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Pregnancy Outcomes in Patients with Vitiligo: A Nationwide Population-based Cohort Study from Korea

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34 **Key words**: abortion, autoimmune, delivery, pregnancy, spontaneous abortion, vitiligo

35

Abstract

Background: Vitiligo is a chronic autoimmune skin disorder affecting 1% of populations worldwide. Few large-scale studies have explored adverse pregnancy outcomes in patients with vitiligo.

Objective: To investigate adverse pregnancy outcomes in patients with vitiligo.

Methods: We performed a retrospective cohort study on 4,738 pregnancies of women with vitiligo and 47,380 pregnancies of age-matched controls without vitiligo using the Korean National Health Insurance (NHI) Claims database from 2007 to 2016. Multivariate logistic regression models were used to evaluate the associations between vitiligo and pregnancy outcomes, including live births, spontaneous abortion, cesarean delivery, preterm delivery, gestational diabetes, stillbirth, pre-eclampsia/eclampsia, and intrauterine growth retardation.

Results: Patients with vitiligo exhibited a significantly lower live birth rate (odds ratio [OR] 0.870, 95% confidence interval [CI] 0.816–0.927) and a higher incidence of spontaneous abortion (OR 1.250, 95% CI 1.148–1.362) than the control group.

Limitation: The NHI Claims database lacks detailed clinical information on individual patients.

Conclusion: Vitiligo was significantly associated with an increased risk of spontaneous abortion. Further studies are needed to determine whether systemic autoimmunity explains our finding.

INTRODUCTION

Vitiligo is a common acquired disorder of the skin and mucosa characterized by circumscribed depigmented macules and patches, affecting 0.5%–1% of populations worldwide.[1] Although patients with vitiligo suffer from stigmatization, low self-esteem, and social isolation,[2] vitiligo has frequently been regarded as simply a cosmetic problem. However, vitiligo profoundly impacts the quality of life [3]; a recent survey found that up to 59% of vitiligo patients were depressed.[4]

Vitiligo is a chronic autoimmune disorder, in which epidermal melanocytes are destroyed by autoreactive cytotoxic T cells.[1] It is frequently associated with other systemic autoimmune diseases including autoimmune thyroid diseases, type 1 diabetes mellitus, Addison's disease, pernicious anemia, systemic lupus erythematosus, and rheumatoid arthritis.[5-7] A genetic predisposition for this condition has been suggested, and more than 40 susceptibility loci were found to be associated with vitiligo in a genome-wide association study.[8,9] Recently, the autoimmune nature of vitiligo has been emphasized, with $CD8^+$ T cells being shown to play a major role in vitiligo dissemination.[1,10]

Increasing evidence suggests that systemic autoimmunity can affect the progress of pregnancy, triggering maternal complications and adverse fetal outcomes. Several poor outcomes, including recurrent abortion, fetal death, pre-eclampsia, intrauterine growth restriction (IUGR) and preterm birth have been observed in women with a variety of autoimmune diseases.[11,12] However, the pregnancy outcomes of patients with vitiligo have not been comprehensively investigated. In the present study, we examined these outcomes using the Korean National Health Insurance (NHI) Claims database.

MATERIALS AND METHODS

Study design and database

We performed a nationwide, population-based, retrospective cohort study using an NHI Claims database that contained all claims information from the NHI and the Korean Medical Aid program from 2007 to 2016. Korea has one of the largest NHI systems worldwide, mandated by law, which covers up to 98% of the 50 million citizens of the country. The database has been shown to afford reliable estimates of the prevalence of certain diseases in Korea.[13,14]

Study population

We included all 4,738 confirmed first-pregnancy women with vitiligo identified between January 1, 2007, and December 31, 2016 in Korea. If a woman had more than one pregnancy during the study period, we evaluated only the first to avoid potential bias associated with multiple outcomes of the same woman. All recorded diagnoses were based on the International Classification of Diseases, Tenth Revision (ICD-10).

We defined women with vitiligo as those who were of child-bearing age (15–50 years) who had made at least two documented physician contacts at which times vitiligo (ICD-10 code L80) was the principal diagnosis (the vitiligo group). The control group included women who had no history of vitiligo during the same period. They were randomly selected (10 controls for each vitiligo patient) after frequency matching in terms of age with the vitiligo group. Patients with diabetes, hypertension, and/or hyperlipidemia were defined as those with at least 10 documented physician contacts attributable to these diseases (ICD-10 codes E10–14 for diabetes, I10 for hypertension, and E78 for hyperlipidemia) when the first diagnosis of any of these diseases was made before the diagnosis of pregnancy. We assumed

that patients with chronic diseases (diabetes, hypertension, and hyperlipidemia) visited hospitals at least once a year.

Pregnancy outcomes

Pregnancy outcomes were divided into four categories: 1) live births ([total labors minus total abortions or stillbirths]/[total confirmed pregnancies, labors, or abortions]; (ICD-10 codes R313, R314, R435, R436, R438, RA31, RA38, RA43, R450, R451, R452, and R500 for labors; O00–O08 for abortions; and Z321, Z33, Z34, and Z35 for confirmed pregnancies); 2) spontaneous abortion (ICD-10 codes O02, O03, O05, and O06); 3) cesarean delivery (ICD-10 codes R450, R451, R452, and R500); and 4) perinatal events (discussed below).

Perinatal events

Perinatal events included the following five sub-classifications: 4-1) preterm delivery (ICD-10 codes O60, O601, and O603); 4-2) pre-eclampsia/eclampsia (ICD-10 codes O11, O13, O14, O15, and O16); 4-3) gestational diabetes mellitus (gestational DM; diabetes during pregnancy [ICD-10 codes O24, O244, and O249] excluding those diagnosed with diabetes before pregnancy [E10, E11, E12, E13, E14]); 4-4) stillbirths (ICD-10 code O364); and 4-5) IUGR (ICD-10 code O365).

Subgroup analyses by the extent of depigmentation

Vitiligo was categorized as limited or extensive by the extent of involvement. In the Korea NHI system, the phototherapy codes are divided into four in terms of the body surface area involved: body surface area < 9 (level 1), 10–18 (level 2), 19–36 (level 3), and ≥ 37% (level 4). Herein, we defined patients who underwent at least one level 4 phototherapy

session as having extensive vitiligo, and the rest as having limited vitiligo. Although we may have omitted some patients who did not undergo phototherapy at all over the 10-year period, we assume that all patients in the extensive vitiligo subgroup had extensive vitiligo.

Statistical analysis

Categorical variables were expressed as percentages and compared using the chi-squared test. We used multivariate logistic regression analyses to explore the associations between vitiligo and adverse pregnancy outcomes after adjustment for age, sex, socioeconomic status, and the presence of diabetes, hypertension, and hyperlipidemia. All analyses were performed with the aid of SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the study population

We identified a total of 4,738 pregnancies in women with vitiligo and 47,380 pregnancies in age-matched women without vitiligo (Table 1). In both groups, the peak age at pregnancy was 21–30 years (50.8%), followed by 31–40 years (42.0%). Of the vitiligo patients, 4,038 (85.2%) had limited lesions, and 700 (14.8%) showed extensive involvement.

Live birth

The total live birth rate was 66.1% of all pregnancies in women with vitiligo and 68.9% in women without vitiligo, which were significantly different (odds ratio [OR] 0.870, 95% confidence interval [CI] 0.816–0.927) after adjusting for the possible confounding factors (Table 2). Upon subgroup analysis by the extent of disease, the live birth rates were found to be lower in patients with both limited disease (OR 0.877, 95% CI 0.819–0.940) and extensive disease (OR 0.828, 95% CI 0.708–0.970) (Table 3).

Spontaneous abortion

Spontaneous abortion was observed in 14.7% of pregnant women with vitiligo and 12.1% of those without vitiligo, which were significantly different (OR 1.250, 95% CI 1.148–1.362) after adjusting for confounding factors (Table 2). On subgroup analysis, the spontaneous abortion rate was found to be significantly higher in patients with both limited disease (OR 1.245, 95% CI 1.136–1.364) and extensive disease (OR 1.282, 95% CI 1.040–1.580) (Table 3).

Cesarean delivery

The cesarean delivery rates were 38.1% in patients with vitiligo and 38.9% in the

control group, which were not significantly different.

Perinatal events

Total perinatal events including preterm delivery, pre-eclampsia, gestational diabetes, stillbirth, and IUGR were observed in 5.5% of women with vitiligo and 6.7% of controls, which were significantly different (OR 0.831, 95% CI 0. 0.708–0.976). Of the individual indicators, only the rate of preterm delivery was significantly lower in vitiligo patients than in controls ($P = 0.002$) (Table 2).

DISCUSSION

In this nationwide cohort study, we found that pregnant women with vitiligo (n = 4,738) had a significantly lower rate of live births (OR 0.870) and a higher incidence of spontaneous abortion (OR 1.250) than women without vitiligo (n = 47,380). These findings conflict with those of a previous study that found no difference in pregnancy outcomes between women with (n = 79) and without vitiligo evaluated in a single institution.[15] Furthermore, upon subgroup analyses stratified by the extent of vitiligo, more extensive disease was shown to be associated with a higher incidence of spontaneous abortion and a lower live birth rate than limited disease. However, such results were also found in those with limited disease, suggesting that the systemic autoimmunity of vitiligo is in play beyond the skin, regardless of the extent of disease.

We investigated both live births and spontaneous abortions to minimize potential selection bias; some spontaneous abortions might have been missed if the appropriate code had not been input by doctors, or if some patients did not visit hospital despite undergoing spontaneous abortion. The live birth rate was the rate of all live births from all enrolled pregnancies. We minimized potential selection bias by checking these two items simultaneously. The live birth and spontaneous abortion rates were mutually complementary, exhibiting similar tendencies.

The higher incidence of spontaneous abortion and the lower live birth rate of vitiligo patients may reflect the autoimmune nature of vitiligo. Many autoimmune diseases are known to affect pregnancy outcomes; these diseases include systemic lupus erythematosus (SLE) and autoimmune thyroid disease. In women with SLE, the incidences of spontaneous abortion, stillbirth, IUGR, and preterm birth were twice those of normal populations.[16] In addition, live births in untreated patients with anti-phospholipid antibody syndrome constituted ≤10% of all pregnancies.[17,18] Several previous studies confirmed that thyroid

autoimmunity in the absence of overt thyroid dysfunction was significantly associated with a three- to fivefold increase in the overall miscarriage rate.[19] Thus, the autoimmunity of vitiligo may be systemic rather than limited to the skin.

The T-cell-mediated autoimmunity that contributes to the pathogenesis of vitiligo may explain the adverse pregnancy outcomes. Rodrigues *et al.* found that, in vitiligo patients, the numbers of autoreactive cytotoxic $CD8^+$ T cells increased in blood and the perilesional skin, and these cells destroy melanocytes of the skin.[1] Another recent report described enhanced Th1 and Th17 responses in the peripheral blood of patients with active vitiligo.[20] Also, maternal effector T cells may play roles in the pathogenesis of adverse pregnancy outcomes including spontaneous abortion, stillbirth, IUGR, and pre-eclampsia; T cells comprised almost half of the total cellular infiltrates into uterine villi, and the CD8:CD4 ratio is typically about 3:1 in such patients.[21] In addition, it showed that women experiencing recurrent spontaneous abortions primarily exhibited a Th1 pattern, whereas normal pregnant women exhibited essentially a Th2 pattern, predictive of pregnancy success.[22] Therefore, the increased levels of particular T cell subsets in vitiligo patients may cause spontaneous abortion, thus reducing live birth numbers.

The cesarean delivery rate did not differ between the two groups. In Korea, this rate is generally high, as in both groups in the present study.[23] Although the preterm delivery rate of vitiligo patients was lower than that of controls, it is unclear whether this is of clinical relevance. One possible explanation is that spontaneous abortion is more common in patients with vitiligo (thus, infants at higher risk of preterm delivery had already been lost). It would thus be best not to overinterpret this finding. In addition, the rates of other perinatal events such as pre-eclampsia, gestational DM, stillbirth, and IUGR were not significantly associated with vitiligo.

We could not examine the impact of corticosteroid use on pregnancy outcomes.

Overall, 5.4% of the vitiligo patients included in the study used systemic corticosteroids for > 6 months over the 10-year study period. However, this does not mean that corticosteroids were used during pregnancy. Few women used corticosteroids during pregnancy; women planning pregnancies either do not use corticosteroids or stop using the drugs when pregnancies are confirmed.

Our study had several limitations. First, the NHI Claims database may contain incorrect diagnoses. However, the database contains all incidents related to pregnancy per se and other pregnancy-related events, because most Korean women visit a clinic for diagnosis and management during their pre-/perinatal periods. Second, the database lacked detailed clinical information on individual patients, such as age at disease onset, disease duration, and the vitiligo subtype, including segmental vitiligo. Thus, we could not explore some possible covariants affecting pregnancy outcomes in detail. Third, we also lacked information on lifestyle factors such as smoking status and the extent of physical activity: both might influence pregnancy outcomes. Fourth, we did not evaluate comorbidities (such as autoimmune rheumatic disorders) in detail; these could affect pregnancy outcomes. Fifth, the control group may have included some patients with vitiligo, even though we excluded those with only a single clinical diagnosis of vitiligo over the 10-year period. Finally, some patients who suffered unrecognized early fetal loss or abortion before the diagnosis of pregnancy may not have been included. However, we consider that the risk of bias is too low to affect the results.

On the other hand, this study had certain strengths. We included an exceptionally large, nationwide, well-defined vitiligo population, and explored various pregnancy outcomes in women with vitiligo. We analyzed not only all deliveries but also all identified pregnancies during the given period. Korea has a very low threshold for medical service; specialists usually deliver primary care. Diagnoses are very reliable, especially in vitiligo patients and

251 those with obstetric issues. Therefore, the large sample size and the minimal recall and
252 selection biases are strengths of our study.

253 In conclusion, we found an increased risk of spontaneous abortion and reduced live
254 births in women with vitiligo in this 10-year, nationwide, retrospective cohort study. Further
255 studies are needed to determine whether systemic autoimmunity underlies this finding. To the
256 best of our knowledge, this is the first large-scaled cohort study to identify adverse pregnancy
257 outcomes in vitiligo patients in the real world. Vitiligo is not a contraindication for pregnancy,
258 but physician consultations with patients addressing the increased risks of both spontaneous
259 abortion and non-attainment of a live birth would be prudent both before and during
260 pregnancy. However, we cannot point to cause-and-result relationships between vitiligo and
261 adverse pregnancy outcomes (spontaneous abortion and a lower live birth rate), and we also
262 do not know if active vitiligo treatment improved pregnancy outcomes. Further work is
263 needed to address these issues.

264

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267

268 The English in this document has been checked by at least two professional editors, both
269 native speakers of English. For a certificate, please see:
270 http://www.textcheck.com/certificate/sOyp8C

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273 ***Abbreviations used*:** BSA: body surface area; CI: confidence interval; DM: diabetes mellitus;
274 ICD-10: International Classification of Diseases Tenth Revision; IUGR: intrauterine growth
275 retardation; NHI: National Health Insurance; OR: odds ratio; SLE: systemic lupus
276 erythematosus

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332 **Table 1. Descriptive characteristics of the study population.**

	Controls without vitiligo	Patients with vitiligo	*P* value
Total	47,380 (100%)	4,738 (100%)	
Age (years)			1.000
15–20	2,090 (4.4%)	209 (4.4%)	
21–30	24,080 (50.8%)	2,408 (50.8%)	
31–40	19,880 (42%)	1,988 (42.0%)	
41–50	1330 (2.8%)	133 (2.8%)	
Insurance type			0.002
Health insurance	46,569 (98.3%)	4,686 (98.9%)	
Medical aid	811 (1.7%)	52 (1.1%)	
Comorbidity			
Diabetes	333 (0.7%)	27 (0.6%)	0.292
Hypertension	396 (0.8%)	21 (0.4%)	0.004
Hyperlipidemia	252 (0.8%)	13 (0.3%)	0.018
Use of corticosteroid (≥ 6 months)		257 (5.4%)	

Table 2. Pregnancy outcomes in women with vitiligo compared with those of age-matched women without vitiligo.

		Univariate analysis		Multivariate analysis	
	Incidence rate	**Unadjusted OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)[1]**	***P* value**
Live birth					
Controls	68.9% (32,668/47,380)	Reference		Reference	
Vitiligo	66.1% (3,131/4,738)	0.877 (0.824–0.935)	< 0.001	0.870 (0.816–0.927)	< 0.001
Spontaneous abortion					
Controls	12.1% (5,756/47,380)	Reference		Reference	
Vitiligo	14.7% (696/4,738)	1.245 (1.144–1.356)	< 0.001	1.250 (1.148–1.362)	< 0.001
Cesarean delivery					
Controls	38.9% (12,719/32,668)	Reference		Reference	
Vitiligo	38.1% (1,193/3,131)	0.966 (0.895–1.041)	0.364	0.983 (0.911–1.060)	0.655
Total perinatal events					
Controls	6.7% (2,188/32,668)	Reference		Reference	
Vitiligo	5.5% (172/3,131)	0.810 (0.690–0.950)	0.010	0.831 (0.708–0.976)	0.024
Preterm delivery					
Controls	2.4% (781/32,668)	Reference		Reference	
Vitiligo	1.5% (47/3,131)	0.622 (0.462–0.837)	0.002	0.625 (0.465–0.842)	0.002
Preeclampsia/eclampsia					
Controls	2.2% (704/32,668)	Reference		Reference	
Vitiligo	1.7% (54/3,131)	0.797 (0.603–1.054)	0.111	0.824 (0.623–1.090)	0.176
Gestational DM					
Controls	1.1% (364/32,668)	Reference		Reference	
Vitiligo	1.1% (36/3,131)	1.033 (0.732–1.457)	0.855	1.149 (0.805–1.639)	0.445
Stillbirth					
Controls	0.3% (114/32,668)	Reference		Reference	
Vitiligo	0.3% (10/3,131)	0.915 (0.479–1.748)	0.788	0.920 (0.481–1.759)	0.801
IUGR					
Controls	1.0% (339/32,668)	Reference		Reference	
Vitiligo	1.1% (36/3,131)	1.109 (0.785–1.567)	0.556	1.101 (0.779–1.555)	0.587

[1]Adjusted by age, socioeconomic status, and the presence of diabetes, hypertension, and hyperlipidemia.

CI, confidence interval; *DM*, diabetes; *IUGR*, intrauterine growth retardation; *OR*, odds ratio.

Table 3. Stratified analysis of the pregnancy outcomes of vitiligo patients according to the extent of disease.

		Univariate analysis		Multivariate analysis	
	Incidence rate	**Unadjusted OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)[1]**	***P* value**
Live birth					
Controls	68.9% (32,668/47,380)	Reference		Reference	
Vitiligo (limited)	66.2% (2,675/4,038)	0.884 (0.826–0.946)	< 0.001	0.877 (0.819–0.940)	< 0.001
Vitiligo (extensive)	65.1% (456/700)	0.842 (0.720–0.984)	0.031	0.828 (0.708–0.970)	0.019
Spontaneous abortion					
Controls	12.1% (5,756/47,380)	Reference		Reference	
Vitiligo (limited)	14.6% (590/4,038)	1.237 (1.129–1.356)	< 0.001	1.245 (1.136–1.364)	< 0.001
Vitiligo (extensive)	15.1% (106/700)	1.291 (1.048–1.590)	0.017	1.282 (1.040–1.580)	0.020
Cesarean delivery					
Controls	38.9% (12,719/32,668)	Reference		Reference	
Vitiligo (limited)	38.8% (1,038/2,675)	0.995 (0.917–1.078)	0.894	1.014 (0.935–1.100)	0.729
Vitiligo (extensive)	34.0% (155/456)	0.808 (0.665–0.982)	0.032	0.813 (0.668–0.988)	0.038
Total perinatal events					
Controls	6.7% (2,188/32,668)	Reference		Reference	
Vitiligo (limited)	5.3% (143/2,675)	0.787 (0.661–0.936)	0.007	0.805 (0.676–0.960)	0.015
Vitiligo (extensive)	6.4% (29/456)	0.946 (0.648–1.382)	0.774	0.986 (0.674–1.441)	0.940
Preterm delivery					
Controls	2.4% (781/32,668)	Reference		Reference	
Vitiligo (limited)	1.5% (40/2,675)	0.620 (0.450–0.854)	0.003	0.623 (0.452–0.858)	0.004
Vitiligo (extensive)	1.5% (7/456)	0.637 (0.301–1.347)	0.238	0.640 (0.303–1.356)	0.244
Preeclampsia/eclampsia					
Controls	2.2% (704/32,668)	Reference		Reference	
Vitiligo (limited)	1.6% (43/2,675)	0.742 (0.544–1.012)	0.060	0.765 (0.560–1.044)	0.091
Vitiligo (extensive)	2.4% (11/456)	1.122 (0.614–2.051)	0.707	1.183 (0.647–2.164)	0.585
Gestational DM					
Controls	1.1% (364/32,668)	Reference		Reference	
Vitiligo (limited)	1.1% (29/2,675)	0.973 (0.665–1.423)	0.886	1.069 (0.722–1.583)	0.738
Vitiligo (extensive)	1.5% (7/456)	1.386 (0.653–2.943)	0.396	1.637 (0.759–3.531)	0.209
Stillbirth					
Controls	0.3% (114/32,668)	Reference		Reference	

Vitiligo (limited)	0.4% (10/2,675)	1.072 (0.561–2.048)	0.834	1.080 (0.565–2.065)	0.816
Vitiligo (extensive)	0.0% (0/456)	NA	NA	NA	NA
IUGR					
Controls	1.0% (339/32,668)	Reference		Reference	
Vitiligo (limited)	1.2% (31/2,675)	1.118 (0.772–1.619)	0.554	1.109 (0.766–1.606)	0.584
Vitiligo (extensive)	1.1% (5/456)	1.057 (0.435–2.569)	0.902	1.052 (0.433–2.556)	0.911

[1]Adjusted by age; socioeconomic status, and the presence of diabetes, hypertension, and hyperlipidemia.

CI, confidence interval; DM, diabetes; NA, not available; IUGR, intrauterine growth retardation; OR, odds ratio.

Capsule summary

- Pregnancy outcomes of patients with vitiligo have not been comprehensively investigated.
- We demonstrated an increased rate of spontaneous abortion and reduced live births in a population-based cohort study of women with vitiligo.
- Obstetricians, primary care physicians, and patients should be educated about the increased risk of adverse outcomes in pregnant women with vitiligo.