children in our study.

Regarding congenital malformations, *in utero* exposure to AA medications may be considered a main factor. Unfortunately, medication history during pregnancy was not evaluated in this study. However, the effects of drugs are expected to be small as AA is not a life-threatening condition, and most patients do not take medications for AA during their pregnancy in Korea. In addition, the medications used in patients with severe AA, including corticosteroids and cyclosporine, have generally failed to cause adverse outcomes related to pregnancy in humans (34–38). Further investigations are necessary to elucidate the mechanism of higher teratogenicity in pregnancy of maternal AA.

Our study has some limitations. First, the NHI claims database may include misdiagnoses that can lead to

misclassification bias. To reduce such errors, we defined patients with AA according to a previously validated algorithm.(15) Second, we were unable to evaluate some factors associated with the outcomes, including medication, body mass index before pregnancy, and history of smoking and alcohol consumption, which might influence pregnancy outcomes. Third, the NHI claims database did not provide detailed clinical information on individual patients, including disease onset, duration, severity, and activity or treatment histories. Finally, some congenital anomalies that are sometimes not identified early in life may not be included. However, the risk was considered to be significantly low, such that it was not expected to affect the results.

In conclusion, Infants born to mothers with AA had an increased risk of birth comorbidities. Further investigation is required to clarify the causal association between maternal AA and these comorbidities in offspring. Preterm birth, LBW, and congenital anomalies are major factors contributing to neonatal mortality and morbidity. Considering that AA is a common skin disease that can occur in women of childbearing age, our results may provide evidence of the appropriateness of close perinatal monitoring and consultation in pregnancy for maternal AA.

ACKNOWLEDGEMENTS

IRB approval status: This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-1811-507-005).

Funding sources: This study was supported by the Seoul National University Bundang Hospital Research Fund (grant no. 02-2020-0037).

Data availability statement: Data subject to third party restrictions.

The authors have no conflicts of interest to declare.

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